PharmacyToday

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DECEMBER 2022

CONTINUING PHARMACY EDUCATION

CPE

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Caution for older adults

APhA

KNOW WHO TO VACCINATE—AND WHY

SHINGRIX delivered **>90%** efficacy against shingles regardless of age in those 50 years and older[1,*]

SHINGRIX
(ZOSTER VACCINE RECOMBINANT, ADJUVANTED)

*Data from the phase 3 ZOE-50 (≥50 years of age) trial (median follow-up period 3.1 years) and pooled data in individuals ≥70 years of age from the phase 3 ZOE-50 and ZOE-70 trials (median follow-up period 4 years) in subjects who received 2 doses of SHINGRIX (n=7344 and 8250, respectively) or placebo (n=7415 and 8346, respectively). These populations represented the modified Total Vaccinated Cohort, defined as patients who received 2 doses (0 and 2 months) of either SHINGRIX or placebo and did not develop a confirmed case of herpes zoster within 1 month after the second dose.[1,2]

Indication

SHINGRIX is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older.

SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

Important Safety Information

- SHINGRIX is contraindicated in anyone with a history of a severe allergic reaction (eg, anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX
- Review immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of SHINGRIX
- In a postmarketing observational study, an increased risk of Guillain-Barré syndrome was observed during the 42 days following vaccination with SHINGRIX
- Syncope (fainting) can be associated with the administration of injectable vaccines, including SHINGRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope
- Solicited local adverse reactions reported in individuals aged 50 years and older were pain (78%), redness (38%), and swelling (26%)
- Solicited general adverse reactions reported in individuals aged 50 years and older were myalgia (45%), fatigue (45%), headache (38%), shivering (27%), fever (21%), and gastrointestinal symptoms (17%)

≥50 YEARS OF AGE= OVER 90% EFFICACY†

†In those 50 years and older, SHINGRIX delivered >90% efficacy against shingles regardless of age.[1,*]

50+ YEARS

They may look healthy, feel healthy, and even act healthy. But even your patients 50-59 years old are at risk for shingles. There's a way to help prevent it.[3,4] Talk to them about SHINGRIX.

The most common solicited adverse reactions in clinical trials were: pain, redness, and swelling at the injection site, myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms.[1]

Are you vaccinating all of your appropriate patients? See who you might be missing at ProfilesSHINGRIX.com

Important Safety Information (cont'd)

- The data are insufficient to establish if there is vaccine-associated risk with SHINGRIX in pregnant women
- It is not known whether SHINGRIX is excreted in human milk. Data are not available to assess the effects of SHINGRIX on the breastfed infant or on milk production/excretion
- Vaccination with SHINGRIX may not result in protection of all vaccine recipients

You are encouraged to report vaccine adverse events to the US Department of Health and Human Services. Visit www.vaers.hhs.gov to file a report, or call 1-800-822-7967.

Please see Brief Summary of Prescribing Information for SHINGRIX on the following pages.

References: 1. Prescribing Information for SHINGRIX. **2.** Data on file. Study 113077 (NCT01165229). GSK Study Register. Study entry at: https://www.gsk-studyregister.com/en/trial-details/?id=113077 **3.** Kilgore PE, Kruszon-Moran D, Seward JF, et al. Varicella in Americans from NHANES III: implications for control through routine immunization. *J Med Virol.* 2003;70(suppl 1):S111-S118. **4.** Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR.* 2008;57(RR-5):1-30.

BRIEF SUMMARY

SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted)

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

SHINGRIX is a vaccine indicated for prevention of herpes zoster (HZ) (shingles) in adults aged 50 years and older.

Limitations of Use:

- SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

2 DOSAGE AND ADMINISTRATION

2.2 Administration Instructions

For intramuscular injection only.

After reconstitution, administer SHINGRIX immediately or store refrigerated between 2° and 8°C (36° and 46°F) and use within 6 hours. Discard reconstituted vaccine if not used within 6 hours.

2.3 Dose and Schedule

Two doses (0.5 mL each) administered intramuscularly according to the following schedule:

- A first dose at Month 0 followed by a second dose administered 2 to 6 months later.

4 CONTRAINDICATIONS

Do not administer SHINGRIX to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX *[see Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of SHINGRIX.

5.2 Guillain-Barré Syndrome (GBS)

In a postmarketing observational study, an increased risk of GBS was observed during the 42 days following vaccination with SHINGRIX *[see Adverse Reactions (6.2)]*.

5.3 Syncope

Syncope (fainting) can be associated with the administration of injectable vaccines, including SHINGRIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. There is the possibility that broad use of SHINGRIX could reveal adverse reactions not observed in clinical trials.

Adults Aged 50 Years and Older

Overall, 17,041 adults aged 50 years and older received at least 1 dose of SHINGRIX in 17 clinical studies.

The safety of SHINGRIX was evaluated by pooling data from 2 placebo-controlled clinical studies (Studies 1 and 2) involving 29,305 subjects aged 50 years and older who received at least 1 dose of SHINGRIX (n = 14,645) or saline placebo (n = 14,660) administered according to a 0- and 2-month schedule. At the time of vaccination, the mean age of the population was 69 years; 7,286 (25%) subjects were aged 50 to 59 years, 4,488 (15%) subjects were aged 60 to 69 years, and 17,531 (60%) subjects were aged 70 years and older. Both studies were conducted in North America, Latin America, Europe, Asia, and Australia. In the overall population, the majority of subjects were White (74%), followed by Asian (18%), Black (1.4%), and other racial/ethnic groups (6%); 58% were female.

Solicited Adverse Reactions: In Studies 1 and 2, data on solicited local and general adverse reactions were collected using standardized diary cards for 7 days following each vaccine dose or placebo (i.e., day of vaccination and the next 6 days) in a subset of subjects (n = 4,886 receiving SHINGRIX, n = 4,881 receiving placebo with at least 1 documented dose). Across both studies, the percentages of subjects aged 50 years and older reporting each solicited local and general adverse reaction following administration of SHINGRIX (both doses combined) were pain (78%), redness (38%), and swelling (26%); and myalgia (45%), fatigue (45%), headache (38%), shivering (27%), fever (21%), and gastrointestinal symptoms (17%).

The reported frequencies of specific solicited local adverse reactions and general adverse reactions (overall per subject), by age group, from the 2 studies are presented in Table 1.

Table 1. Percentage of Subjects with Solicited Local and General Adverse Reactions within 7 Days[a] of Vaccination in Adults Aged 50 to 59 Years, 60 to 69 Years, and 70 Years and Older[b] (Total Vaccinated Cohort with 7-Day Diary Card)

Adverse Reactions	Aged 50-59 Years		Aged 60-69 Years		Aged ≥70 Years	
	SHINGRIX	Placebo[c]	SHINGRIX	Placebo[c]	SHINGRIX	Placebo[c]
Local Adverse Reactions	**n=1,315 %**	**n=1,312 %**	**n=1,311 %**	**n=1,305 %**	**n=2,258 %**	**n=2,263 %**
Pain	88	14	83	11	69	9
Pain, Grade 3[d]	10	1	7	1	4	0.2
Redness	39	1	38	2	38	1
Redness, >100 mm	3	0	3	0	3	0
Swelling	31	1	27	1	23	1
Swelling, >100 mm	1	0	1	0	1	0
General Adverse Reactions	**n=1,315 %**	**n=1,312 %**	**n=1,309 %**	**n=1,305 %**	**n=2,252 %**	**n=2,264 %**
Myalgia	57	15	49	11	35	10
Myalgia, Grade 3[e]	9	1	5	1	3	0.4
Fatigue	57	20	46	17	37	14
Fatigue, Grade 3[e]	9	2	5	1	4	1
Headache	51	22	40	16	29	12
Headache, Grade 3[e]	6	2	4	0.2	2	0.4
Shivering	36	7	30	6	20	5
Shivering, Grade 3[e]	7	0.2	5	0.3	2	0.3
Fever	28	3	24	3	14	3
Fever, Grade 3[f]	0.4	0.2	1	0.2	0.1	0.1
GI[g]	24	11	17	9	14	8
GI, Grade 3[e]	2	1	1	1	1	0.4

Total vaccinated cohort for safety included all subjects with at least 1 documented dose (n).

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Data for subjects aged 50 to 59 years and 60 to 69 years are based on Study 1. Data for subjects 70 years and older are based on pooled data from Study 1: NCT01165177 and Study 2: NCT01165229.

[c] Placebo was a saline solution.

[d] Grade 3 pain: Defined as significant pain at rest; prevents normal everyday activities.

[e] Grade 3 myalgia, fatigue, headache, shivering, and GI: Defined as preventing normal activity.

[f] Fever defined as ≥37.5°C/99.5°F for oral, axillary, or tympanic route, or ≥38°C/100.4°F for rectal route; Grade 3 fever defined as >39.0°C/102.2°F.

[g] GI = Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain.

The incidence of solicited local and general reactions was lower in subjects aged 70 years and older compared with those aged 50 to 69 years.

The local and general adverse reactions seen with SHINGRIX had a median duration of 2 to 3 days.

(continued on next page)

There were no differences in the proportions of subjects reporting any or Grade 3 solicited local reactions between Dose 1 and Dose 2. Headache and shivering were reported more frequently by subjects after Dose 2 (28% and 21%, respectively) compared with Dose 1 (24% and 14%, respectively). Grade 3 solicited general adverse reactions (headache, shivering, myalgia, and fatigue) were reported more frequently by subjects after Dose 2 (2.3%, 3%, 4%, and 4%, respectively) compared with Dose 1 (1.4%, 1.4%, 2.3%, and 2.4%, respectively).

Unsolicited Adverse Events: Unsolicited adverse events that occurred within 30 days following each vaccination (Day 0 to 29) were recorded on a diary card by all subjects. In the 2 studies, unsolicited adverse events occurring within 30 days of vaccination were reported in 51% and 32% of subjects who received SHINGRIX (n = 14,645) or placebo (n = 14,660), respectively (Total Vaccinated Cohort). Unsolicited adverse events that occurred in ≥1% of recipients of SHINGRIX and at a rate at least 1.5-fold higher than placebo included chills (4% versus 0.2%), injection site pruritus (2.2% versus 0.2%), malaise (1.7% versus 0.3%), arthralgia (1.7% versus 1.2%), nausea (1.4% versus 0.5%), and dizziness (1.2% versus 0.8%).

Gout (including gouty arthritis) was reported by 0.18% (n = 27) versus 0.05% (n = 8) of subjects who received SHINGRIX or placebo, respectively, within 30 days of vaccination; available information is insufficient to determine a causal relationship with SHINGRIX.

Serious Adverse Events (SAEs): In the 2 studies, SAEs were reported at similar rates in subjects who received SHINGRIX (2.3%) or placebo (2.2%) from the first administered dose up to 30 days post-last vaccination. SAEs were reported for 10.1% of subjects who received SHINGRIX and for 10.4% of subjects who received placebo from the first administered dose up to 1 year post-last vaccination. One subject (<0.01%) reported lymphadenitis and 1 subject (<0.01%) reported fever greater than 39°C; there was a basis for a causal relationship with SHINGRIX.

Optic ischemic neuropathy was reported in 3 subjects (0.02%) who received SHINGRIX (all within 50 days after vaccination) and 0 subjects who received placebo; available information is insufficient to determine a causal relationship with SHINGRIX.

Deaths: From the first administered dose up to 30 days post-last vaccination, deaths were reported for 0.04% of subjects who received SHINGRIX and 0.05% of subjects who received placebo in the 2 studies. From the first administered dose up to 1 year post-last vaccination, deaths were reported for 0.8% of subjects who received SHINGRIX and for 0.9% of subjects who received placebo. Causes of death among subjects were consistent with those generally reported in adult and elderly populations.

Potential Immune-Mediated Diseases: In the 2 studies, new onset potential immune-mediated diseases (pIMDs) or exacerbation of existing pIMDs were reported for 0.6% of subjects who received SHINGRIX and 0.7% of subjects who received placebo from the first administered dose up to 1 year post-last vaccination. The most frequently reported pIMDs occurred with comparable frequencies in the group receiving SHINGRIX and the placebo group.

Dosing Schedule: In an open-label clinical study, 238 subjects 50 years and older received SHINGRIX as a 0- and 2-month or 0- and 6-month schedule. The safety profile of SHINGRIX was similar when administered according to a 0- and 2-month or 0- and 6-month schedule and was consistent with that observed in Studies 1 and 2.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of SHINGRIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

General Disorders and Administration Site Conditions

Decreased mobility of the injected arm which may persist for 1 or more weeks.

Immune System Disorders

Hypersensitivity reactions, including angioedema, rash, and urticaria.

Nervous System Disorders

Guillain-Barré syndrome.

Postmarketing Observational Study of the Risk of Guillain-Barré Syndrome following Vaccination with SHINGRIX

The association between vaccination with SHINGRIX and GBS was evaluated among Medicare beneficiaries aged 65 years or older. Using Medicare claims data, from October 2017 through February 2020, vaccinations with SHINGRIX among beneficiaries were identified through National Drug Codes, and potential cases of hospitalized GBS among recipients of SHINGRIX were identified through International Classification of Diseases codes.

The risk of GBS following vaccination with SHINGRIX was assessed in self-controlled case series analyses using a risk window of 1 to 42 days post-vaccination and a control window of 43 to 183 days post-vaccination. The primary analysis (claims-based, all doses) found an increased risk of GBS during the 42 days following vaccination with SHINGRIX, with an estimated 3 excess cases of GBS per million doses administered to adults aged 65 years or older. In secondary analyses, an increased risk of GBS was observed during the 42 days following the first dose of SHINGRIX, with an estimated 6 excess cases of GBS per million doses administered to adults aged 65 years or older, and no increased risk of GBS was observed following the second dose of SHINGRIX. These analyses of GBS diagnoses in claims data were supported by analyses of GBS cases confirmed by medical record review. While the results of this observational study suggest a causal association of GBS with SHINGRIX, available evidence is insufficient to establish a causal relationship.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The data are insufficient to establish if there is vaccine-associated risk with SHINGRIX in pregnant women *[see Use in Specific Populations (8.1) of full prescribing information]*.

8.2 Lactation

Risk Summary

It is not known whether SHINGRIX is excreted in human milk. Data are not available to assess the effects of SHINGRIX on the breastfed infant or on milk production/excretion *[see Use in Specific Populations (8.2) of full prescribing information]*.

8.5 Geriatric Use

Adults Aged 60 Years and Older

Of the total number of subjects who received at least 1 dose of SHINGRIX in Studies 1 and 2 (n = 14,645), 2,243 (15%) were aged 60 to 69 years, 6,837 (47%) were aged 70 to 79 years, and 1,921 (13%) were 80 years and older. There were no clinically meaningful differences in efficacy across the age groups *[see Clinical Studies (14.1, 14.2, 14.3) of full prescribing information]*.

The frequencies of solicited local and general adverse reactions in subjects aged 70 years and older were lower than in younger adults (aged 50 through 69 years). *[See Adverse Reactions (6.1).]*

17 PATIENT COUNSELING INFORMATION

- Inform patients of the potential benefits and risks of immunization with SHINGRIX and of the importance of completing the 2-dose immunization series according to the schedule.
- Inform patients about the potential for adverse reactions that have been temporally associated with administration of SHINGRIX.
- Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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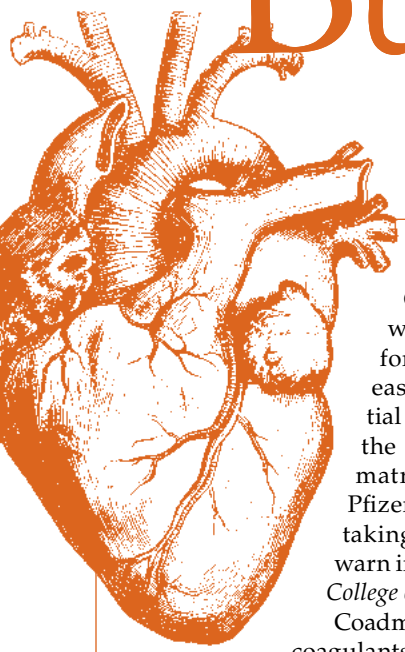


Experts flag potential risk with Paxlovid and cardiovascular drugs

Clinicians treating patients with COVID-19 who are at risk for progression to acute disease should be aware of potential drug–drug interactions when the oral antiviral treatment nirmatrelvir/ritonavir (Paxlovid—Pfizer) is administered to people taking common CV drugs, experts warn in a new *Journal of the American College of Cardiology* article.

Coadministration with certain anticoagulants and antiplatelet agents, for instance, can elevate bleeding risk, while hypotension can develop in patients who take Paxlovid and blood pressure drugs. Cushing's syndrome and adrenal suppression are possible after concomitant use of the antiviral with anti-inflammatories, according to the authors.

Heart transplant patients undergoing immunosuppressive therapy are also particularly vulnerable due to the toxic effects created by co-use of Paxlovid and cyclosporine, tacrolimus, or sirolimus.

Because of the long list of severe adverse effects that might develop due to interactions with CV medications—including certain lipid-lowering agents, anti-anginal drugs, heart failure therapeutics, and pulmonary hypertension treatments—flagged CV medications may need to be paused or, at the very least, have the dose dialed down.

In the event that a potentially interacting CV medication cannot be safely discontinued for a short time or the dose adjusted, experts recommend that providers avoid Paxlovid therapy altogether. ■

ISMP releases survey on pharmacists' support during a code

A recent survey from the Institute for Safe Medication Practices (ISMP) puts the pharmacist's role during code situations into focus.

Although they may be called on to assist with basic life support, defibrillation, or intubation, according to the survey, pharmacists may more often be relied upon to prepare medications, retrieve drugs and/or equipment from code carts or elsewhere, and consult on appropriate interventions and dosages.

Among 410 pharmacists who completed the ISMP poll, most had some level of experience responding to codes, with only 5% reporting none. Despite the high level of exposure, more than one-third of respondents expressed feeling ill-equipped to handle code situations.

More than one-half received instruction on the indications, preparation, and adult doses of medications often used during codes, and an even greater share were trained on where to find medications in the code cart.

However, very few had an opportunity to shadow another pharmacist during a code or to participate in a mock event. No required training at all was reported by 7% of all respondents. The survey responses also revealed a high level of worry among pharmacists about making medication errors during a code due not only to inexperience or inadequate training, but also due to lack of clear communication, chaos in a crowded and rushed environment, lack of patient information, and other issues.

In light of the poll results, ISMP offered recommendations for code preparation, including requiring pharmacy participation, conducting practice simulations, and clearly spelling out responsibilities. The organization also advised steps to follow during a code; for instance, double-checking doses as well as securing and replenishing supplies for the next episode after a code. ■

FDA releases draft guidance to spur development of CDI drugs

New guidance released by FDA provides advice for sponsors on developing drugs for treating *Clostridioides difficile* infection (CDI). The draft guidance discusses how to design trials and trial populations, efficacy and safety endpoints, nonclinical studies, and pharmacokinetic studies.

CDC described *C. difficile* as "threat-level urgent" in its 2019 Antimicrobial Threats Report and estimates that *C. difficile* causes the hospitalizations of 223,900 individuals per year and 12,800 annual deaths.

The guidance examines the development of CDI treatments consisting of small molecule drugs and biological products and how to reduce the recurrence of CDI, especially in at-risk patients.

Clinical trials should be randomized, double-blinded, and use an active control for both CDI treatment and curbing CDI recurrence, FDA's guidance document said.

To demonstrate efficacy, sponsors should supply evidence from 2 competent and well-controlled trials, with one trial demonstrating efficacy only for treatment and another trial for preventing CDI. Sponsors are advised to submit safety data from at least 300 individuals exposed to the proposed investigational drug treatment. Clinical programs for drugs developed only for preventing CDI may require a larger safety database.

Sponsors should discuss a suitable size of the premarket safety database with FDA during clinical development. For nonclinical studies, applicants should test the investigational drug in vitro and in animal models prior to submitting an investigational new drug application.

FDA also recommends an I.V. toxicology study in at least one mammalian species to identify possible risks, noting that CDI may increase oral drug absorption because of the disruption of the intestinal barrier. ■

Researchers continue to study effectiveness of ivermectin for COVID-19

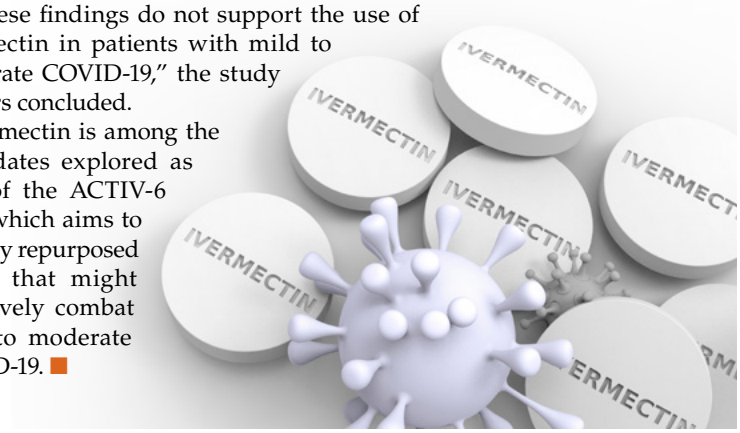
Researchers wanted to find out if ivermectin compared to placebo shortened symptom duration for adult patients in the United States with symptomatic mild to moderate COVID-19. According to results of the randomized clinical trial published in *JAMA* on October 21, 2022, the research team found that among outpatients with mild to moderate COVID-19, treatment with ivermectin compared with placebo did not significantly improve time to recovery.

The analysis included 1,591 U.S. adult outpatients age 30 years and older who had confirmed COVID-19 during the Delta and Omicron waves and presented with at least 2 symptoms of acute infection.

A total of 817 participants were randomly assigned to treatment with 400 mcg/kg of ivermectin while the remaining 774 participants received a placebo. The median time to recovery was 12 and 13 days, respectively, for the intervention and control groups. In addition to having no significant effect on symptom duration, ivermectin demonstrated no benefit over placebo for secondary endpoints, including hospital admission, mortality, or acute care visits.

"These findings do not support the use of ivermectin in patients with mild to moderate COVID-19," the study authors concluded.

Ivermectin is among the candidates explored as part of the ACTIV-6 trial, which aims to identify repurposed drugs that might effectively combat mild to moderate COVID-19. ■



One in ten older adults in the U.S. has dementia, study suggests

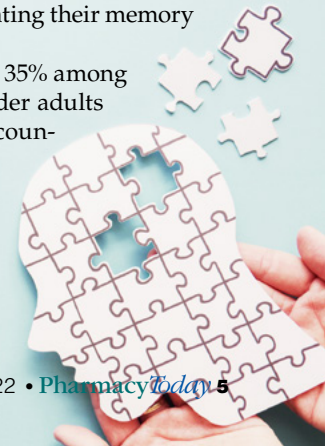
A new study published in *JAMA Neurology* estimated that in the United States, 1 in 10 adults over the age of 65 years has dementia and 1 in 5 has cognitive difficulties.

The study was based on information from the Health and Retirement Study, specifically test results from 2016–2017 comprising almost 3,500 study participants age 65 years and older. They underwent tests to gauge their memory, attention, and comprehension as well as their ability to live independently and how their faculties changed over the previous decade.

According to the findings, about 10% of U.S. adults aged 65 and older have dementia and 22% have mild cognitive impairment, indicating their memory and other functions are affected.

About 3% of people in their 60s had dementia, rising to 35% among people in their 90s. The dementia rate was higher for older adults identified as non-Hispanic Black compared with their counterparts.

The study found that 15% of older Black adults have dementia, compared with 11% of older white adults and 10% of older Hispanic adults. In addition, 13% of people with no high school diploma had dementia, compared with 9% among those who finished high school or attended college, according to the study. ■



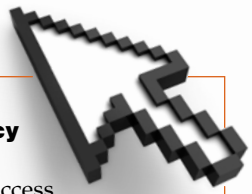
Over 1 million Americans with diabetes rationed insulin, says new report

A new report published in the *Annals of Internal Medicine* found that an estimated 1.3 million U.S. adults with diabetes rationed their insulin in the past year, representing 16.5% of those who use prescribed insulin.

The report found that people with diabetes rationed their insulin by delaying when they refill their prescription, skipping doses, or using a smaller dose. The report also indicated that rationing was more widespread among lower- and middle-income participants (15% and 20%, respectively) compared with higher income people (11%). Black participants were found to ration (23%) more frequently compared with white or Hispanic participants (16%).

Rationing was most frequent among uninsured individuals, with 29% saying they had rationed insulin. Among those with private insurance, 19% rationed the drug, citing high copays, along with 14% of Medicare recipients, and 12% of Medicaid recipients.

The report was based on data from an ongoing CDC health research project in which researchers were studying a nationally representative sample of 982 adults who use insulin to treat diabetes. Findings indicate the rationing is linked to the high price of insulin and "inadequate" insurance coverage. ■



New interactive map promotes access to pharmacy services

Dima M. Qato, PharmD, MPH, PhD, regards pharmacy access as a human rights issue. Qato, an associate professor at the School of Pharmacy at the University of Southern California (USC) and a senior fellow at the USC Leonard D. Schaeffer Center for Health Policy & Economics, developed an interactive, nationwide mapping tool that reveals the presence of "pharmacy deserts" around the country. The map identifies nearly 1 in 4 neighborhoods as being areas with pharmacy shortages.

"By collaborating, we have been able to attack the problem on a national scale using faster spatial computation and spatial analysis to better understand geographic contexts, like urban versus rural areas," said Robert Vos, PhD, in a news release. Vos is an associate professor of spatial sciences with the USC Spatial Sciences Institute who helped build the tool.

The map defines a pharmacy shortage area as one where the distance to a pharmacy is greater than 10 miles in a rural area, 2 miles in a suburban area, 1 mile in an urban area, and 0.5 miles in neighborhoods where its residents have low income and low vehicle ownership. Qato hopes the mapping tool will inform federal and state policy changes that enhance health equity.

"In terms of the equitable implementation of federal and state policies, it's important to ensure that local pharmacies are actually stocking essential medicines and offering essential services they are authorized to provide," Qato said. ■

CDC releases updated pain management guidelines

CDC's updated guideline on pain management represents a welcome improvement over earlier guidance, according to APhA. They commend the government for including pharmacists in the multidisciplinary plan.

The 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain—updated from the 2016 version—promotes tailored care for acute, subacute, and chronic pain through shared decision making between patients and their care teams.

"Pharmacists have an important role to play in pain management across the spectrum," a statement from APhA noted. They go on to say that the new guideline, which has a multimodal focus and also addresses health inequities in the provision of pain treatment, "will be helpful to pharmacists in delivering effective pain care."

While it appreciates CDC's effort to avoid unintended consequences stemming from the previous guideline by identifying inappropriate interpretations of use, APhA encourages the agency to pay attention to current laws, regulations, and policies that might interfere with clinicians' ability to work within the practice recommendations. ■

CDC: Antihistamines could be contributing to opioid overdoses

New CDC findings highlight the hidden dangers of antihistamines for those who have concomitant exposure to opioids.

Looking at about 92,000 overdose fatalities across the nation between 2019 and 2020, investigators found that diphenhydramine—the active ingredient in Benadryl and other antihistamines—were implicated in no less than 18% of the deaths studied.

The study authors suspect some opioid users may take antihistamines to enhance the effects of the narcotic, but they believe others may use them to alleviate allergies or to get relief from itching, nausea, poor sleep, and other adverse effects linked to allergies.

Regardless of the motivation, antihistamines can exacerbate opioid-induced respiratory depression (the most common cause of mortality during an overdose), deepening sedation to unsafe levels.

To worsen matters, naloxone by itself may not effectively reverse an overdose under these circumstances. ■

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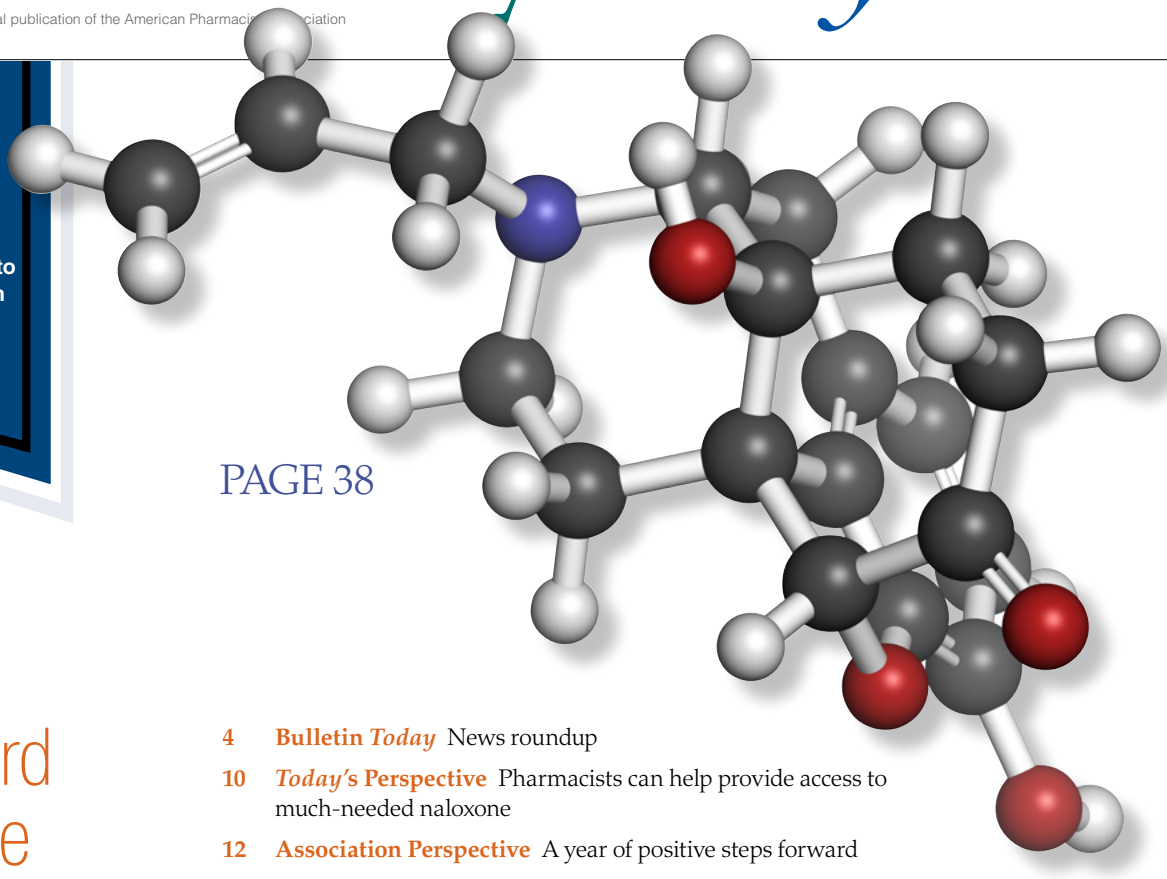

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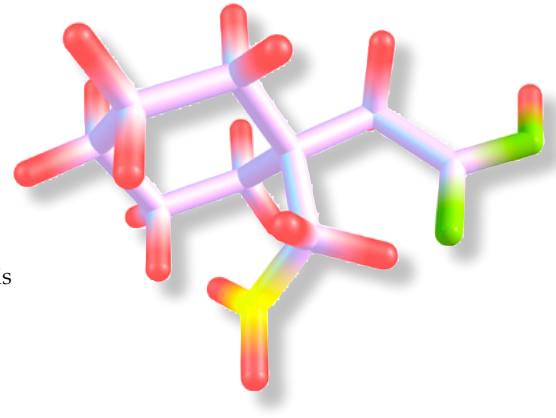

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Pharmacists can help provide access to much-needed naloxone

According to CDC, nearly 50,000 people died from an opioid-involved overdose in 2019, and this number jumped to about 100,000 deaths in 2020.

Why are opioid-related deaths on the rise? The answer involves many factors, including reduced access to medications for substance use disorder, an increase in drugs contaminated with fentanyl, and, notably, limited naloxone for the patients who need it most. It is estimated that bystanders are present in more than one in three overdoses involving opioids. These individuals can assist patients in need, and pharmacists can help ensure that naloxone is getting into the right hands.

This month's *Pharmacy Today* cover story provides the latest on community-based harm reduction programs and their role in decreasing opioid overdose deaths. These largely untapped resources are increasingly in the spotlight since a recent FDA exemption for distributing naloxone made it easier for harm reduction groups to get it. This is a vital piece of the puzzle.

Community-based program workers are on the front lines to reverse an opioid overdose with naloxone, and pharmacists can help increase access to naloxone in these programs. Stocking accessible and affordable forms of naloxone is essential. Naloxone nasal spray costs at least 3 times the price an I.M. injection. More solutions are on the horizon. Expect to see naloxone become more widely available, showing up in vending machines or OTC forms in future years.

In this issue of *Today*, you'll also get an update on OTC options for treating constipation, learn about the health benefits of beets, and get the latest on the controversial new drug for amyotrophic lateral sclerosis. You can also read about upcoming biosimilars for adalimumab (Humira–AbbVie Inc.) in 2023 and get recent guidance on non-COVID-19–related vaccine errors. Catch up on your CPE credits with this month's article on the role of pharmacists in increasing access to reproductive health care.

Keep in mind that naloxone alone will not solve the opioid crisis. According to Nabarun Dasgupta, MPH, PhD, an epidemiologist at the University of North Carolina at Chapel Hill, "We need prevention, we need treatment, we need all sorts of services, but when the overdose death rate is increasing at the pace that it has been, we have to have more emergency antidote available until there are no more overdose deaths." This is a lofty goal, but one that we as pharmacists can help achieve by educating patients and providers, working to decrease the stigma surrounding naloxone, and ensuring easy access to affordable forms of naloxone.

Have a great *Today!*

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

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†U.S. News & World Report, Pharmacy Times, 2022-2023.
‡IQVIA, ProVoice Survey: Latest 12 months rolling, ending Nov 2021.

A year of positive steps forward

What a year! As 2022 winds to a close, I'm filled with awe and gratitude for the amazing accomplishments of APhA and our members.

In spring of 2022, the Equitable Community Access to Pharmacist Services (ECAPS) Act, a groundbreaking piece of legislation, was introduced into the House of Representatives. The legislation, H.R. 7213, would allow Medicare patients to continue to receive treatment from pharmacists for pandemic-related health services and would permit pharmacists to respond to ongoing and future public health crises. Spearheaded by APhA in partnership with the Future of Pharmacy Care Coalition, this exciting bill may be introduced into the Senate very soon.

This is one example of the overarching theme of 2022: ensuring that pharmacy has a seat at the important policy tables. Not just a seat, but a voice that is heard, loud and clear. APhA worked hard to amplify the incredible impact that pharmacy had on the health and well-being of our nation across the entire spectrum of potential patient interventions.

We could do that because we heard you. We heard you through social media, we heard you through news reports, and we heard your personal stories through Pharmacy Workplace and Well-being Reporting (PWWR).

PWWR serves as a safe space to submit both positive and negative pharmacy workplace experiences in a confidential and anonymous manner. In September 2022, APhA and the National Alliance of State Pharmacy Associations released the third installment of trends and findings that revealed a breakdown in communication between pharmacy staffers and upper management, and an increase in harassment and abuse. This is a critical, complex issue, and in order to make real change and change policies we need evidence-based data and information. Through your documented stories submitted via PWWR, we now have that evidence-based data to enable us to fight for solid solutions and reliable remedies.

We know that pharmacists make a significant impact on patients' health, and now we have the quantifiable data to prove it. A featured article in the November/December 2022 issue of *JAPhA* showed pharmacists cared for more than 5.4 million COVID-19 hospitalized patients, administered more than 42 million tests for COVID-19, over 270 million COVID-19 vaccine doses, and provided more than 100,000 monoclonal antibody treatments for COVID-19. The study found that using conservative estimates, the pandemic interventions by pharmacists and members of the pharmacy team averted more than 1 million U.S. deaths, more than 8 million hospitalizations, and $450 billion in health care costs.

Armed with such strong stories and profound data, APhA is successfully amplifying your voice through numerous and frequent calls and formal and informal meetings with FTC, state boards, and companies. We're already seeing success in molding and implementing measures to create real reform for all pharmacists and pharmacy teams. I'm excited about all the state wins across the country. We've seen PBM reform, increased scope of practice, increased access to COVID-19 oral therapeutics, and more as APhA joins with our partners to increase access to care and expand reimbursement models for pharmacists, their teams, and their patients.

Thank you for all you've done this year and invite you to join us as we continue this good work in 2023! ■

ILISA BG BERNSTEIN
PharmD, JD, FAPhA
Interim Executive Vice President and CEO
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20810

NEW DRUGS

FUTIBATINIB
(Lytgobi—Taiho Oncology)

Drug class: Futibatinib is a kinase inhibitor.

Indication: Lytgobi is indicated for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements.

Recommended dosage and administration: The recommended dose is 20 mg orally (five 4-mg tablets) once daily until disease progression or unacceptable toxicity occurs. The tablets should be swallowed whole, with or without food.

Common adverse effects: The most common adverse effects are nail toxicity, musculoskeletal pain, constipation, diarrhea, fatigue, dry mouth, alopecia, stomatitis, abdominal pain, dry skin, arthralgia, dysgeusia, dry eye, nausea, decreased appetite, urinary tract infection, palmar-plantar erythrodysesthesia syndrome, and vomiting.

Warnings and precautions: Avoid coadministration with dual P-glycoprotein and strong CYP3A inhibitors and dual P-glycoprotein and strong CYP31 inducers. Lytgobi should not be used in patients who are breastfeeding.

Lytgobi can cause retinal pigment epithelial detachment. A comprehensive ophthalmological examination including optical coherence tomography should be performed prior to initiation of therapy, every 2 months for the first 6 months, every 3 months thereafter, and urgently at any time for visual symptoms. Increases in phosphate levels can cause hyperphosphatemia leading to soft tissue mineralization, calcinosis, nonuremic calciphylaxis, and vascular calcification.

Patients should be monitored for hyperphosphatemia and the dose of Lytgobi should be withheld, reduced, or permanently discontinued based on the duration and severity. Lytgobi can cause fetal harm. Patients of reproductive potential should be advised on this potential risk and to use effective contraception.

NEW DOSAGE FORM

FUROSEMIDE
(Furoscix—scPharmaceuticals Inc.)

Drug class: Furosemide is a loop diuretic.

Indication: Furoscix is indicated for the treatment of congestion due to fluid overload in adults with New York Heart Association (NYHA) Class II/III chronic heart failure.

Recommended dosage and administration: The single use, on-body infusor is preprogrammed to deliver 30 mg of Furoscix over the first hour then 12.5 mg per hour for the subsequent 4 hours.

Common adverse effects: The most common adverse effects are administration side and skin reactions, erythema, bruising, edema, and infusion site pain.

Warnings and precautions: Furoscix is contraindicated in patients with anuria, hypersensitivity to furosemide or medical adhesives, hepatic cirrhosis, or ascites.

Furoscix is not indicated for emergency situations or in patients with acute pulmonary edema. It is not for chronic use and should be replaced with oral diuretics as soon as practical.

Serum electrolytes, CO_2, BUN, creatinine, glucose, and uric acid should be monitored regularly. Avoid use with aminoglycoside antibiotics as the combination increases the potential of ototoxicity.

Avoid combination with ethacrynic acid due to risk of ototoxicity. When used with salicylates, there is risk of salicylate toxicity. When combined with cisplatin and nephrotoxic drugs, there is a risk of ototoxicity and nephrotoxicity. Use of Furoscix with lithium increases risk of lithium toxicity.

In patients taking adrenergic blocking drugs, there is risk of potentiation. There is risk of toxicity potentiation when Furoscix is used in combination with drugs that undergo renal tubular secretion.

NEW INDICATION

COBIMETINIB FUMARATE
(Cotellic—Genentech Inc.)

Drug class: Cobimetinib fumarate is a kinase inhibitor.

Amoxicillin supply constraints

On October 28, 2022, FDA listed a shortage for the oral powder dosage form of amoxicillin. Amoxicillin is one of the most commonly prescribed antibiotics, especially for pediatric patients, and is used to treat bacterial infections such as pneumonia and bronchitis. The reason for the supply interruption is thought to be due to a significant demand for the medication in the United States, Canada, and Europe. On top of the increased demand, the pandemic has put manufacturing constraints on some of the key manufacturers of the drug. Manufacturers of amoxicillin have acknowledged the shortage and are taking steps to meet demand, such as increasing worker shifts.

Amoxicillin is available in a variety of dosage forms and strengths. While patients may struggle to find the exact strength that they were prescribed, if a pharmacy has a different strength available then the pharmacist and provider can have a discussion to determine an appropriate regimen for the patient. Additionally, alternative antibiotics can be used if necessary. ■

Indication: Cotellic is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation in combination with vemurafenib or as a single agent for the treatment of adult patients with histiocytic neoplasms.

Recommended dosage and administration: The recommended dose is 60 mg orally once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity.

Common adverse effects: The most common adverse effects are diarrhea, photosensitivity reactions, nausea, pyrexia, acneiform dermatitis, infection, fatigue, edema, maculopapular rash, dry skin, pruritis, dyspepsia, dyspnea, vomiting, increased gamma-glutamyl transferase (GGT), increased creatine phosphokinase (CPK), hypophosphatemia, hyponatremia, hypokalemia, hypocalcemia, leukopenia, increased alanine transaminase (ALT), lymphopenia, increased aspartate aminotransferase (AST), and anemia.

Warnings and precautions: Do not breastfeed while taking Cotellic. Avoid concomitant administration with strong or moderate CYP3A inducers or inhibitors.

Patients taking Cotellic should be monitored for new malignancies prior to initiation of therapy, while on therapy, and for up to 6 months following the last dose. Major hemorrhagic events can occur so patients should be monitored for signs and symptoms of bleeding.

Evaluate left ventricular ejection fraction (LVEF) before treatment, after 1 month of treatment, then every 3 months thereafter during treatment with Cotellic as there is a risk for cardiomyopathy. Cotellic doses may need to be reduced, interrupted, or discontinued if severe dermatologic reactions occur. Ophthalmological evaluations should be performed at regular intervals and for any visual disturbances. Permanently discontinue Cotellic if retinal vein occlusion occurs.

Monitor liver laboratory tests during treatment and as clinically indicated. Monitor creatine phosphokinase periodically and as clinically indicated for signs and symptoms of rhabdomyolysis. Advise patients to avoid sun exposure. Advise patients of reproductive potential of the possible risk to a fetus and to use effective contraception.

RETEVMO

(Selpercatinib—Loxo Oncology Eli Lilly)

Drug class: Selpercatinib is a kinase inhibitor.

Indication: Retevmo is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with a RET gene fusion; adult and pediatric patients 12 years and older with advanced or metastatic medullary thyroid cancer with a RET mutation who require systemic therapy; adult and pediatric patients 12 years and older with advanced or metastatic medullary thyroid cancer with a RET mutation who require systemic therapy and are radioactive iodine–refractory; and adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment who have no satisfactory alternative treatment options.

Recommended dosage and administration: The recommended dosage in adults and pediatric patients 12 years or older is based on weight. If weight is < 50 kg, the recommended dosage is 120 mg orally twice daily. If weight is ≥ 50 kg, recommended dosage is 160 mg orally twice daily.

Common adverse effects: The most common adverse effects are edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, headache, decreased lymphocytes, increased ALT, increased AST, decreased sodium, and decreased calcium.

Warnings and precautions: Retevmo should not be used in patients who are breastfeeding. Monitor open growth plates in adolescent patients and consider interrupting or discontinuing treatment if abnormalities occur. Reduce the dose of Retevmo in patients with severe hepatic impairment. ALT and AST should be monitored prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Doses of Retevmo may need to be reduced, withheld, or discontinued based on severity of hepatotoxicity. Monitor for new or worsening pulmonary symptoms.

Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week of treatment and at least monthly thereafter and as clinically indicated. Monitor patients who are at significant risk of developing QTc prolongation. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage. If a hypersensitivity reaction occurs, withhold Retevmo and initiate corticosteroids. Closely monitor patients at risk of tumor lysis syndrome and treat as clinically indicated. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. Monitor thyroid function before treatment with Retevmo and periodically during treatment. Retevmo may cause fetal harm and patients of reproductive potential should be advised of the possible risk to a fetus and to use effective contraception. ■

Also in this issue
Relyvrio: a new oral treatment approved for ALS (page 24).

Movin' right along

Mary Warner

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), constipation is defined as having fewer than three bowel movements a week; stools that are hard, dry, or lumpy; stools that are difficult or painful to pass; or a feeling that not all stool has passed. It's important to note, however, that people have different bowel movement patterns, and "normal" can vary enormously among patients.

Constipation is common in male and female patients of all ages, although older adults (> 65 years old) are 5 times more likely to experience constipation than younger adults and women are more than 3 times more likely than men to be affected. Untreated constipation can lead to development of hemorrhoids or anal fissures, rectal prolapse, fecal impaction, or other complications, so it's important to address frequent constipation.

Constipation occurs when the colon absorbs too much water from waste, making the stool dry, hard, and difficult to pass. This can be caused by daily habits (inadequate fluid or fiber intake and lack of exercise) or medications (such as antiacids, antidepressants, ACE inhibitors, and calcium channel blockers). Pregnant women are especially prone to constipation because of hormonal changes and compression of the intestines by the growing fetus, which slows the passage of stool.

In some cases, constipation can be indicative of another medical problem. For example, opiate use can lead to chronic constipation and the opioid epidemic has led to an increase in patients seeking relief. In addition, diseases such as Parkinson's disease, multiple sclerosis, irritable bowel syndrome, and diverticulitis/diverticulosis can result in constipation, as can endocrine problems, colorectal cancer, and lazy bowel syndrome.

Treating constipation

The first line of treatment for constipation is to increase fluid and fiber intake and get more exercise. If those daily life adjustments don't work sufficiently, numerous other options are available on the OTC shelf of the pharmacy.

Bulk-forming laxatives such as psyllium seed, methylcellulose, and calcium polycarbophil absorb water to soften stool, increase bulk, and facilitate elimination. They're available as tablets or capsules; powders to be mixed with water or other liquids; and fiber chews, wafers, or gummies, and the safest, most natural treatment for constipation. Relief generally occurs within 12 to 24 hours, but may take up to 72 hours to work. There are few adverse effects, making them a good choice for patients with chronic constipation. However, patients with fluid restrictions should avoid using these laxatives, as should patients using digoxin or warfarin.

Emollient laxatives, or stool softeners, contain anionic surfactants (docusate sodium) that act in the small and large intestine to increase the wetting efficiency of intestinal fluid. They can take 2 to 3 days to generate relief and should only be used on a short-term basis. Although stool softeners can be taken for occasional constipation, they are more often used in combination with a stimulant laxative for opioid-induced constipation.

The first line of treatment for constipation is to increase fluid and fiber intake and get more exercise.

Saline laxatives, such as magnesium hydroxide, magnesium citrate, and magnesium sulfate, use nonabsorbable magnesium cations to create an osmotic gradient to pull water into the intestine. These laxatives can be quick-acting, providing relief in 30 minutes to an hour when taken orally. Adverse effects of saline laxatives may include abdominal cramping, nausea, vomiting, or dehydration.

Stimulant laxatives, including anthraquinones (senna), diphenylmethanes (biscodyl), and castor oil, stimulate bowel activity and increase secretion of fluids into the bowel. The time to onset of action for senna and bisacodyl is usually 6 to 10 hours after oral administration but may take up to 24 hours. Stimulant laxatives should be used sparingly, as impaired colon function can occur with chronic use.

Hyperosmotic laxatives contain glycerin or polyethylene glycol 3350 (PEG 3350) that draws water into the colon or rectum through osmosis to stimulate bowel movement. These laxatives are supplied as oral capsules or suppositories and can take effect within 30 minutes.

Combination laxatives often contain a stimulant and an emollient (e.g., senna with docusate sodium) or a stimulant and psyllium. Other available combination laxatives include those with psyllium, bisacodyl, or docusate combined with glycerin.

Common OTC laxatives

Type	Generic name	Brand names	Possible adverse effects
Bulk-forming	Psyllium seed	Metamucil, Konsyl	Bloating, gas, cramping, or increased constipation if not taken with enough water
	Methylcellulose	Citrucel	
	Calcium polycarbophil	FiberCon	
Emollient	Docusate sodium	Colace, Surfak	Stomach pain, cramping, diarrhea
Saline	Magnesium hydroxide	Milk of Magnesia	Abdominal cramping, nausea, vomiting, or dehydration; electrolyte imbalance with prolonged use
	Magnesium citrate	Magnesium citrate	
	Magnesium sulfate	Epsom salts	
Hyperosmotic	PEG3350, glycerin	Miralax, Fleet	Bloating, abdominal discomfort, cramping, and flatulence
Stimulant	Senna, biscodyl, castor oil	Dulcolax, Senokot, Ex-Lax, Correctol	Belching, cramping, diarrhea, or nausea; urine discoloration with senna derivatives
Combination products	Senna plus docusate sodium	Senokot-S	Based on stimulant used

Special populations

Children and pregnant/lactating patients should not take laxatives without first trying nonpharmacologic treatement (diet, exercise) and consulting with a pharmacist or physician.

Constipation in children should first be treated by increasing fluid and dietary fiber intake. If further treatment is needed, glycerin suppositories, docusate sodium, and magnesium hydroxide are approved for children 2 to 6 years old. For children 6 to 12 years old, glycerin or bisacodyl suppositories or bulk-forming laxatives, docusate or magnesium hydroxide should be used first, reserving oral stimulate laxatives for use only when other treatments fail.

If those daily life adjustments don't work sufficiently, numerous other options are available on the OTC shelf of the pharmacy.

Constipation affects up to one-third of patients throughout pregnancy and the postpartum period, primarily caused by compression of the colon by the growing uterus, increasing progesterone levels, low fluid and fiber intake, and the constipating effects of iron and calcium in prenatal supplements.

When increasing fiber and fluids aren't effective at relieving constipation, bulk-forming laxatives should be considered first, along with docusate for those with primarily dry, hard stools. When needed, short-term use of senna or bisacodyl is considered a low-risk approach in pregnancy, as is PEG 3350, though less information is available on the use of PEG 3350 during pregnancy.

Some laxatives, including castor oil, mineral oil, and saline laxatives, should be used cautiously or avoided for pregnant patients. Specific risks have been recognized with use in pregnancy, so such products should be used only very cautiously or perhaps avoided altogether in this setting.

Castor oil has been associated with uterine contraction and rupture, mineral oil may impair absorption of fat-soluble vitamins, and high doses or long-term use of saline laxatives may cause electrolyte imbalances.

Laxatives also may be used postpartum to reestablish normal bowel function. Senna, bisacodyl, PEG 3350, and docusate have a low risk of adverse effects when used by breastfeeding patients. However, castor oil and mineral oil should be avoided during breastfeeding.

What to tell your patients

To avoid constipation, patients should include plenty of fiber and water in their diet and avoid caffeine-containing drinks that can lead to dehydration.

Advise patients to exercise regularly and not to wait if they feel the urge to move their bowels. Patients should understand that excessive laxative use can lead to acute-onset episodes of diarrhea and vomiting, fluid and electrolyte losses (especially hypokalemia), and dehydration.

If patients see blood in the stool, are losing weight unintentionally, have severe abdominal pain, or constipation has lasted more than 3 weeks, they should see a physician to rule out medication- or disease-related causes.

For more information on laxatives, including treatment for special populations and medication interactions, see chapter 15 of APhA's *Handbook of Nonprescription Drugs*, available in print or online on pharmacylibrary.com. ■

Dancing to the beet

Mickie Cathers

Beetroot juice is well-known in the sports community as a postworkout must and performance enhancer. This unassuming vegetable is becoming a popular supplement and superfood promoted as enhancing mental alertness, focus, lower blood pressure, and exercise stamina. But is the hype all it's made out to be?

Background

Beets are a root vegetable like carrots, turnips, and parsnips, and they're available in a variety of shapes and colors. Beets' rich colors come from betalains, which are nitrogen-containing pigments that are considered to be free radical scavengers. Beets provide high quantities of essential vitamins and minerals, including folate, potassium, iron, magnesium, manganese, sodium, zinc, copper, and selenium. The leafy top of the beet provides more nutritional value than the bulbous root, but it is the root—and its juice—that are used, and studied, more often.

Is there a benefit?

Most research on beetroot juice focuses on its cardiovascular benefits, including lowered blood pressure and increased exercise stamina. The benefits are tied to its naturally high concentration of nitrate, which is rapidly absorbed in the gut and converted to nitric oxide in the blood. Ingestion of beetroot juice results in significant increases in plasma levels of nitric oxide, which has a vasodilatory effect, increasing oxygen and nutrient delivery, within 3 hours.

One study showed a significant reduction of systolic and diastolic blood pressure in hypertensive patients who drank 250 mL of beet juice daily over the course of 4 weeks. Kapil and colleagues conducted a randomized, phase 2, double-blind, placebo-controlled study published in the February 2015 issue of *Hypertension*. The authors randomly assigned 68 patients with hypertension to receive either 250 mL beetroot juice or 250 mL of nitrate-free beetroot juice daily for 4 weeks. Results showed reduction in blood pressure for the nitrate group as well as improvement in endothelial function and reduction in arterial stiffness with no change observed in the placebo group.

Beetroot juice has also been shown to improve muscle efficiency and endurance, promoting muscle recovery, relieving fatigue, and reducing inflammation and muscle damage, making it a favorite supplement among athletes. One study showed that trained cyclists drinking 2 cups of beet juice daily shaved approximately 12 seconds off their 10-kilometer time trials while also benefitting from reduced maximum oxygen output.

In addition to improving exercise endurance, beetroot juice has been demonstrated to improve and modulate regional cerebral blood flow in the prefrontal cortex during cognitive tasks. Knowing that beet roots' high concentration of nitrates (also found in celery, cabbage, and spinach) help to expand blood vessels, Petrie and colleagues designed a randomized double-blind placebo-controlled study to examine how that increased blood flow and oxygen uptake affected the aging brain in conjunction with exercise.

Over a 6-week period, researchers studied 26 hypertensive, sedentary older adults with a mean age of 65.4 years randomly assigned to moderate intensity exercise and beetroot juice or placebo. Participants received 560 mg of nitrate or a placebo containing 1.1 mg nitrate. Pre- and postintervention MRI scans revealed improved neuroplasticity in the primary motor cortex, somatosensory cortex, and midline supplementary motor regions in the patients who exercised and consumed beetroot juice. The study was published in the September 2017 issue of *The Journals of Gerontology: Series A*.

Dosage

Beetroot is available as a concentrated juice or powder and as gummies and chewables. Then there is always the vegetable itself, which can be eaten cooked, added raw to smoothies, or juiced. While there is no official suggested dose, study doses ranged from 100 mL to the more common dose of 250 mL/day.

What to tell your patients

Beets are a healthy addition to any diet. The juice is considered safe, even as a concentrate, in supplements, smoothies, and as a food additive. Advise patients that, though perhaps surprising, it is harmless to have pink or red urine or stools from drinking beetroot juice.

Few adverse effects have been reported, but caution those with already low blood pressure to monitor carefully when drinking beet juice regularly. Patients subject to calcium oxalate kidney stones should avoid beetroot juice as beets are high in oxalate content. ■

The next era of severe asthma management has emerged

Rise above the complexity

The ***FIRST & ONLY*** biologic approved for severe asthma without phenotypic or biomarker limitations[1]

INDICATION

TEZSPIRE is indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

TEZSPIRE is not indicated for the relief of acute bronchospasm or status asthmaticus.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to tezepelumab-ekko or excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, rash and allergic conjunctivitis) can occur following administration of TEZSPIRE. These reactions can occur within hours of administration, but in some instances have a delayed onset (ie, days). In the event of a hypersensitivity reaction, initiate appropriate treatment as clinically indicated and then consider the benefits and risks for the individual patient to determine whether to continue or discontinue treatment with TEZSPIRE.

Please see additional Important Safety Information throughout and accompanying brief summary of Prescribing Information.

TEZSPIRE™
(tezepelumab-ekko) Subcutaneous Injection 210 mg

Aim higher.

THE *FIRST & ONLY* BIOLOGIC APPROVED FOR SEVERE ASTHMA WITHOUT PHENOTYPIC OR BIOMARKER LIMITATIONS[1]

Blocks

TSLP at the top and reduces downstream inflammation[1-5]

Up to

71% exacerbation reduction in a broad, all-comer patient population[1,2*]

NAVIGATOR demonstrated a 56% reduction in exacerbations.[1,4*]

79% reduction in exacerbations requiring ED visits,[†] urgent care visits, or hospitalizations[1,4,5‡]

The analyses of this endpoint were not multiplicity protected. Results are descriptive only.

THINK TEZSPIRE FOR YOUR NEXT PATIENT WITH SEVERE ASTHMA. GO TO: www.tezspirehcp.com

*PATHWAY AAER: TEZSPIRE + SOC 0.20 (n=137) vs placebo + SOC 0.72 (n=138); RR: 0.29 (95% CI: 0.16-0.51); NAVIGATOR AAER: TEZSPIRE + SOC 0.93 (n=528) vs placebo + SOC 2.10 (n=531); RR: 0.44 (95% CI: 0.37-0.53).[1]

†An emergency room visit was defined as evaluation and treatment for <24 hours in an ER or urgent care center that required systemic corticosteroids.[6]

‡NAVIGATOR AAER: TEZSPIRE + SOC 0.06 vs placebo + SOC 0.28; RR: 0.21 (95% CI: 0.12-0.37).

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Acute Asthma Symptoms or Deteriorating Disease

TEZSPIRE should not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm, or status asthmaticus.

Abrupt Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with TEZSPIRE. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

It is unknown if TEZSPIRE will influence a patient's response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with TEZSPIRE. If patients become infected while receiving TEZSPIRE and do not respond to anti-helminth treatment, discontinue TEZSPIRE until infection resolves.

Live Attenuated Vaccines

The concomitant use of TEZSPIRE and live attenuated vaccines has not been evaluated. The use of live attenuated vaccines should be avoided in patients receiving TEZSPIRE.

TEZSPIRE is an add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. TEZSPIRE is not indicated for the relief of acute bronchospasm or status asthmaticus.

Study Design

PATHWAY and NAVIGATOR: 52-week, phase-2, dose-ranging (PATHWAY) or phase-3 (NAVIGATOR), randomized, double-blind, placebo-controlled, multicenter studies of patients 18-75 (PATHWAY) or 12-80 (NAVIGATOR) years of age with uncontrolled severe asthma despite treatment with medium- to high-dose ICS plus LABA with or without other controllers, including OCS for ≥6 months (PATHWAY), or medium- to high-dose ICS for ≥12 months plus ≥1 additional controller with or without OCS for ≥3 months (NAVIGATOR). At baseline, patients had an ACQ-6 score ≥1.5, and a history of ≥2 exacerbations defined as worsening of asthma requiring systemic corticosteroids or a temporary doubling (PATHWAY) or increase (NAVIGATOR) of maintenance OCS for ≥3 days, an ED visit requiring systemic corticosteroids, resulting in hospitalization (NAVIGATOR only) or 1 exacerbation resulting in hospitalization (PATHWAY only) in the prior 12 months. Patients were randomized to receive tezepelumab 70 mg SC Q4W (n=138), TEZSPIRE 210 mg SC Q4W (n=137), tezepelumab 280 mg SC Q2W (n=137), or placebo (n=138) in PATHWAY and to receive TEZSPIRE 210 mg SC Q4W (n=528) or placebo (n=531) in NAVIGATOR. All patients remained on stable doses of the background asthma treatments they were receiving at study entry (SOC). The primary endpoint for both trials was AAER versus placebo at week 52. Exacerbations were defined as they were for study entry. Key secondary endpoints in NAVIGATOR included changes from baseline in pre-bronchodilator FEV_1, ACQ-6, and AQLQ(S)+12 scores at week 52.[1,2,4,6,7]

AAER=annualized asthma exacerbation rate; AQLQ(S)+12=Asthma Quality of Life Questionnaire (standardized) for patients 12 years of age or older; ACQ-6=Asthma Control Questionnaire-6; ED=emergency department; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroid; LABA=long-acting β_2-adrenergic agonist; OCS=oral corticosteroids; RR=rate ratio; SC=subcutaneously; SOC=standard of care; TSLP=thymic stromal lymphopoietin.

References: 1. TEZSPIRE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. **2.** Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med.* 2017;377(10):936-946. **3.** Corren J, Parnes JR, Wang L, et al. Appendix to: Tezepelumab in adults with uncontrolled asthma. *N Engl J Med.* 2017;377(10):936-946. **4.** Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med.* 2021;384(19):1800-1809. **5.** Menzies-Gow A, Corren J, Bourdin A, et al. Appendix to: Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384(19):1800-1809. **6.** Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma [study protocol]. *N Engl J Med.* 2021;384(19):1800-1809. **7.** Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma [study protocol]. *N Engl J Med.* 2017;377(10):936-946.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥3%) are pharyngitis, arthralgia, and back pain.

USE IN SPECIFIC POPULATIONS

There are no available data on TEZSPIRE use in pregnant women to evaluate for any drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Placental transfer of monoclonal antibodies such as tezepelumab-ekko is greater during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

Please see additional Important Safety Information throughout and accompanying brief summary of Prescribing Information.

AMGEN® AstraZeneca

TEZSPIRE™ (tezepelumab-ekko) Subcutaneous Injection 210 mg

Aim higher.

This product information is intended for US Healthcare Professionals only.

TEZSPIRE™ (tezepelumab-ekko) subcutaneous injection 210 mg

Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

TEZSPIRE is indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

Limitations of Use:

TEZSPIRE is not indicated for the relief of acute bronchospasm or status asthmaticus.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of TEZSPIRE is 210 mg administered subcutaneously once every 4 weeks.

Missed Dose Information

If a dose is missed, administer the dose as soon as possible. Thereafter, the patient can continue (resume) dosing on the usual day of administration. If the next dose is already due, then administer as planned.

Preparation and Administration Instructions

TEZSPIRE is intended for administration by a healthcare provider.

Each vial and pre-filled syringe contains a single dose of TEZSPIRE.

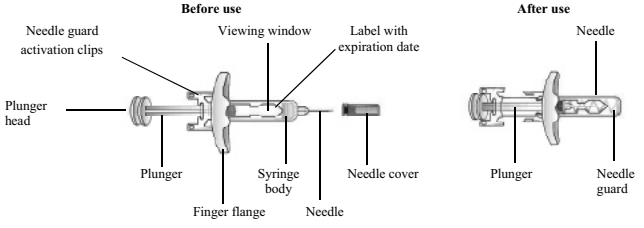
- Prior to administration, remove TEZSPIRE from the refrigerator and allow it to reach room temperature. This generally takes 60 minutes. Do not expose to heat and do not shake. Do not use if the security seal on the carton has been broken. Do not put back in the refrigerator once TEZSPIRE has reached room temperature. After removal from the refrigerator, TEZSPIRE must be used within 30 days or discarded *[see How Supplied/ Storage and Handling (16) in the full Prescribing Information].*
- Visually inspect TEZSPIRE for particulate matter and discoloration prior to administration. TEZSPIRE is a clear to opalescent, colorless to light yellow solution. Do not use TEZSPIRE if liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter. Do not use if the vial or pre-filled syringe has been dropped or damaged or if the expiration date has passed.
- Inject TEZSPIRE 210 mg (contents of one vial or one pre-filled syringe as described below) subcutaneously into the upper arm, thigh, or abdomen, except for the 2 inches (5 cm) around the navel. TEZSPIRE should not be injected into areas where the skin is tender, bruised, erythematous, or hardened. It is recommended to rotate the injection site with each injection.

Administration Instructions for Single-Dose Pre-filled Syringe

Refer to Figure 1 to identify the pre-filled syringe components for use in the administration steps.

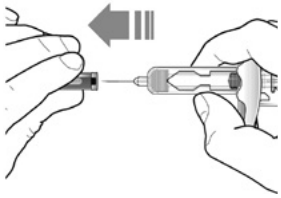
Do not remove the needle cover until Step 2 of these instructions when you are ready to inject TEZSPIRE. Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

Figure 1 TEZSPIRE Pre-filled Syringe Components

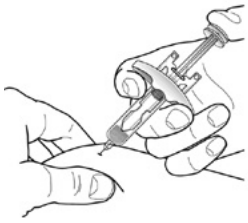


1. Grasp the syringe body to remove the pre-filled syringe from its tray. Do not grab the pre-filled syringe by the plunger.

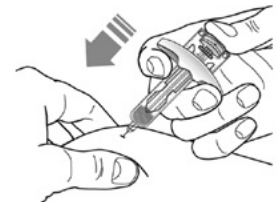
   The pre-filled syringe may contain small air bubbles; this is normal. Do not expel the air bubbles prior to administration.

2. 

   Do not remove the needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover. You may see a drop of liquid at the end of the needle. This is normal.

3. 

   Gently pinch the skin and administer subcutaneously at approximately 45º angle into the recommended injection site (i.e., upper arm, thigh, or abdomen).

4. 

   Inject all of the medication by pushing in the plunger all the way until the plunger head is completely between the needle guard activation clips. This is necessary to activate the needle guard.

5. 

   After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. Do not re-cap the pre-filled syringe.

6. Discard the used syringe into a sharps container.

CONTRAINDICATIONS

TEZSPIRE is contraindicated in patients who have known hypersensitivity to tezepelumab-ekko or any of its excipients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., rash and allergic conjunctivitis) can occur following administration of TEZSPIRE *[see Contraindications (4) and Adverse Reactions (6) in the full Prescribing Information]*. These reactions can occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, consider the benefits and risks for the individual patient to determine whether to continue or discontinue treatment with TEZSPIRE.

Acute Asthma Symptoms or Deteriorating Disease

TEZSPIRE should not be used to treat acute asthma symptoms or acute exacerbations. Do not use TEZSPIRE to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with TEZSPIRE.

Risk Associated with Abrupt Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with TEZSPIRE. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Thymic stromal lymphopoietin (TSLP) may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if TEZSPIRE will influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with TEZSPIRE. If patients become infected while receiving treatment with TEZSPIRE and do not respond to anti-helminth treatment, discontinue treatment with TEZSPIRE until infection resolves.

Live Attenuated Vaccines

The concomitant use of TEZSPIRE and live attenuated vaccines has not been evaluated. The use of live attenuated vaccines should be avoided in patients receiving TEZSPIRE.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TEZSPIRE was based on the pooled safety population from PATHWAY and NAVIGATOR, which consists of 665 adult and pediatric patients 12 years of age and older with severe asthma who received at least one dose of TEZSPIRE 210 mg subcutaneously once every 4 weeks. The two placebo-controlled clinical trials were of 52 weeks duration. In addition, a similar safety profile was seen in a trial that enrolled 150 adult patients with severe asthma who required treatment with daily oral corticosteroids *[see Clinical Studies (14)]*.

Adverse reactions that occurred at an incidence greater than or equal to 3% and more common than in the placebo group from the pooled safety population (PATHWAY and NAVIGATOR) are shown in Table 1.

Table 1 Adverse Reactions with TEZSPIRE with Incidence Greater than or Equal to 3% and More Common than Placebo in Patients with Severe Asthma in the Pooled Safety Population (PATHWAY and NAVIGATOR)

Adverse Reaction	TEZSPIRE N=665 %	Placebo N=669 %
Pharyngitis*	4	3
Arthralgia	4	3
Back pain	4	3

* Pharyngitis (including Pharyngitis, Pharyngitis bacterial, Pharyngitis streptococcal and Viral pharyngitis)

Specific Adverse Reaction

Injection Site Reactions

In the pooled safety population, injection site reactions (e.g., injection site erythema, injection site swelling, injection site pain) occurred at a rate of 3.3% in patients treated with TEZSPIRE compared with 2.7% in patients treated with placebo.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies described below with the incidence of antibodies in other studies or to other tezepelumab products may be misleading.

In NAVIGATOR and an additional trial, anti-drug antibodies (ADA) were detected at any time in 29 (5%) out of 601 patients who received TEZSPIRE at the recommended dosing regimen during the 48 to 52-week study period. Of these 29 patients, 11 patients (2% of patients treated with TEZSPIRE) developed treatment-emergent antibodies and 1 patient (<1% of patients treated with TEZSPIRE) developed neutralizing antibodies. ADA titers were generally low and often transient. No evidence of ADA impact on pharmacokinetics, pharmacodynamics, efficacy, or safety was observed.

DRUG INTERACTIONS

No formal drug interaction studies have been performed with TEZSPIRE.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on TEZSPIRE use in pregnant women to evaluate for any drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Placental transfer of monoclonal antibodies such as tezepelumab-ekko is greater during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In an enhanced pre- and post-natal development (ePPND) study conducted in cynomolgus monkeys, placental transport of tezepelumab-ekko was observed but there was no evidence of fetal harm following intravenous administration of tezepelumab-ekko throughout pregnancy at doses that produced maternal exposures up to 168 times the exposure at the maximum recommended human dose (MRHD) of 210 mg administered subcutaneously *[see Data]*.

The estimated background risk of major birth defects and miscarriages for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk:

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In the ePPND study, pregnant cynomolgus monkeys received tezepelumab-ekko from GD20 to GD22 (dependent on pregnancy determination), at the beginning of organogenesis, and once every 7 days until the end of gestation at doses that produced exposures up to 168 times that achieved with the MRHD (on an AUC basis with maternal intravenous doses up to 300 mg/kg/week). There were no tezepelumab-ekko related adverse effects on maternal health, pregnancy outcome, embryo-fetal development, or neonatal growth and development up to 6.5 months of age. Tezepelumab-ekko crossed the placenta in cynomolgus monkeys and tezepelumab-ekko serum concentrations were 0.5- to 6.7-fold higher in infants relative to maternal animals.

Lactation

Risk Summary

There is no information regarding the presence of tezepelumab-ekko in human milk, its effects on the breastfed infant, or its effects on milk production. However, tezepelumab-ekko is a human monoclonal antibody immunoglobulin G2λ (IgG2λ), and immunoglobulin G (IgG) is present in human milk in small amounts. Tezepelumab-ekko was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TEZSPIRE and any potential adverse effects on the breastfed infant from TEZSPIRE or from the underlying maternal condition.

Data

Animal Data

In a prenatal and postnatal development study in cynomolgus monkeys, tezepelumab-ekko concentrations in milk were up to 0.5% of the maternal serum concentrations after intravenous administration of tezepelumab-ekko up to 300 mg/kg/week (168 times the exposures based on AUC achieved at MRHD). The concentration of tezepelumab-ekko in animal milk does not necessarily predict the concentration of drug in human milk.

Pediatric Use

The safety and effectiveness of TEZSPIRE for the add-on maintenance treatment of severe asthma have been established in pediatric patients aged 12 years and older *[see Adverse Reactions (6.1) and Clinical Studies (14) in the full Prescribing Information]*. Use of TEZSPIRE for this indication is supported by evidence from a total of 82 pediatric patients aged 12 to 17 years enrolled in NAVIGATOR and received treatment with TEZSPIRE 210 mg subcutaneously every 4 weeks (n=41) or placebo (n=41). Compared with placebo, improvements in annualized asthma exacerbation (rate ratio 0.70; 95% CI 0.34, 1.46) and FEV_1 (LS mean change versus placebo 0.17 L; 95% CI -0.01, 0.35) were observed in pediatric patients treated with TEZSPIRE. The safety profile and pharmacodynamic responses in pediatric patients were generally similar to the overall study population.

The safety and effectiveness in patients younger than 12 years of age have not been established.

Geriatric Use

Of the 665 patients with asthma treated with TEZSPIRE in clinical trials (PATHWAY and NAVIGATOR) for severe asthma, 119 patients (18%) were 65 years or older. No overall differences in safety or effectiveness of TEZSPIRE have been observed between patients 65 years of age and older and younger patients *[see Adverse Reactions (6.1) and Clinical Studies (14) in the full Prescribing Information]*.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., rash and allergic conjunctivitis) can occur following administration of TEZSPIRE *[see Contraindications (4) and Adverse Reactions (6) in the full Prescribing Information]*. These reactions can occur within hours of administration, but in some instances have a delayed onset (i.e., days). Instruct patients to contact their healthcare provider if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that TEZSPIRE does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with TEZSPIRE *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Risk Associated with Abrupt Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a healthcare provider. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Administration of Vaccines

Instruct patients to inform the healthcare provider that they are taking TEZSPIRE prior to a potential vaccination *[see Warnings and Precautions (5.5) in the full Prescribing Information]*.

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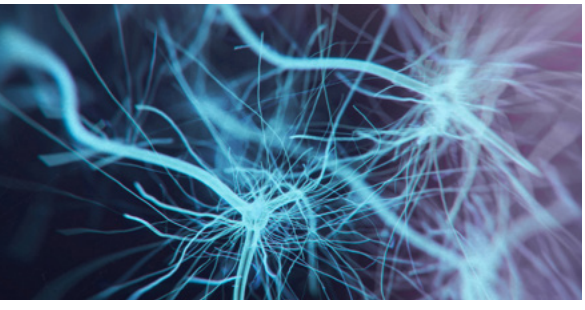
12/2021 US-59908 12/21

Approval of new ALS drug comes with controversy

Lauren Howell, PharmD

After 5 years with no breakthroughs for patients living with amyotrophic lateral sclerosis (ALS), FDA has approved a new oral treatment called Relyvrio from Amylyx Pharmaceuticals. This new medication is approved for the treatment of ALS in adults; however, the decision was made despite controversy surrounding the safety and efficacy of the drug.

Independent advisors to FDA voted and recommended against FDA approval in March 2022 due to an insufficient amount of evidence showing effectiveness from a single clinical trial with only 137 patients.



In September 2022, the group revoted and recommended that the drug be approved after additional analyses were submitted by Amylyx. Although uncertainties remain, the lack of effective treatment options for such a severe disease swayed the opinions of the panel.

Amylyx officials have vowed to remove Relyvrio from the market if a larger, 600-participant study fails to show effectiveness once completed late next year or in early 2024.

Recommended dosage and how it works

Relyvrio is packaged as a powder that needs to be mixed with 8 oz of room temperature water and stirred vigorously prior to administration. The recommended dosage is 1 packet (3 g sodium phenylbutyrate and 1 g taurursodiol) administered orally or via feeding tube daily for the first 3 weeks of therapy. After this initiation period, the dose should be increased to 1 packet twice daily.

Relyvrio is a combination of sodium phenylbutyrate and taurursodiol. The mechanism by which Relyvrio works as treatment for ALS is unknown. Sodium phenylbutyrate is used to treat individuals with urea cycle disorders and works by enhancing a pathway that removes nitrogen through the kidneys. It is hypothesized that it may also have an effect on misfolded proteins, which could explain the impact on progression of ALS. Taurursodiol is a bile acid that may interfere with apoptosis. It is speculated that the combination of these mechanisms could explain Relyvrio's effectiveness.

> The mechanism by which Relyvrio works as treatment for ALS is unknown.

Drug interactions

Relyvrio should not be taken with bile acid sequestering agents as this may interfere with the absorption of the taurursodiol component of the medication. Additionally, use of strong inhibitors of the bile salt export pump should be avoided. If concomitant use is medically necessary, serum transaminases and bilirubin should be monitored.

Aluminum-based antacids may interfere with the absorption of taurursodiol and should be avoided if other acid-lowering agents are available. The use of probenecid with Relyvrio should be avoided. Phenylbutyrate is a pan-histone deacetylase (HDAC) inhibitor and use of other HDAC inhibitors should not be used concomitantly with Relyvrio. Avoid use of Relyvrio with inhibitors of OATP1B3, as Relyvrio has been identified as a substrate of OATP1B3 during in vitro studies.

Clinical trial highlights

The clinical trial used to demonstrate the efficacy of Relyvrio was a 24-week, multicenter, randomized, double-blinded, placebo-controlled, parallel group study of 137 adult participants with ALS. The participants were randomized to either receive Relyvrio or placebo for 24 weeks. The primary endpoint was a comparison of the rate of reduction in the ALSFRS-R total scores from baseline to week 24.

Study investigators found a statistically significant difference in the rate of reduction in the ALSFRS-R total score from baseline to week 24 in patients treated with Relyvrio compared to patients treated with placebo.

Adverse effects and contraindications

There are currently no contraindications for treatment with Relyvrio. The most common adverse reactions are diarrhea, abdominal pain, nausea, and upper respiratory tract infection.

In patients with enterohepatic circulation disorders, pancreatic disorders, intestinal disorders, or another disorder that interferes with bile acid circulation, consulting with a specialist should be considered. These conditions may lead to decreased absorption of Relyvrio. These patients should be monitored for new or worsening diarrhea.

Additionally, Relyvrio has a high sodium content and sodium levels should be monitored in patients sensitive to salt intake.

Patient counseling

Patients should be advised on how to mix Relyvrio packets with water prior to administration. The dose must be taken within an hour after mixing.

Any unused Relyvrio should be discarded after one hour. Relyvrio should be taken before a snack or meal. ■

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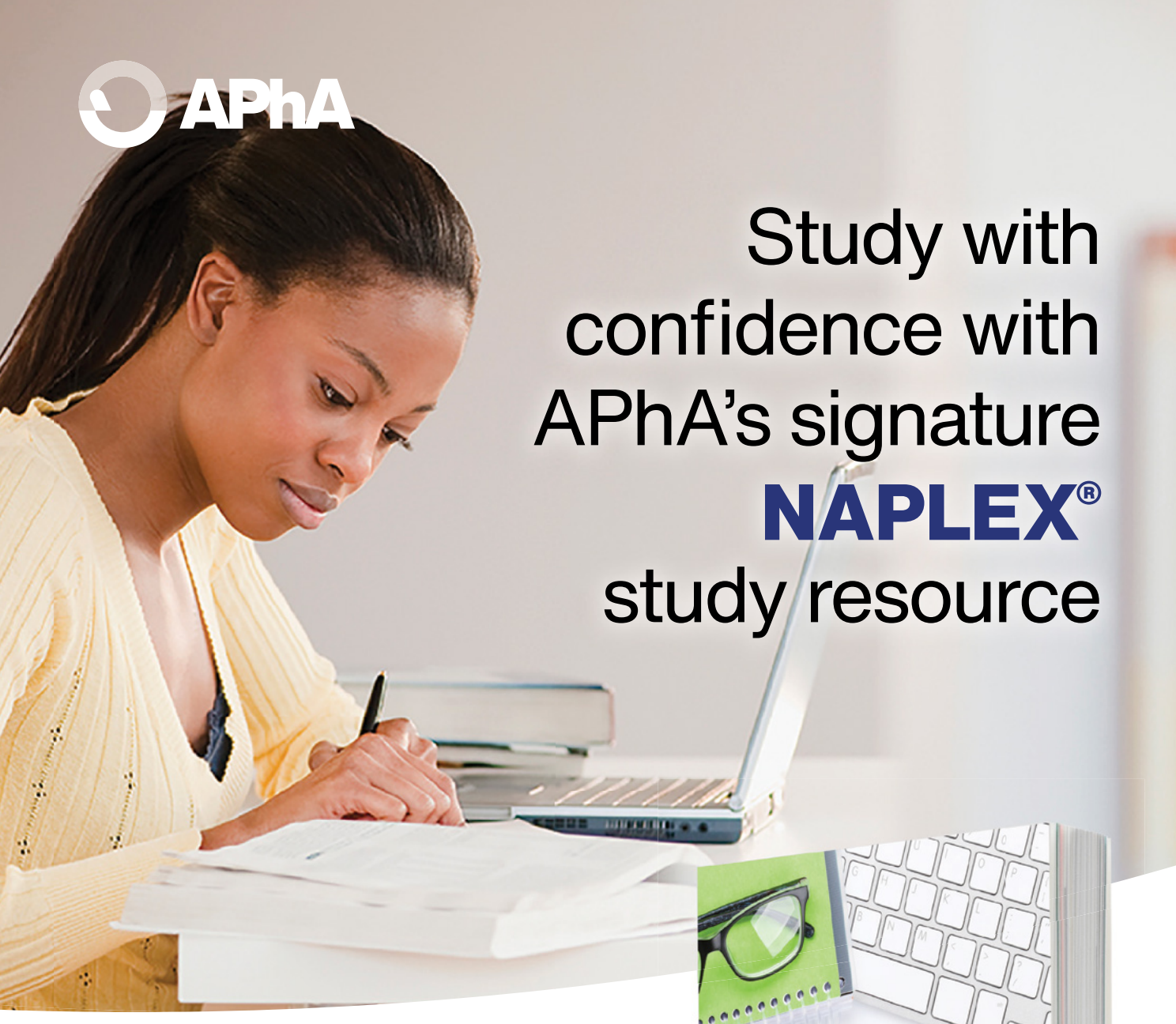

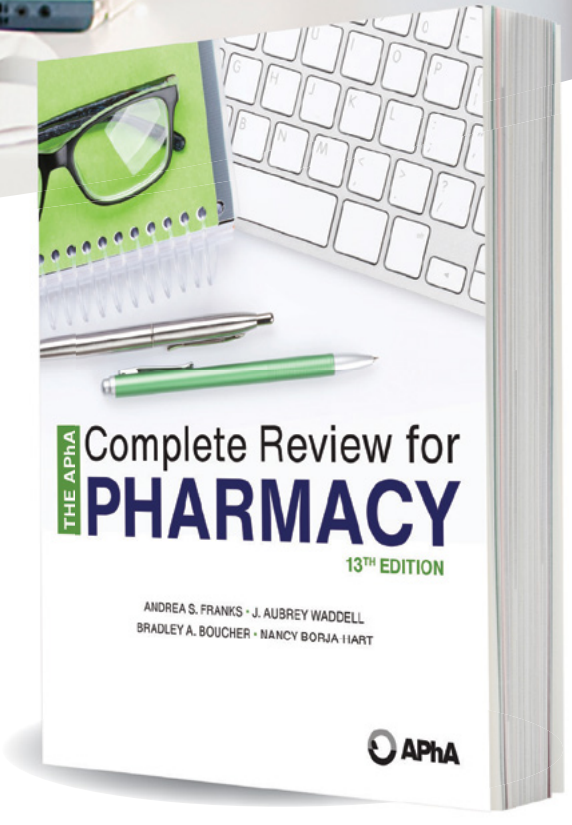

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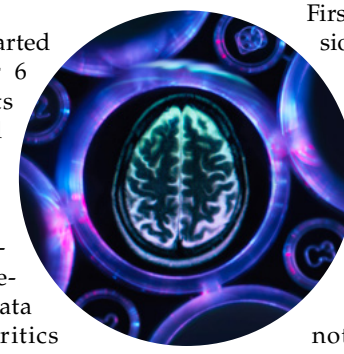
Eisai to seek FDA approval for lecanemab, one of dozens of drugs in the Alzheimer pipeline

Sonya Collins

This fall, biotech Biogen and pharmaceutical company Eisai released topline data on their new antiamyloid monoclonal antibody lecanemab. In the confirmatory phase 3 Clarity AD study, a double-blind, placebo-controlled clinical trial that included 1,795 participants with mild cognitive impairment and early Alzheimer disease (AD), the drug slowed cognitive decline by 27% over 18 months compared to placebo.

This drug may represent a second chance for Biogen after the failure of its aducanumab (Aduhelm–Biogen) hit the market last year. Both drugs are antiamyloid monoclonal antibodies, which seem to be where the field's focus currently lies in its efforts to change the course of the disease at an earlier stage.

"I think we are going to see a lot happening in the monoclonal antibodies space," said Kristin Zimmerman, PharmD, associate professor in the department of pharmacotherapy and outcomes science at Virginia Commonwealth University School of Pharmacy. "When it comes to early, prodromal disease, it's mostly biologics—that is, monoclonal antibodies—in the pipeline. So, pharmacists will need to be oriented toward those."



"Pharmacy has a role to play in potentially assisting in the screening and med review process."

Lecanemab and other monoclonal antibodies for Alzheimer disease

Like aducanumab, lecanemab is a monoclonal antibody that targets amyloid beta. Patients receive it by I.V. infusion.

In the clinical trial, the drug slowed cognitive decline, based on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) scale, which was the study's primary endpoint. The drug also reduced amyloid levels in the brain as measured by PET scan, the study's secondary endpoint. The drug started to show effects after 6 months and patients continued to respond to it at 18 months.

While some groups responded, such as Alzheimer's Association in an official statement, to the initial data with enthusiasm, critics argue that the effect on cognitive decline was too small to be meaningful.

"There's some controversy over using the CDR-SB as the primary endpoint. Cognitive assessments like the Alzheimer's Disease Assessment Scale for Cognition are considered the gold standard," Zimmerman said.

"So some people weren't swayed by the use of this scale and the degree of change in the scale. There's not a lot of agreement on what would be clinically significant change."

Along with the release of its topline data, Eisai announced that it will publish its findings in a peer-reviewed journal and file for traditional FDA approval by the end of March 2023. This regulatory distinction may help ensure the drug earns the Medicare coverage that its predecessor aducanumab did not.

Also in clinical trials is Eli Lilly's donanemab, another amyloid-targeted monoclonal antibody. Researchers published results of a positive phase 2 trial in the *New England Journal of Medicine* last year. Biologics that target tau are currently in the works as well.

I.V. drugs come with access challenges

Pharmacists should be aware of the barriers that come with monoclonal antibody therapies for AD and the role pharmacists might play in helping mitigate them.

First, a shortage of I.V. infusion centers may make it difficult for patients to access these drugs.

"Some drugmakers are looking at subcutaneous formulations, which would help enhance accessibility," Zimmerman said.

Next, Zimmerman notes, the health care workforce is not well-trained to screen patients for mild cognitive impairment and mild dementia, the stages for which these new drugs would be approved. Patients will also need biomarker testing to be eligible for the drugs and ongoing MRI monitoring.

"I can't emphasize these barriers enough," she said. "Pharmacy has a role to play in potentially assisting in the screening and med review process."

Small molecules hold lion's share of drug pipeline

While I.V.-infused monoclonal antibodies seem to garner more attention, small molecule oral medications occupy a much larger proportion of the Alzheimer's drug development pipeline from phase 1 to phase 3 clinical trials, according to a recent review in *Alzheimer's & Dementia: Translational Research & Clinical Interventions.*

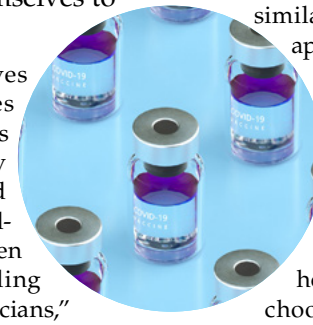
Many of these drugs, however, are repurposed drugs, such as metformin and levetiracetam, which pharmacists already know well. Unlike biologics for AD, the focus of many small molecules in development is later stage dementia. ■

Ten Humira biosimilars headed to market in 2023

Sonya Collins

At least 7 biosimilars for adalimumab (Humira–AbbVie, Inc.) are expected to hit the market in 2023. Pharmacists may find themselves managing patients on these new prescription drugs, encouraging physicians to switch their patients, or motivating patients themselves to accept these new options.

"Pharmacists play an extremely valuable role in biosimilars—in communications about these drugs with both physicians and patients," said Ryan Haumschild, PharmD, director of pharmaceutical services at Emory University Hospital Midtown in Atlanta, GA. "Pharmacy needs to come up with standardized language to use around all biosimilars, not just Humira."



Ten individual biosimilars

Amgen's Amjevita (adalimumab-atto), which earned FDA approval in 2016, is expected to enter the market in January 2023. By the following July, up to 9 other biosimilars may join it.

While Humira has indications that span rheumatology, dermatology, gastroenterology, and ophthalmology, not all of its biosimilars will be indicated for all the same conditions.

The 10 biosimilars also differ from one another in their interchangeability designations. So far, only Cyltezo (adalimumab-adbm) has earned the designation. Hadlima (adalimumab-bwwd) is expected to have the designation after its launch. Applications for 2 others are currently under review.

Regardless of interchangeability, in general, patients should notice little to no difference between reference drugs and their biosimilar counterparts.

"We can rely on the data we've seen on other biosimilars to feel confident they will have appropriate disease control," Haumschild said. "For the most part, patients make the transition between agents pretty seamlessly."

As for other differences among the 10 biosimilars, there are low- and high-concentration options as well as citrate-free and citrate formulations.

"It's important for pharmacists to familiarize themselves with the differences when these biosimilars reach the market so they can be more informed when they are counseling patients and when they are recommending these therapies to physicians," said Haumschild.

Counseling patients, educating prescribers

Patients who have their chronic conditions well controlled on Humira may be hesitant to switch to a biosimilar. Pharmacists might be in a position to recommend this switch to the patient or prescriber. Or, in some cases, the switch may be triggered automatically when payers will no longer cover the reference drug. In this case, the patient might learn for the first time that their prescription has changed when they pick it up at the pharmacy.

> Pharmacists may need to counsel patients or educate prescribers on biosimilars and their relationship to the reference drug.

On the other hand, prescribers may write prescriptions with the footnote "Dispense as written" or "Brand medically necessary." Sometimes this is because the patient has expressed concerns about switching and the provider doesn't want to force the patient.

In any of these cases, pharmacists may need to counsel patients or educate prescribers on biosimilars and their relationship to the reference drug.

"We've seen time and again that switching does not cause any significant increase in immunogenicity or any exaggeration of disease," Haumschild said. "We can explain the similarities, the similar efficacy, and the highly similar product profile that was approved by the FDA."

When applicable, pharmacists might also point out to patients or prescribers that the switch to a biosimilar will save the patient money. This may not always be the case; however, as sometimes PBMs choose to cover the reference drug exclusively.

"Anytime we recognize financial toxicity, we should feel comfortable reaching out to the provider if it will benefit the patient," Haumschild said.

Why biosimilars?

Overall, biosimilars deliver very "similar" results to the reference drugs. Besides potential cost-savings, biosimilars bring patients more options, which always yields advantages. More options can open up additional patient assistance programs. It can also offer alternatives in the face of shortages.

These are all talking points pharmacists can emphasize in conversations with patients and prescribers.

"When we are able to engage the patient, we can decrease their fear of starting the medication and help ensure better uptake and compliance, which will hopefully lead to better outcomes," said Haumschild. ■

APhA offers a pharmacist's guide to patient's frequently asked questions about biologics and biosimilars. Visit apha.us/BiosimilarsFAQ for more information.

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What additional medications might be best for patients taking metformin?

Johanna Taylor Katroscik, PharmD

Two recently published articles in the *New England Journal of Medicine* looked at the comparative efficacy of different medications for the treatment of type 2 diabetes.

Researchers hoped to learn more about what drug(s) might be the best addition for patients who are already taking metformin. They examined the difference in efficacy of the addition of insulin glargine, liraglutide, sitagliptin, and glimepiride when added to a metformin regimen, and found that patients who received insulin glargine or liraglutide had lower HbA1C levels than patients who received glimepiride or sitagliptin.

The patients who received insulin glargine or liraglutide were also less likely to have HbA1C levels greater than 7% than patients who received glimepiride or sitagliptin. For secondary outcomes, there were no significant differences between treatment groups.

Unfortunately, the trial did not include sodium-glucose cotransporter-2 (SGLT-2) inhibitors, one of the current pillars of guideline-directed therapy.

Trial design and overview

Researchers were looking at a primary outcome of the amount time it would take patients to reach an HbA1C level of greater than 7% while on a dual therapy regimen. The secondary outcome was the amount of time it would take patients to reach an HbA1C level of greater than 7.5% while on dual therapy.

Other outcomes were published in a companion article. In the companion article, researchers wanted to know if there was a difference in incidence of microvascular or cardiovascular outcomes such as hypertension, dyslipidemia, albuminuria, and reduced eGFR.

The trial—The Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) Study—was a randomized, multicenter, parallel group, comparative efficacy trial that enrolled 5,047 participants and followed them for a mean of 5 years. Key inclusion criteria were that patients must have had a diagnosis of type 2 diabetes for less than 10 years and had to have been diagnosed with diabetes when they were 30 years or older (20 years or older for Native Americans).

Additionally, patients were required to have HbA1C levels between 6.8% and 8.5%, taking a minimum daily dose of 1,000 mg of metformin when the trial started, and willing to self-administer daily subcutaneous injections.

All patients who received an additional glucose-lowering therapy with metformin experienced reduced HbA1C levels.

Exclusion criteria were numerous and included patients who had been taking metformin for more than 10 years prior to randomization; current or previous use of other blood-glucose–lowering medications; patients who had a major cardiovascular event within the previous year prior to randomization; previous organ transplant, liver failure, reduced kidney function; and more.

Potential impact on practice

The study left out a key treatment option for patients who have been diagnosed with diabetes: SGLT-2 inhibitors. The reason for this exclusion from the trial was that at the time the study was initiated, SGLT-2 inhibitors had not yet gained FDA approval.

SGLT-2 inhibitors are one of the key medication recommendations in the 2022 Standards of Medical Care in Diabetes published by the American Diabetes Association. This raises an issue when trying to utilize the data from this study because it is not a true comparison of all potential therapies.

Additionally, this study had extensive exclusion criteria, and other studies have been done since that do show a benefit for certain patients with some of the conditions excluded in this trial, particularly patients with cardiovascular and/or renal issues.

While this study was not able to assess all medications or drug classes, it did show that all patients who received an additional glucose-lowering therapy with metformin experienced reduced HbA1C levels.

It also showed that patients who received insulin glargine or liraglutide were able to achieve and maintain lower HbA1C levels when compared with patients who were on glimepiride or sitagliptin.

Although the study did not necessarily show pharmacists anything they might not already know, it does provide pharmacists more data to justify certain clinical decisions. ■

Help patients seeking weight loss to control cravings with CONTRAVE®[1,2]

Not an actual patient.

Indication

CONTRAVE is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (eg, hypertension, type 2 diabetes mellitus, or dyslipidemia)

Limitations of Use

The effect of CONTRAVE on cardiovascular morbidity and mortality has not been established. The safety and effectiveness of CONTRAVE in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Suicidality and Antidepressant Drugs

CONTRAVE® is not approved for use in the treatment of major depressive disorder or other psychiatric disorders. CONTRAVE contains bupropion, the same active ingredient as some other antidepressant medications (including, but not limited to, WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, and APLENZIN). Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older. In patients of all ages who are started on CONTRAVE, monitor closely for worsening, and for the emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. CONTRAVE is not approved for use in pediatric patients.

When it comes to treating obesity, one size does NOT fit all[3]

CONTRAVE is clinically proven to help patients lose weight and keep it off by targeting the parts of the brain that regulate hunger and cravings*[1,2]

Consider CONTRAVE for your patients seeking weight loss who struggle with emotional eating[3]

Scan the QR code to learn more about how CONTRAVE can help your patients lose weight and keep it off.

*The exact neurochemical effects of CONTRAVE leading to weight loss are not fully understood.

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8 mg/90 mg • Extended-Release Tablets

Control starts now.

IMPORTANT SAFETY INFORMATION (cont'd)

Contraindications

CONTRAVE is contraindicated in: uncontrolled hypertension; seizure disorder or a history of seizures; use of other bupropion-containing products; bulimia or anorexia nervosa, which increase the risk for seizure; chronic opioid or opiate agonist (eg, methadone) or partial agonist (eg, buprenorphine) use, or acute opiate withdrawal; patients undergoing an abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs; use during/within 14 days following treatment with monoamine oxidase inhibitors (MAOIs), as there is an increased risk of hypertensive reactions when CONTRAVE is used concomitantly with MAOIs, including reversible MAOIs such as linezolid or intravenous methylene blue; known allergy to any component of CONTRAVE, as anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported

WARNINGS AND PRECAUTIONS

Suicidal Behavior and Ideation

All patients being treated with antidepressants for any indication should be monitored and observed for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of suicidality, anxiety, agitation, irritability, unusual changes in behavior, and other symptoms, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for CONTRAVE should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Please see Important Safety Information throughout this advertisement, and the adjacent pages for the Brief Summary of Full Prescribing Information for CONTRAVE.

IMPORTANT SAFETY INFORMATION (cont'd)

Neuropsychiatric Adverse Events and Suicide Risk in Smoking Cessation Treatment

CONTRAVE is not approved for smoking cessation. Serious neuropsychiatric adverse events have been reported in patients taking bupropion for smoking cessation. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide.

Some patients who stopped smoking may have been experiencing symptoms of nicotine withdrawal, including depressed mood. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these adverse events occurred in patients taking bupropion who continued to smoke.

Neuropsychiatric adverse events occurred in patients without and with pre-existing psychiatric disease; some patients experienced worsening of their psychiatric illnesses. Observe patients for the occurrence of neuropsychiatric adverse events. Advise patients and caregivers that the patient should stop taking CONTRAVE and contact a healthcare provider immediately if agitation, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior.

Seizures

Bupropion, a component of CONTRAVE, can cause seizures. The risk of seizure is dose-related. Discontinue treatment and do not restart CONTRAVE in patients who experience a seizure. Use caution when prescribing CONTRAVE to patients with an elevated risk of seizure, including: history of head trauma or prior seizure, severe stroke, arteriovenous malformation, central nervous system tumor or infection, or metabolic disorders (eg, hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia); excessive use of alcohol or sedatives, addiction to cocaine or stimulants, or withdrawal from sedatives; patients with diabetes treated with insulin and/or oral diabetic medications (sulfonylureas and meglitinides) that may cause hypoglycemia; concomitant administration of medications that may lower the seizure threshold, including other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic steroids.

Clinical experience with bupropion suggests that the risk of seizure may be minimized by adhering to the recommended dosing recommendations, in particular: the total daily dose of CONTRAVE does not exceed 360 mg of the bupropion component (ie, four tablets per day); the daily dose is administered in divided doses (twice daily); the dose is escalated gradually; no more than two tablets are taken at one time; coadministration of CONTRAVE with high-fat meals is avoided; if a dose is missed, a patient should wait until the next scheduled dose to resume the regular dosing schedule.

Patients Receiving Opioid Analgesics

Vulnerability to Opioid Overdose: CONTRAVE should not be administered to patients receiving chronic opioids, due to the naltrexone component, which is an opioid receptor antagonist. If chronic opiate therapy is required, CONTRAVE treatment should be stopped. In patients requiring intermittent opiate treatment, CONTRAVE therapy should be temporarily discontinued and lower doses of opioids may be needed. Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after CONTRAVE treatment is discontinued. An attempt by a patient to overcome any naltrexone opioid blockade by administering large amounts of exogenous opioids is especially dangerous and may lead to a fatal overdose or life-threatening opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opioid blockade.

Precipitated Opioid Withdrawal: An opioid-free interval of a minimum of 7 to 10 days is recommended for patients previously dependent on short-acting opioids, and those patients transitioning from buprenorphine or methadone may need as long as two weeks. Patients should be made aware of the risks associated with precipitated withdrawal and encouraged to give an accurate account of last opioid use.

Increase in Blood Pressure (BP) and Heart Rate (HR)

CONTRAVE can cause an increase in systolic BP, diastolic BP, and/or resting HR. These events were observed in both patients with and without evidence of preexisting hypertension. In clinical practice with other bupropion-containing products, hypertension, in some cases severe and requiring acute treatment, has been reported. Blood pressure and pulse should be measured prior to starting therapy with CONTRAVE and should be monitored at regular intervals consistent with usual clinical practice, particularly among patients with controlled hypertension prior to treatment.

Allergic Reactions

Anaphylactoid/anaphylactic reactions and symptoms suggestive of delayed hypersensitivity have been reported with bupropion, as well as rare spontaneous reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock. Instruct patients to discontinue CONTRAVE and consult a healthcare provider if they develop an allergic or anaphylactoid/anaphylactic reaction (eg, skin rash, pruritus, hives, chest pain, edema, or shortness of breath) during treatment.

Please see Important Safety Information throughout this advertisement, and the adjacent pages for the Brief Summary of Full Prescribing Information for CONTRAVE.

IMPORTANT SAFETY INFORMATION (cont'd)

Hepatotoxicity

Cases of hepatitis, clinically significant liver dysfunction, and transient asymptomatic hepatic transaminase elevations have been observed with naltrexone exposure. Warn patients of the risk of hepatic injury and advise them to seek medical attention if they experience symptoms of acute hepatitis. Use of CONTRAVE should be discontinued in the event of symptoms and/or signs of acute hepatitis.

Activation of Mania

Bupropion, a component of CONTRAVE, is a drug used for the treatment of depression. Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating CONTRAVE, screen patients for history of bipolar disorder and the presence of risk factors for bipolar disorder (eg, family history of bipolar disorder, suicide, or depression). CONTRAVE is not approved for use in treating bipolar depression.

Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs, including bupropion, may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Hypoglycemia with Use of Antidiabetic Medications

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (eg, sulfonylureas). Measurement of blood glucose levels prior to starting CONTRAVE and during CONTRAVE treatment is recommended in patients with type 2 diabetes. Decreases in medication doses for antidiabetic medications that are non-glucose-dependent should be considered to mitigate the risk of hypoglycemia.

Adverse Reactions

Most common adverse reactions (≥5%) include: nausea (32.5%), constipation (19.2%), headache (17.6%), vomiting (10.7%), dizziness (9.9%), insomnia (9.2%), dry mouth (8.1%), and diarrhea (7.1%).

Drug Interactions

Use caution and consider dose reduction of drugs metabolized by CYP2D6 when using with CONTRAVE. Avoid concomitant use with MAOIs and CYP2B6 inducers. Reduce CONTRAVE dose when taken with CYP2B6 inhibitors. Dose CONTRAVE with caution when used with drugs that lower seizure threshold. Use caution and monitor for CNS toxicity when using CONTRAVE concomitantly with dopaminergic drugs (levodopa and amantadine). CONTRAVE can cause false positive urine test results for amphetamines.

Please see the adjacent pages for the Brief Summary of Full Prescribing Information for CONTRAVE.

References: 1. CONTRAVE (naltrexone HCl and bupropion HCl) [prescribing information]. Brentwood, TN: Currax Pharmaceuticals LLC; 2021. **2.** Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. *Int J Obes (Lond).* 2015;39(8):1188-1196. doi:10.1038/ijo.2015.59. **3.** Acosta A, Camilleri M, Dayyeh BA, et al. Selection of antiobesity medications based on phenotypes enhances weight loss: a pragmatic trial in an obesity clinic. *Obesity (Silver Spring).* 2021;29(4):662-671. doi:10.1002/oby.23120.

Currax pharmaceuticals LLC

Contrave®
(naltrexone HCl/bupropion HCl)
8 mg/90 mg • Extended-Release Tablets

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete product information, please see the full Prescribing Information, including Medication Guide, available at www.CONTRAVEHCP.com.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

SUICIDALITY AND ANTIDEPRESSANT DRUGS

CONTRAVE® is not approved for use in the treatment of major depressive disorder or other psychiatric disorders. CONTRAVE contains bupropion, the same active ingredient as some antidepressant medications (including, but not limited to, WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, and APLENZIN). Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older. In patients of all ages who are started on CONTRAVE, monitor closely for worsening, and for the emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. CONTRAVE is not approved for use in pediatric patients *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

CONTRAVE is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Limitations of Use:

- The effect of CONTRAVE on cardiovascular morbidity and mortality has not been established.
- The safety and effectiveness of CONTRAVE in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.

4 CONTRAINDICATIONS

CONTRAVE is contraindicated in

- Uncontrolled hypertension *[see Warnings and Precautions (5.5)]*
- Seizure disorder or a history of seizures *[see Warnings and Precautions (5.3)]*
- Use of other bupropion-containing products (including, but not limited to, WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, APLENZIN and ZYBAN)
- Bulimia or anorexia nervosa, which increase the risk for seizure *[see Warnings and Precautions (5.3)]*
- Chronic opioid or opiate agonist (e.g., methadone) or partial agonists (e.g., buprenorphine) use, or acute opiate withdrawal *[see Warnings and Precautions (5.4) and Drug Interactions (7.2)]*
- Patients undergoing an abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs *[see Warnings and Precautions (5.3) and Drug Interactions (7.7)]*
- Concomitant administration of monoamine oxidase inhibitors (MAOI). At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with CONTRAVE. There is an increased risk of hypertensive reactions when CONTRAVE is used concomitantly with MAOIs. Starting CONTRAVE in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is also contraindicated *[see Dosage and Administration (2.4) in the full Prescribing Information, Drug Interactions (7.1)]*
- Known allergy to bupropion, naltrexone or any other component of CONTRAVE.

Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion *[see Warnings and Precautions (5.6)]*

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Behavior and Ideation

CONTRAVE contains bupropion, a dopamine and norepinephrine re-uptake inhibitor that is similar to some drugs used for the treatment of depression; therefore, the following precautions pertaining to these products should be considered when treating patients with CONTRAVE.

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

In placebo-controlled clinical trials with CONTRAVE for the treatment of obesity in adult patients, no suicides or suicide attempts were reported in studies up to 56 weeks duration with CONTRAVE (equivalent to bupropion doses of 360 mg/day). In these same studies, suicidal ideation was reported by 3 (0.20%) of 1,515 patients treated with placebo compared with 1 (0.03%) of 3,239 treated with CONTRAVE.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (selective serotonin re-uptake inhibitors [SSRIs] and others) show that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term clinical trials did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24; there was a reduction with antidepressants compared with placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials of antidepressant drugs in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of nine antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of two months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in *Table 2*.

Table 2. Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Subjects

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18 to 24	5 additional cases
	Decreases Compared to Placebo
25 to 64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the antidepressant pediatric trials. There were suicides in the adult antidepressant trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. This warning applies to CONTRAVE because one of its components, bupropion, is a member of an antidepressant class.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of anxiety, agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for CONTRAVE should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

5.2 Neuropsychiatric Adverse Events and Suicide Risk in Smoking Cessation Treatment

CONTRAVE is not approved for smoking cessation treatment, but serious neuropsychiatric adverse events have been reported in patients taking bupropion for smoking cessation. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide *[see Warnings and Precautions (5.1)]*. Some patients who stopped smoking may have been experiencing symptoms of nicotine withdrawal, including depressed mood. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these adverse events occurred in patients taking bupropion who continued to smoke.

Neuropsychiatric adverse events occurred in patients without and with pre-existing psychiatric disease; some patients experienced worsening of their psychiatric illnesses. Observe patients for the occurrence of neuropsychiatric adverse events. Advise patients and caregivers that the patient should stop taking CONTRAVE and contact a healthcare provider immediately if agitation, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of bupropion was reported. However, the symptoms persisted in some cases, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

Depression, suicide, attempted suicide and suicidal ideation have been reported in the postmarketing experience with naltrexone used in the treatment of opioid dependence. No causal relationship has been demonstrated.

5.3 Seizures

Bupropion, a component of CONTRAVE, can cause seizures. The risk of seizure is dose-related. The incidence of seizure in patients receiving CONTRAVE in clinical trials was approximately 0.1% vs 0% on placebo. CONTRAVE should be discontinued and not restarted in patients who experience a seizure while being treated with CONTRAVE.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with CONTRAVE. CONTRAVE is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or

bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs. Caution should be used when prescribing CONTRAVE to patients with predisposing factors that may increase the risk of seizure including:

- history of head trauma or prior seizure, severe stroke, arteriovenous malformation, central nervous system tumor or infection, or metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia)
- excessive use of alcohol or sedatives, addiction to cocaine or stimulants, or withdrawal from sedatives
- patients with diabetes treated with insulin and/or oral diabetic medications (sulfonylureas and meglitinides) that may cause hypoglycemia
- concomitant administration of medications that may lower the seizure threshold, including other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, systemic steroids

Recommendations for Reducing the Risk of Seizure:
Clinical experience with bupropion suggests that the risk of seizure may be minimized by adhering to the recommended dosing recommendations *[see Dosage and Administration (2) in the full Prescribing Information]*, in particular:

- the total daily dose of CONTRAVE does not exceed 360 mg of the bupropion component (i.e., four tablets per day)
- the daily dose is administered in divided doses (twice daily)
- the dose is escalated gradually
- no more than two tablets are taken at one time
- coadministration of CONTRAVE with high-fat meals is avoided *[see Dosage and Administration (2.1) in the full Prescribing Information and Clinical Pharmacology (12.3) in the full Prescribing Information]*
- if a dose is missed, a patient should wait until the next scheduled dose to resume the regular dosing schedule

5.4 Patients Receiving Opioid Analgesics

Vulnerability to Opioid Overdose: CONTRAVE should not be administered to patients receiving chronic opioids, due to the naltrexone component, which is an opioid receptor antagonist *[see Contraindications (4)]*. If chronic opiate therapy is required, CONTRAVE treatment should be stopped. In patients requiring intermittent opiate treatment, CONTRAVE therapy should be temporarily discontinued and lower doses of opioids may be needed. Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after CONTRAVE treatment is discontinued.

An attempt by a patient to overcome any naltrexone opioid blockade by administering large amounts of exogenous opioids is especially dangerous and may lead to a fatal overdose or life-threatening opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opioid blockade.

Precipitated Opioid Withdrawal: The symptoms of spontaneous opioid withdrawal, which are associated with the discontinuation of opioid in a dependent individual, are uncomfortable, but they are not generally believed to be severe or necessitate hospitalization. However, when withdrawal is precipitated abruptly, the resulting withdrawal syndrome can be severe enough to require hospitalization. To prevent occurrence of either precipitated withdrawal in patients dependent on opioids or exacerbation of a pre-existing subclinical withdrawal symptoms, opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free (including tramadol) before starting CONTRAVE treatment. An opioid-free interval of a minimum of 7 to 10 days is recommended for patients previously dependent on short-acting opioids, and those patients transitioning from buprenorphine or methadone may need as long as two weeks. Patients should be made aware of the risks associated with precipitated withdrawal and encouraged to give an accurate account of last opioid use.

5.5 Increase in Blood Pressure and Heart Rate

CONTRAVE can cause an increase in systolic and/or diastolic blood pressure as well as an increase in resting heart rate. In clinical practice with other bupropion-containing products, hypertension, in some cases severe and requiring acute treatment, has been reported. The clinical significance of the increases in blood pressure and heart rate observed with CONTRAVE treatment is unclear, especially for patients with cardiac and cerebrovascular disease, since patients with a history of myocardial infarction or stroke in the previous 6 months, life-threatening arrhythmias, or congestive heart failure were excluded from CONTRAVE clinical trials. Blood pressure and pulse should be measured prior to starting therapy with CONTRAVE and should be monitored at regular intervals consistent with usual clinical practice, particularly among patients with controlled hypertension prior to treatment *[see Dosage and Administration (2.1) in the full Prescribing Information]*. CONTRAVE should not be given to patients with uncontrolled hypertension *[see Contraindications (4)]*.

Among patients treated with CONTRAVE in placebo-controlled clinical trials, mean systolic and diastolic blood pressure was approximately 1 mmHg higher than baseline at Weeks 4 and 8, similar to baseline at Week 12, and approximately 1 mmHg below baseline between Weeks 24 and 56. In contrast, among patients treated with placebo, mean blood pressure was approximately 2 to 3 mmHg below baseline throughout the same time points, yielding statistically significant differences between the groups at every assessment during this period. The largest mean differences between the groups were observed during the first 12 weeks (treatment difference +1.8 to +2.4 mmHg systolic, all $p<0.001$; +1.7 to +2.1 mmHg diastolic, all $p<0.001$).

For heart rate, at both Weeks 4 and 8, mean heart rate was statistically significantly higher (2.1 bpm) in the CONTRAVE group compared with the placebo group; at Week 52, the difference between groups was +1.7 bpm ($p<0.001$).

In an ambulatory blood pressure monitoring substudy of 182 patients, the mean change from baseline in systolic blood pressure after 52 weeks of treatment was -0.2 mmHg for the CONTRAVE group and -2.8 mmHg for the placebo group (treatment difference, +2.6 mmHg, $p=0.08$); the mean change in diastolic blood pressure was +0.8 mmHg for the CONTRAVE group and -2.1 mmHg for the placebo group (treatment difference, +2.9 mmHg, $p=0.004$).

A greater percentage of subjects had adverse reactions related to blood pressure or heart rate in the CONTRAVE group compared to the placebo group (6.3% vs 4.2%, respectively), primarily attributable to adverse reactions of Hypertension/Blood Pressure Increased (5.9% vs 4.0%, respectively). These events were observed in both patients with and without evidence of preexisting hypertension. In a trial that enrolled individuals with diabetes, 12.0% of patients in the CONTRAVE group and 6.5% in the placebo group had a blood pressure-related adverse reaction.

5.6 Allergic Reactions

Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. Instruct patients to discontinue CONTRAVE and consult a healthcare provider if they develop an allergic or anaphylactoid/anaphylactic reaction (e.g., skin rash, pruritus, hives, chest pain, edema, or shortness of breath) during treatment.

Arthralgia, myalgia, fever with rash, and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

5.7 Hepatotoxicity

Cases of hepatitis and clinically significant liver dysfunction were observed in association with naltrexone exposure during naltrexone clinical trials and in postmarketing reports for patients using naltrexone. Transient, asymptomatic hepatic transaminase elevations were also observed. When patients presented with elevated transaminases, there were often other potential causative or contributory etiologies identified, including pre-existing alcoholic liver disease, hepatitis B and/or C infection, and concomitant usage of other potentially hepatotoxic drugs. Although clinically significant liver dysfunction is not typically recognized as a manifestation of opioid withdrawal, opioid withdrawal that is precipitated abruptly may lead to systemic sequelae, including acute liver injury.

Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Use of CONTRAVE should be discontinued in the event of symptoms and/or signs of acute hepatitis.

In CONTRAVE clinical trials, there were no cases of elevated transaminases greater than three times the upper limit of normal (ULN) in conjunction with an increase in bilirubin greater than two times ULN.

5.8 Activation of Mania

Bupropion, a component of CONTRAVE, is a drug used for the treatment of depression. Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating CONTRAVE, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). CONTRAVE is not approved for use in treating bipolar depression. No activation of mania or hypomania was reported in the clinical trials evaluating effects of CONTRAVE in obese patients; however, patients receiving antidepressant medications and patients with a history of bipolar disorder or recent hospitalization because of psychiatric illness were excluded from CONTRAVE clinical trials.

5.9 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including bupropion, a component of CONTRAVE, may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.10 Potential Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Antidiabetic Therapy

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas). Measurement of blood glucose levels prior to starting CONTRAVE and during CONTRAVE treatment is recommended in patients with type 2 diabetes. Decreases in medication doses for antidiabetic medications which are non-glucose-dependent should be considered to mitigate the risk of hypoglycemia. If a patient develops hypoglycemia after starting CONTRAVE, appropriate changes should be made to the antidiabetic drug regimen.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Suicidal Behavior and Ideation *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Neuropsychiatric Adverse Events *[see Warnings and Precautions (5.2)]*
- Seizures *[see Contraindications (4), Warnings and Precautions (5.3)]*
- Increase in Blood Pressure and Heart Rate *[see Warnings and Precautions (5.5)]*
- Allergic Reactions *[see Warnings and Precautions (5.6)]*
- Angle-Closure Glaucoma *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

CONTRAVE was evaluated for safety in five double-blind placebo controlled trials in 4,754 overweight or obese patients (3,239 patients treated with CONTRAVE and 1,515 patients treated with placebo) for a treatment period up to 56 weeks. The majority of patients were treated with CONTRAVE 32 mg/360 mg total daily dose. In addition, some patients were treated with other combination daily doses including naltrexone up to 50 mg and bupropion up to 400 mg. All subjects received study drug in addition to diet and exercise counseling. One trial (N=793) evaluated patients participating in an intensive behavioral modification program and another trial (N= 505) evaluated patients with type 2 diabetes. In these randomized, placebo-controlled trials, 2,545 patients received CONTRAVE 32 mg/360 mg for a mean treatment duration of 36 weeks (median, 56 weeks). Baseline patient characteristics included a mean age of 46 years, 82% women, 78% white, 25% with hypertension, 13% with type 2 diabetes, 56% with dyslipidemia, 25% with BMI greater than 40 kg/m^2, and less than 2% with coronary artery disease. Dosing was initiated and increased weekly to reach the maintenance dose within 4 weeks.

In CONTRAVE clinical trials, 24% of subjects receiving CONTRAVE and 12% of subjects receiving placebo discontinued treatment because of an adverse event. The most frequent adverse reactions leading to discontinuation with CONTRAVE were nausea (6.3%), headache (1.7%) and vomiting (1.1%).

Common Adverse Reactions

Adverse reactions that were reported by greater than or equal to 2% of patients, and were more frequently reported by patients treated with CONTRAVE compared to placebo, are summarized in *Table 3*.

Table 3. Adverse Reactions Reported by Obese or Overweight Patients With an Incidence (%) of at Least 2% Among Patients Treated with CONTRAVE and More Common than with Placebo

Adverse Reaction	CONTRAVE 32 mg/360 mg N=2545 %	Placebo N=1515 %
Nausea	32.5	6.7
Constipation	19.2	7.2
Headache	17.6	10.4
Vomiting	10.7	2.9
Dizziness	9.9	3.4
Insomnia	9.2	5.9
Dry mouth	8.1	2.3
Diarrhea	7.1	5.2
Anxiety	4.2	2.8
Hot flush	4.2	1.2
Fatigue	4.0	3.4
Tremor	4.0	0.7
Upper abdominal pain	3.5	1.3
Viral gastroenteritis	3.5	2.6
Influenza	3.4	3.2
Tinnitus	3.3	0.6
Urinary tract infection	3.3	2.8
Hypertension	3.2	2.2
Abdominal pain	2.8	1.4
Hyperhidrosis	2.6	0.6
Irritability	2.6	1.8
Blood pressure increased	2.4	1.5
Dysgeusia	2.4	0.7
Rash	2.4	2.0
Muscle strain	2.2	1.7
Palpitations	2.1	0.9

Other Adverse Reactions

The following additional adverse reactions were reported in less than 2% of patients treated with CONTRAVE but with an incidence at least twice that of placebo:

Cardiac Disorders: tachycardia, myocardial infarction

Ear and Labyrinth Disorders: vertigo, motion sickness

Gastrointestinal Disorders: lower abdominal pain, eructation, lip swelling, hematochezia, hernia

General Disorders and Administration Site Conditions: feeling jittery, feeling abnormal, asthenia, thirst, feeling hot

Hepatobiliary Disorders: cholecystitis

Infections and Infestations: pneumonia, staphylococcal infection, kidney infection

Investigations: increased blood creatinine, increased hepatic enzymes, decreased hematocrit

Metabolism and Nutrition Disorders: dehydration

Musculoskeletal and Connective Tissue Disorders: intervertebral disc protrusion, jaw pain

Nervous System Disorders: disturbance in attention, lethargy, intention tremor, balance disorder, memory impairment, amnesia, mental impairment, presyncope

Psychiatric Disorders: abnormal dreams, nervousness, dissociation (feeling spacey), tension, agitation, mood swings

Renal and Urinary Disorders: micturition urgency

Reproductive System and Breast Disorders: vaginal hemorrhage, irregular menstruation, erectile dysfunction, vulvovaginal dryness

Skin and Subcutaneous Tissue Disorders: alopecia

Psychiatric and Sleep Disorders

In the one-year controlled trials of CONTRAVE, the proportion of patients reporting one or more adverse reactions related to psychiatric and sleep disorders was higher in the CONTRAVE 32/360 mg group than the placebo group (22.2% and 15.5%, respectively). These events were further categorized into sleep disorders (13.8% CONTRAVE, 8.4% placebo), depression (6.3% CONTRAVE, 5.9% placebo), and anxiety (6.1% CONTRAVE, 4.4% placebo). Patients who were 65 years or older experienced more psychiatric and sleep disorder adverse reactions in the CONTRAVE group (28.6%) compared to placebo (6.3%), although the sample size in this subgroup was small (56 CONTRAVE, 32 placebo); the majority of these events were insomnia (10.7% CONTRAVE, 3.1% placebo) and depression (7.1% CONTRAVE, 3.1% placebo).

Neurocognitive Adverse Reactions

Adverse reactions involving attention, dizziness, and syncope occurred more often in individuals randomized to CONTRAVE 32/360 mg group compared to placebo (15.0% and 5.5%, respectively). The most common cognitive-related adverse reactions were attention disorders (2.5% CONTRAVE, 0.6% placebo). Adverse reactions involving dizziness and syncope were more common in patients treated with CONTRAVE (10.6%) than in placebo-treated patients (3.6%); dizziness accounted for almost all of these reported events (10.4% CONTRAVE, 3.4% placebo). Dizziness was the primary reason for discontinuation for 0.9% and 0.3% of patients in the CONTRAVE and placebo groups, respectively.

Increases in Serum Creatinine

In the one-year controlled trials of CONTRAVE, larger mean increases in serum creatinine from baseline to trial endpoint were observed in the CONTRAVE group compared with the placebo group (0.07 mg/dL and 0.01 mg/dL, respectively) as well as from baseline to the maximum value during follow-up (0.15 mg/dL and 0.07 mg/dL, respectively). Increases in serum creatinine that exceeded the upper limit of normal and were also greater than or equal to 50% higher than baseline occurred in 0.6% of subjects receiving CONTRAVE compared to 0.1% receiving placebo. The observed increase in serum creatinine may be the result of OCT2 inhibition *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of CONTRAVE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Loss of consciousness, malaise

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors (MAOI)

Concomitant use of MAOIs and bupropion is contraindicated. Bupropion inhibits the re-uptake of dopamine and norepinephrine and can increase the risk for hypertensive reactions when used concomitantly with drugs that also inhibit the re-uptake of dopamine or norepinephrine, including MAOIs. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAOI phenelzine. At least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with CONTRAVE. Conversely, at least 14 days should be allowed after stopping CONTRAVE before starting an MAOI *[*see *Contraindications (4)]*.

7.2 Opioid Analgesics

Patients taking CONTRAVE may not fully benefit from treatment with opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations, and opioid analgesics. In patients requiring intermittent opiate treatment, CONTRAVE therapy should be temporarily discontinued and opiate dose should not be increased above the standard dose. CONTRAVE may be used with caution after chronic opioid use has been stopped for 7 to 10 days in order to prevent precipitation of withdrawal *[see Contraindications (4) and Warnings and Precautions (5.4)]*.

During CONTRAVE clinical studies, the use of concomitant opioid or opioid-like medications, including analgesics or antitussives, were excluded.

7.3 Potential for CONTRAVE to Affect Other Drugs

Metabolized by CYP2D6

In a clinical study, CONTRAVE (32 mg naltrexone/360 mg bupropion) daily was coadministered with a 50 mg dose of metoprolol (a CYP2D6 substrate). CONTRAVE increased metoprolol AUC and C_{max} by approximately 4- and 2-fold, respectively, relative to metoprolol alone. Similar clinical drug interactions resulting in increased pharmacokinetic exposure of CYP2D6 substrates have also been observed with bupropion as a single agent with desipramine or venlafaxine.

Coadministration of CONTRAVE with drugs that are metabolized by CYP2D6 isozyme including certain antidepressants (SSRIs and many tricyclics), antipsychotics (e.g., haloperidol, risperidone and thioridazine), beta-blockers (e.g., metoprolol) and Type 1C antiarrhythmics (e.g., propafenone and flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If CONTRAVE is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Digoxin

Coadministration of CONTRAVE with digoxin may decrease plasma digoxin levels. Monitor plasma digoxin levels in patients treated concomitantly with CONTRAVE and digoxin *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

7.4 Potential for Other Drugs to Affect CONTRAVE

Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between CONTRAVE and drugs that are inhibitors or inducers of CYP2B6.

Inhibitors of CYP2B6: Ticlopidine and Clopidogrel: Concomitant treatment with these drugs can increase bupropion exposure but decrease hydroxybupropion exposure. During concomitant use with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel), the CONTRAVE daily dose should not exceed two tablets (one tablet each morning and evening) *[see Dosage and Administration (2.5) in the full Prescribing Information and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Inducers of CYP2B6: Ritonavir, Lopinavir, and Efavirenz: Concomitant treatment with these drugs can decrease bupropion and hydroxybupropion exposure and may reduce efficacy. Avoiding concomitant use with ritonavir, lopinavir, or efavirenz is recommended *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

7.5 Drugs That Lower Seizure Threshold

Use extreme caution when coadministering CONTRAVE with other drugs that lower seizure threshold (e.g., antipsychotics, antidepressants, theophylline, or systemic corticosteroids). Use low initial doses and increase the dose gradually. Concomitant use of other bupropion-containing products is contraindicated *[see Contraindications (4) and Warnings and Precautions (5.3)*].

7.6 Dopaminergic Drugs (Levodopa and Amantadine)

Bupropion, levodopa, and amantadine have dopamine agonist effects. CNS toxicity has been reported when bupropion was coadministered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Use caution and monitor for such adverse reactions when administering CONTRAVE concomitantly with these drugs.

7.7 Use with Alcohol

In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with CONTRAVE should be minimized or avoided.

7.8 Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. This is due to lack of specificity of some screening tests. False-positive test results may result even following discontinuation of bupropion therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Weight loss offers no benefit to a pregnant patient and may cause fetal harm. When a pregnancy is recognized, advise the pregnant patient of the risk to the fetus, and discontinue CONTRAVE (*see Clinical Considerations)*. Available pharmacovigilance data and data from clinical trials with

the individual components of CONTRAVE use in pregnant patients have not demonstrated a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

Bupropion

Data from epidemiological studies of pregnant patients exposed to bupropion in the first trimester have not identified an increased risk of congenital malformations overall *(see Data)*. When bupropion was administered to pregnant rats during organogenesis, there was no evidence of fetal malformations at doses up to approximately 20 times the maximum recommended human dose (MRHD) of 360 mg/day. When given to pregnant rabbits during organogenesis, non-dose–related increases in incidence of fetal malformations, and skeletal variations were observed at doses approximately twice the MRHD and greater. Decreased fetal weights were seen at doses 5 times the MRHD and greater *(see Data)*.

Naltrexone

Limited case report data of pregnant patients exposed to naltrexone in the first trimester have not identified an increased risk of congenital malformations overall. Daily oral administration of naltrexone during the period of organogenesis has been shown to increase the incidence of early fetal loss in rats and rabbits at doses ≥ 15 times and ≥ 60 times the MRHD of 32 mg/day, respectively. There was no evidence of fetal malformations in rats and rabbits at doses up to approximately 100 and 200 times the MHRD, respectively. *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Appropriate weight gain based on pre-pregnancy weight is currently recommended for all pregnant patients, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Data

Human Data

In clinical studies, 21 (0.7%) of 3,024 women became pregnant while taking CONTRAVE: 11 carried to term and gave birth to a healthy infant, three had elective abortions, four had spontaneous abortions, and the outcome of three pregnancies were unknown.

Data from the international bupropion Pregnancy Registry (675 first trimester exposures) and a retrospective cohort study using the United Healthcare database (1,213 first trimester exposures) did not show an increased risk for malformations overall.

No increased risk for cardiovascular malformations overall has been observed after bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester from the international Pregnancy Registry was 1.3% (9 cardiovascular malformations out of 675 first-trimester maternal bupropion exposures), which is similar to the background rate of cardiovascular malformations (approximately 1%). Data from the United Healthcare database and a case-control study (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular malformations) from the National Birth Defects Prevention Study (NBDPS) did not show an increased risk for cardiovascular malformations overall after bupropion exposure during the first trimester.

Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted odds ratio [OR] = 2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk for LVOTO.

Study findings on bupropion exposure during the first trimester and risk for ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n = 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0) but did not find increased risk for any other cardiovascular malformations studied (including LVOTO as above). The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion exposure and VSD.

For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control studies.

Animal Data

Reproduction and developmental studies have not been conducted for the combined products naltrexone and bupropion in CONTRAVE. Separate studies with bupropion and naltrexone have been conducted in pregnant rats and rabbits. Safety margins were estimated using body surface area exposure (mg/m^2) based on a body weight of 100 kg.

Daily oral administration of naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses ≥30 mg/kg/day (15 times the MHRD on a mg/m^2 basis) and to rabbits at oral doses ≥60 mg/kg/day (60 times the MHRD on a mg/m^2 basis).

Daily oral administration of naltrexone to rats and rabbits during the period of organogenesis did not induce malformations at doses up to 200 mg/kg/day (approximately 100 and 200 times the MHRD, respectively, on a mg/m^2 basis).

Rats do not form appreciable quantities of the major human metabolite, 6-beta-naltrexol; therefore, the potential reproductive toxicity of the metabolite in rats is not known. In studies conducted in pregnant rats and rabbits, bupropion was administered orally during the period of organogenesis at doses of up to 450 and 150 mg/kg/day, respectively (approximately 20 and 14 times the MRHD, respectively, on a mg/m^2 basis). There was no evidence of fetal malformations in rats. When given to pregnant rabbits during organogenesis, non-dose-related increases in incidence of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately 2 times the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were observed at doses of 50 mg/kg/day (approximately 5 times the MRHD on a mg/m^2 basis) and greater. No maternal toxicity was evident at doses of 50 mg/kg/day or less.

In a pre- and postnatal development study, bupropion administered orally to pregnant rats at doses of up to 150 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis) from embryonic implantation through lactation had no effect on pup growth or development.

8.2 Lactation

Risk Summary

Data from published literature report the presence of bupropion and its metabolites in human milk. Limited data from postmarketing reports with bupropion use during lactation have not identified a clear association of adverse effects on a breastfed infant *(see Data)*. Naltrexone and its major metabolite, 6β-naltrexol, are present in human milk. There are no data on bupropion, naltrexone, or their metabolites on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CONTRAVE and any potential adverse effects on the breastfed infant from CONTRAVE or from the mother's underlying condition.

Data

In a lactation study of ten women, levels of orally dosed bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL/kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Postmarketing reports have described seizures in breastfed infants. The relationship of bupropion exposure and these seizures is unclear.

8.4 Pediatric Use

The safety and effectiveness of CONTRAVE in pediatric patients below the age of 18 have not been established and the use of CONTRAVE is not recommended in pediatric patients.

8.5 Geriatric Use

Of the 3,239 subjects who participated in clinical trials with CONTRAVE, 62 (2%) were 65 years and older and none were 75 years and older. Clinical studies of CONTRAVE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Older individuals may be more sensitive to the central nervous system adverse effects of CONTRAVE. Naltrexone and bupropion are known to be substantially excreted by the kidney, and the risk of adverse reactions to CONTRAVE may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. CONTRAVE should be used with caution in patients over 65 years of age.

8.6 Renal Impairment

In a pharmacokinetic study conducted for CONTRAVE in subjects with renal impairment (mild, moderate and severe), exposure to naltrexone metabolite, 6-beta naltrexol, and bupropion metabolites, threohydrobupropion, and erythrohydrobupropion was increased. Therefore, the maximum recommended daily maintenance dose for CONTRAVE is two tablets (one tablet each morning and evening) in patients with moderate or severe renal impairment. CONTRAVE is not recommended for use in patients with end-stage renal disease *[see Dosage and Administration (2.2) in the full Prescribing Information and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

8.7 Hepatic Impairment

In a pharmacokinetic study conducted for CONTRAVE in subjects with hepatic impairment (mild, moderate, and severe), exposure to naltrexone, bupropion, and their metabolites were increased. Therefore, the maximum recommended daily maintenance dose of CONTRAVE is two tablets (one tablet each morning and evening) in patients with moderate hepatic impairment. CONTRAVE is not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.3) in the full Prescribing Information and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

10 OVERDOSAGE

Human Experience

Overdoses of up to 30 grams or more of bupropion (equivalent of up to 83 times the recommended daily dose of CONTRAVE 32 mg/360 mg) have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, mental status changes, sinus tachycardia, ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias, clonus, myoclonus, and hyperreflexia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

Animal Experience

In the mouse, rat, and guinea pig, the oral LD_{50}s for naltrexone were 1,100 to 1,550 mg/kg; 1,450 mg/kg; and 1,490 mg/kg; respectively. High doses of naltrexone (generally greater than or equal to 1,000 mg/kg) produced salivation, depression/reduced activity, tremors, and convulsions. Mortality in animals due to high-dose naltrexone administration usually was due to clonic-tonic convulsions and/or respiratory failure.

Overdosage Management

If over-exposure occurs, call your poison control center at 1-800-222-1222. There are no known antidotes for CONTRAVE. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Induction of emesis is not recommended.

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GETTING NALOXONE IN THE HANDS OF **THOSE WHO NEED IT MOST**

LOREN BONNER

Harm reduction experts know that naloxone isn't the single solution to the opioid overdose crisis.

"Naloxone isn't the end-all-be-all," said Nabarun Dasgupta, MPH, PhD, an epidemiologist at the University of North Carolina at Chapel Hill. "We need prevention, we need treatment, we need all sorts of services, but when the overdose death rate is increasing at the pace that it has been, we have to have more emergency antidote available until there are no more overdose deaths."

According to the latest figures from CDC, reduced access to addiction treatment and services combined with fentanyl contaminating drug supplies resulted in an estimated 100,000 fatal overdoses in 2020 alone.

Adding to the crisis is the lack of naloxone in the hands of those who need it most. CDC estimates that only one naloxone prescription is dispensed for every 70 high-dose opioid prescriptions nationwide. For those who are at the highest risk of an overdose—such as those using illicit drugs—the ratio of naloxone to opioids distributed remains unknown.

Dasgupta works with an organization called Remedy Alliance/For The People. They order and distribute naloxone to harm reduction groups through a unique arrangement, which was formalized this August 2022. Injectable naloxone is manufactured exclusively for Remedy Alliance at a discount and then the Remedy Alliance team processes orders and ships naloxone directly to harm reduction groups.

Many harm reduction programs have historically had difficulty acquiring naloxone. Additionally, these groups as well as many nongovernmental groups and community health centers, have to use their own limited budgets to purchase naloxone at cost or rely on mutual aid networks.

Reduced access to addiction treatment and services combined with fentanyl contaminating drug supplies resulted in an estimated 100,000 fatal overdoses in 2020 alone.

"Right now, there are standing orders allowing pharmacy distribution of naloxone or layperson distribution," said Dasgupta. "Where those laws fall short is they don't cover bulk purchasing. State laws that have been passed are all dealing within state law in pharmacy practice more or less, but in order to even get the naloxone, you are dealing with interstate commerce and federal regulations because it's the industry that is being regulated and not the boards of pharmacy."

Efforts from the Remedy Alliance team members reached all the way to FDA and other federal agencies, who agreed to waive the regulations for bulk purchasing through an exception in the federal Drug Supply Chain Security Act (DSCSA).

In a formal announcement about the DSCSA exemption, FDA said they were aware of the contributing factors "to be the current availability of approved naloxone products only as prescription drugs and certain requirements under the [DSCSA] for distribution of FDA-approved prescription drug products, e.g., being an 'authorized' trading partner."

Through the exemption, FDA is advocating for more naloxone to be widely available and accessible in order to reduce opioid overdose deaths.

"Now we can have centralized distribution," said Jeffrey Bratberg, PharmD, FAPhA, clinical professor at the University of Rhode Island College of Pharmacy. "Anyone like [Remedy Alliance] can do this."

Bratberg believes it's crucial to expand naloxone access to community programs because they can reach the individuals who face stigma and are normally excluded from health care systems and pharmacy-based naloxone access. They are also the people who are most likely to use naloxone to reverse a witnessed opioid overdose.

Dasgupta said the impact of this new distribution model through the DSCSA exemption has been "immediate and amazing."

"We've been operating under this naloxone scarcity mentality for decades, that this is something that's been locked up, something that's expensive, something that's precious, and we need to move to a mentality of naloxone abundance," said Dasgupta. "The only way to do that is with cheap naloxone." Remedy Alliance has affordable naloxone available.

What is harm reduction?

According to the Substance Abuse and Mental Health Services Administration (SAMHSA), harm reduction is an "approach that emphasizes engaging directly with people who use drugs to prevent overdose and infectious disease transmission, improve the physical, mental, and social wellbeing of those served, and offer low-threshold options for accessing substance use disorder treatment and other health care services."

"Harm reduction is defined as celebrating any positive change that the individual wants to make and being there to support that," said Nabarun Dasgupta, MPH, PhD, an epidemiologist at the University of North Carolina at Chapel Hill.

"If that means using a little bit less tomorrow, great, if that's what they want. If it means that they want to step away from opioids in their lives all together, that's great, too," he said.

Harm reduction is not a defined set of interventions either, even though there are particular interventions that go with it, according to Dasgupta.

SAMHSA has worked on defining harm reduction for the United States population and will release a toolkit soon.

Visit SAMHSA's website at www.samhsa.gov/find-help/harm-reduction to find out more. ■

"The nasal spray is great, but when it costs $50 for a box whereas ours costs a couple bucks [for an injectable], that perpetuates the mentality," he said.

Pharmacy and community access

Naloxone access laws have now been passed in every U.S. state with the goal of making naloxone available to those at risk of an opioid overdose as well as bystanders who may encounter a person in an overdose situation.

To date, all states give pharmacists the authority to dispense naloxone with a prescription, either through statewide protocols, standing orders, or direct prescriptive authority.

However, naloxone still appears difficult for individuals to obtain in the community, especially in pharmacies.

A recent study from July 2022 published in the *Journal of the American Pharmacists Association (JAPhA)* found that many barriers still remain that make it more difficult to obtain naloxone from a community pharmacy.

"One of the key findings of the study was that naloxone accessibility seems to be much more limited from independent pharmacies than chain pharmacies," said lead author Kirk Evoy, PharmD, BCACP, a clinical assistant professor at the University of Texas at Austin College of Pharmacy.

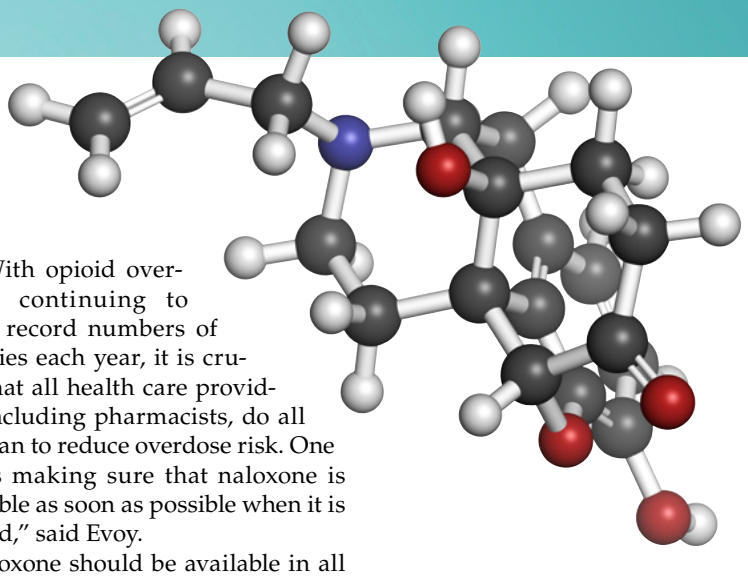
In the pooled data analyzing 30 studies, the research team found that naloxone was immediately accessible without a prescription from 64% of the chain pharmacies versus only 20% of the independent pharmacies.

"It was also interesting that almost all the pharmacies stocking naloxone had the nasal spray available but very few stocked any other formulations," said Evoy. "This is particularly important for patients who are underinsured or who have financial limitations, as the nasal spray cost generally around $120–150 without insurance coverage versus $20–50 for intramuscular injection formulations."

According to CDC, 71% of Medicare prescriptions, compared to 42% of commercial insurance carriers, require copayments upwards of $80 for naloxone.

Evoy said there also seem to be many opportunities to address potentially problematic misunderstandings regarding naloxone access laws among pharmacists, such as thinking that they cannot bill insurance companies when dispensing naloxone without a prescription, that naloxone access laws preclude dispensing to adolescents, or that increasing naloxone access could lead to more harmful drug use behaviors.

"With opioid overdoses continuing to cause record numbers of fatalities each year, it is crucial that all health care providers, including pharmacists, do all they can to reduce overdose risk. One key is making sure that naloxone is available as soon as possible when it is needed."



"With opioid overdoses continuing to cause record numbers of fatalities each year, it is crucial that all health care providers, including pharmacists, do all they can to reduce overdose risk. One key is making sure that naloxone is available as soon as possible when it is needed," said Evoy.

Naloxone should be available in all the right places, too.

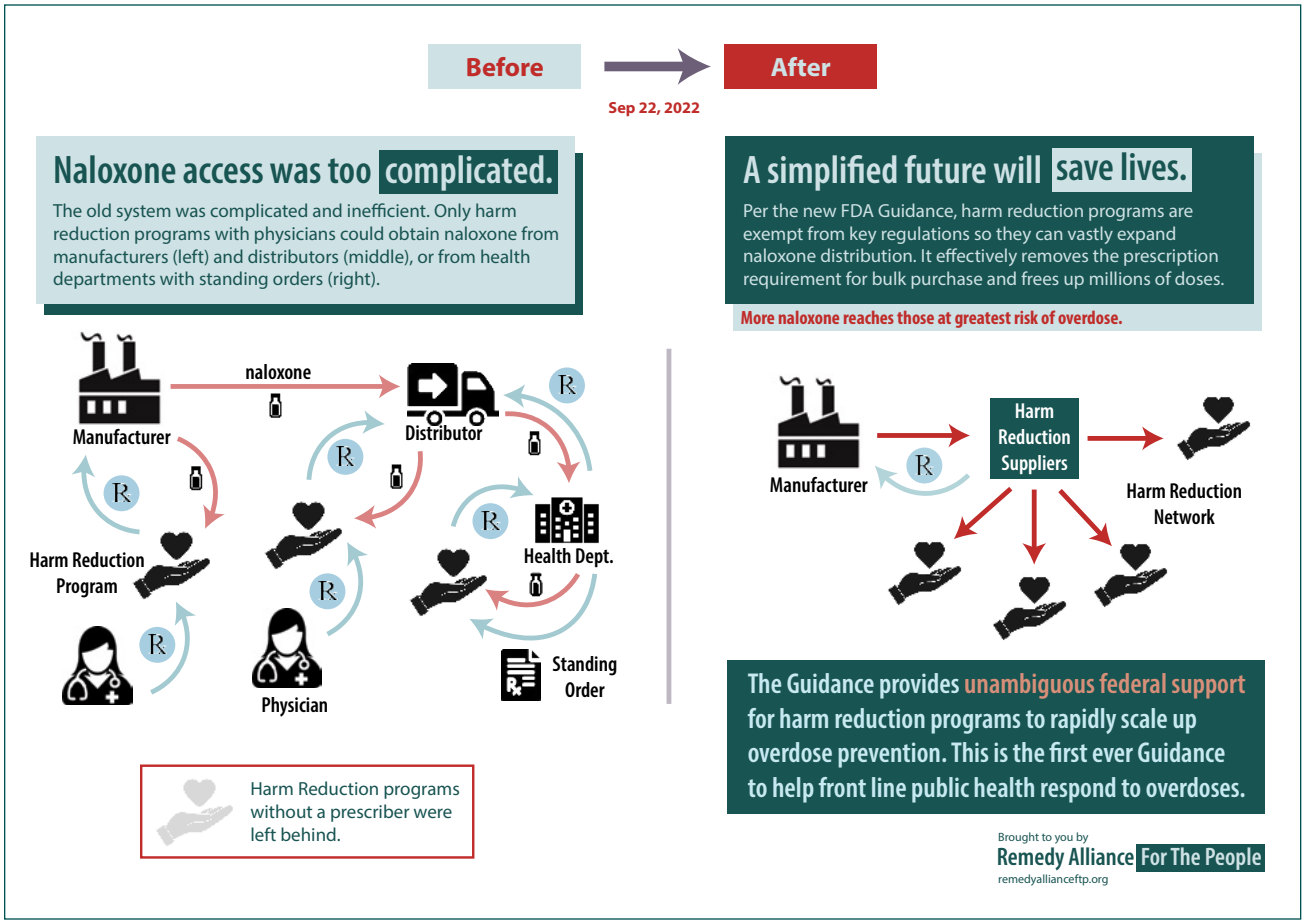
"It's all hands on deck," said Bratberg. It should be available in pharmacies, mental health clinics, primary care clinics, and mental health clinics—even in vending machines, according to Bratberg. In Bratberg's home state of Rhode Island, vending machines distribute naloxone, harm reduction supplies, and even personal hygiene kits without stigma and at no cost to the recipient, according to Bratberg. The machines and supplies are paid for through grants.

"We've been operating under this naloxone scarcity mentality for decades, that this is something that's been locked up, something that's expensive, something that's precious, and we need to move to a mentality of naloxone abundance."

OTC naloxone

In July 2022, FDA granted the nonprofit pharmaceutical company Harm Reduction Therapeutics fast track designation for their OTC naloxone nasal spray, RiVive (3.0 mg naloxone). The product is currently in development and is expected to be launched in early 2024.

Harm reduction experts have been



advocating for an OTC intranasal naloxone formulation for years. Naloxone meets all FDA criteria to become an OTC product: The drug's benefits outweigh its risks; it treats a condition that can be identified without a medical professional's guidance; it has a low misuse potential; and the instructions are understandable by a layperson.

"If an OTC transition occurs, educational outreach and funding for clinical innovations will continue to be crucial."

But OTC status should come with some caveats, according to Bratberg. A main concern—once again—is cost.

Bratberg said OTC naloxone could mean individuals would have to pay for naloxone out of pocket when they may have previously relied on insurance to cover or lower the cost. But some insurance companies may choose not to include OTC naloxone formulations on their insurance formularies.

According to an NIH paper published online February 15, 2021, that Evoy and colleagues wrote, federal- or state-level legislation could mandate insurance coverage for OTC naloxone formulations. Additionally, laws in certain states such as New York and Rhode Island that already require insurance coverage for naloxone, could be extended to cover OTC as well as prescription versions of the medication.

It's also most likely that not all formulations of naloxone will transition to OTC status, the authors of the paper point out.

"If an OTC transition occurs, educational outreach and funding for clinical innovations will continue to be crucial given the important role of health professionals in recommending naloxone to people at risk for experiencing or witnessing an [opioid-related overdose]," Evoy and colleagues wrote.

To learn more about harm reduction, check out the January/February 2023 issue of *JAPhA*. ■

Fentanyl test strips in harm reduction services

The deaths of three "high-achieving" New Yorkers made news headlines last year. All three individuals were found dead after purchasing cocaine laced with fentanyl, supposedly a result of a scheme to lace cocaine with fentanyl to make it more addictive.

Stories like these seem to exemplify the issue of how deadly and prevalent fentanyl is within the drug supply. Fentanyl is increasingly being laced with other drugs—not just illicit opioids.

Fentanyl test strips have been around for years, but they have been criticized widely and are still illegal in many states. Some lawmakers argue they facilitate drug use. However, according to Kelly Gable, PharmD, BCPP, they have a place in harm reduction services.

"Where they are most valuable now is when the drug is not an [opioid] product," said Gable who is from Southern Illinois University Edwardsville School of Pharmacy. "Fentanyl is in everything."

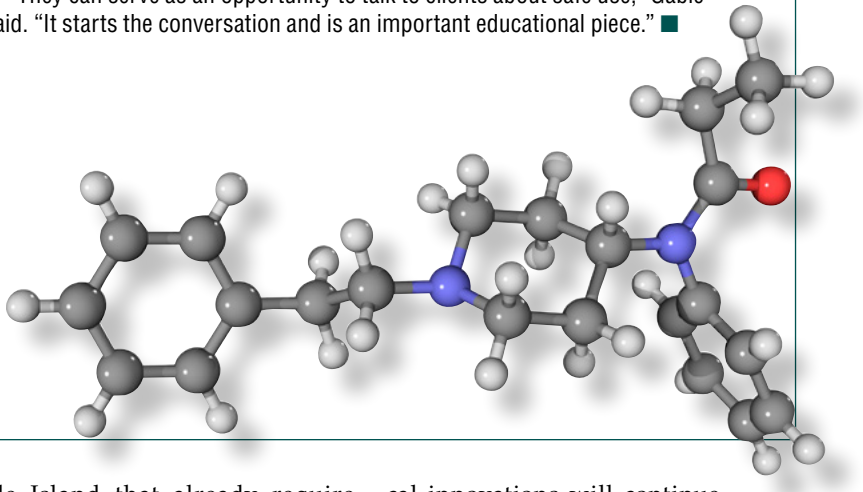
Fentanyl test strips can detect the presence of fentanyl in heroin, methamphetamine, cocaine, and other drugs.

"Fentanyl testing strips need to be accessible in any space where people can get other harm reduction things like naloxone," said Gable. "And they need to be free or low-cost."

Gable would like to see them more widely available at syringe exchanges, even pharmacies. "This is valuable tool in harm reduction space. We need more out there," said Gable.

Gable and a research team conducted a study, published online September 28, 2022, in *JAPhA*, to assess knowledge and understanding of illicit fentanyl and the motivation to use fentanyl test strips to prevent an overdose. Responses were collected from those receiving residential- or office-based substance use treatment services. The researchers found that many respondents lacked understanding of how to use fentanyl test strips for harm reduction.

"They can serve as an opportunity to talk to clients about safe use," Gable said. "It starts the conversation and is an important educational piece." ■



Pharmacists have future role in atrial fibrillation management

Loren Bonner

Pharmacists are a potentially untapped resource for atrial fibrillation (AFib) management, according to a new research paper in the *American Journal of Medicine*. The authors make the case that a pharmacist's skill set places them in the perfect position to put integrated AFib care into practice across the continuum of health care.

"While it's not surprising to see that pharmacists improve care, what's most surprising is the sheer amount of literature supporting [pharmacists'] role in the management of atrial fibrillation," said Caitlin Gibson, PharmD, BCPS, BCCP, who was not involved with the research.

Dozens of studies, which are put forth in the paper, demonstrate the value that pharmacists add to the collaborative care of patients with AFib. Gibson, who is an associate professor at Virginia Commonwealth University School of Pharmacy, noted that more data on how to best train pharmacists for participation in these initiatives is warranted as well.

"Pharmacists should continue to publish on their initiatives—successful or not—so that our profession can further delineate best practices and focus our resources and efforts on meaningful initiatives," she said.

"Gold standard"

In the paper published August 20, 2022, the researchers summarized the findings from previous research studies of pharmacist interventions that can be mapped to the "CC to ABC" model for patients with AFib.

The Atrial Fibrillation Better Care (ABC) pathway—the "gold standard" within Europe and Asia-Pacific—was first proposed in 2017 as a framework for integrated care to align generalist and specialist AFib management across health care settings.

The pathway is comprised of: Anticoagulation/Avoid stroke (A), Better symptom management (B), and Cardiovascular and other comorbidity optimization (C). European guidelines not only recommend the ABC pathway, but they also highlight two steps that precede the ABC pathway in practice: "CC to ABC." This consists of "C"—Confirming the AFib diagnosis with a 12-lead electrocardiogram (ECG) or single-lead ECG tracing of ≥ 30 seconds, followed by "C"—Characterization of AFib including stroke risk, symptom severity, severity of AFib burden, and substrate severity.

"As the scope of pharmacist practice continues to evolve and includes prescribing, it seems feasible for pharmacists to deliver all components of the ABC pathway across the health care continuum," the study authors conclude. "Hospital pharmacists could perform targeted medication reviews for atrial fibrillation patients, optimizing therapies with cardiology input as needed and providing education. In primary care, pharmacists could lead screening programs, check medication adherence, provide new medicine reviews, monitor for adverse effects, monitor blood pressure, blood glucose, and cholesterol, and reinforce key educational messages."

Growth in the U.S.

The research paper characterizes the role pharmacists have played in screening for AFib in Europe and Australasia. While this practice is much less common in the United States, Gibson said it represents a potential area to expand pharmacy services under collaborative practice agreements or through new initiatives in community pharmacies.

The paper does confirm the value of many common pharmacy practices in the United States, however, such as anticoagulation management clinics, as well as optimization of rate and rhythm control therapy in ambulatory and hospitalized patients.

"As a U.S.-based pharmacist, I'm interested to learn how pharmacists contribute to patient care in other countries," Gibson said. "A significant number of screening interventions outside of the U.S. occur in community pharmacies; this may be an underutilized opportunity for pharmacists in critical access areas or underserved communities to identify and care for patients living with atrial fibrillation."

The practices highlighted in the research run the gamut—from community to outpatient to hospitals—which Gibson said only demonstrates "the tremendous breadth and depth of our ability to manage symptoms, optimize anticoagulation to prevent strokes, improve patient satisfaction and knowledge, and ultimately improve patient outcomes."

In fact, the APhA Foundation developed the Solution for Atrial Fibrillation Edvocacy (SAFE) project, which puts the focus on community pharmacy practice settings as an access point for AFib screening, detection, and referral to a physician.

"Pharmacists are well-positioned to offer these patient care services due to the frequency of patient interactions," said Benjamin Bluml, RPh, APhA Foundation executive director and senior vice president of research and innovation. "Through this project we've seen pharmacists bring hundreds of patients into a shared decision-making process and facilitate a team-based approach to care. We're extremely proud of the pharmacists we've partnered with across the U.S." ■

> "This may be an underutilized opportunity for pharmacists in critical access areas or underserved communities to identify and care for patients living with atrial fibrillation."

Veklury®
remdesivir 100 MG FOR INJECTION

For patients hospitalized with **COVID-19**,[1]

HELP REDUCE DISEASE PROGRESSION AND SHORTEN RECOVERY TIME[1,2]

INDICATION

VEKLURY is indicated for the treatment of COVID-19 in adults and pediatric patients (≥28 days old and weighing ≥3 kg) with positive results of SARS-CoV-2 viral testing, who are:

- Hospitalized, or
- Not hospitalized, have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

IMPORTANT SAFETY INFORMATION

Contraindication

- VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any of its components.

Warnings and precautions

- **Hypersensitivity, including infusion-related and anaphylactic reactions:** Hypersensitivity, including infusion-related and anaphylactic reactions, has been observed during and following administration of VEKLURY; most reactions occurred within 1 hour. Monitor patients during infusion and observe for at least 1 hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate. Symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates (maximum infusion time of up to 120 minutes) can potentially prevent these reactions. If a severe infusion-related hypersensitivity reaction occurs, immediately discontinue VEKLURY and initiate appropriate treatment (see Contraindications).
- **Increased risk of transaminase elevations:** Transaminase elevations have been observed in healthy volunteers and in patients with COVID-19 who received VEKLURY; these elevations have also been reported as a clinical feature of COVID-19. Perform hepatic laboratory testing in all patients (see Dosage and administration). Consider discontinuing VEKLURY if ALT levels increase to >10x ULN. Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation.
- **Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine:** Coadministration of VEKLURY with chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments, demonstrating potential antagonism, which may lead to a decrease in the antiviral activity of VEKLURY.

Adverse reactions

- The most common adverse reaction (≥5% all grades) was nausea.
- The most common lab abnormalities (≥5% all grades) were increases in ALT and AST.

Drug interactions

- Drug interaction trials of VEKLURY and other concomitant medications have not been conducted in humans.

Dosage and administration

- **Dosage:**
  - For adults and pediatric patients weighing ≥40 kg: 200 mg on Day 1, followed by once-daily maintenance doses of 100 mg from Day 2, administered only via intravenous infusion.
  - For pediatric patients ≥28 days old and weighing ≥3 kg to <40 kg: 5 mg/kg on Day 1, followed by once-daily maintenance doses of 2.5 mg/kg from Day 2, administered only via intravenous infusion.

ECMO=extracorporeal membrane oxygenation.

In the ACTT-1 overall study population, patients experienced

Median 10 days with VEKLURY vs 15 days with placebo; recovery rate ratio: 1.29 (95% CI, 1.12 to 1.49), p<0.001[1,2]

- Recovery was defined as patients who were no longer hospitalized or hospitalized but no longer required ongoing COVID-19 medical care

Significantly greater likelihood of improvement in clinical status, a key secondary endpoint[1]

- Patients were 54% more likely to have improved clinical status on Day 15 vs placebo; odds ratio for improvement: 1.54 (95% CI, 1.25 to 1.91)

Helped reduce progression to more severe disease, an additional secondary endpoint[1-3]

- 7% absolute reduction in incidence of new noninvasive ventilation or high-flow oxygen with VEKLURY (17%, n=307) vs placebo (24%, n=266) in patients who did not receive either at baseline (95% CI, -14 to -1)
- 10% absolute reduction in incidence of new mechanical ventilation or ECMO with VEKLURY (13%, n=402) vs placebo (23%, n=364) in patients who did not receive either at baseline (95% CI, -15 to -4)

Adverse reaction frequency was comparable between VEKLURY and placebo[1]

- All adverse reactions (ARs), Grades ≥3: 41 (8%) with VEKLURY vs 46 (9%) with placebo; serious ARs: 2 (0.4%)* vs 3 (0.6%); ARs leading to treatment discontinuation: 11 (2%)† vs 15 (3%)

ACTT-1 was a randomized, double-blind, placebo-controlled, phase 3 clinical trial in hospitalized patients with confirmed SARS-CoV-2 infection and mild, moderate, or severe COVID-19. Patients received VEKLURY (n=541) or placebo (n=521) for up to 10 days. The primary endpoint was time to recovery within 29 days after randomization. Secondary endpoints included clinical status of patients on Day 15 as assessed on an 8-point ordinal scale and incidence of new high-flow oxygen requirement or new mechanical ventilation or ECMO.[1]

*Seizure (n=1), infusion-related reaction (n=1).

†Seizure (n=1), infusion-related reaction (n=1), transaminases increased (n=3), ALT increased and AST increased (n=1), GFR decreased (n=2), acute kidney injury (n=3).

IMPORTANT SAFETY INFORMATION (cont'd)

Dosage and administration (cont'd)

- **Treatment duration:**
  - For patients who are hospitalized and require invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 10 days. VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19.
  - For patients who are hospitalized and do not require invasive mechanical ventilation and/or ECMO, the recommended treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended up to 5 additional days, for a total treatment duration of up to 10 days.
  - For patients who are not hospitalized, diagnosed with mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death, the recommended total treatment duration is 3 days. VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 and within 7 days of symptom onset.
- **Testing prior to and during treatment:** Perform eGFR, hepatic laboratory, and prothrombin time testing prior to initiating VEKLURY and during use as clinically appropriate.
- **Renal impairment:** VEKLURY is not recommended in individuals with eGFR <30 mL/min.
- **Dose preparation and administration:**
  - There are two different formulations of VEKLURY: VEKLURY for injection (supplied as 100 mg lyophilized powder in vial), the only approved dosage form of VEKLURY for pediatric patients weighing 3 kg to <40 kg; and VEKLURY injection (supplied as 100 mg/20 mL [5 mg/mL] solution in vial). See full Prescribing Information.
  - Administration should take place under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible.

Pregnancy and lactation

- **Pregnancy:** A pregnancy registry has been established. There are insufficient human data on the use of VEKLURY during pregnancy. COVID-19 is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.
- **Lactation:** It is not known whether VEKLURY can pass into breast milk. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Please see Brief Summary of full Prescribing Information on the following page.

References: 1. Veklury. Prescribing Information. Gilead Sciences, Inc.; 2022. **2.** Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med*. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764 **3.** Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group. Remdesivir for the treatment of COVID-19—final report. Supplementary appendix. *N Engl J Med*. 2020;383(19):1813-1826. Accessed May 24, 2022. https://www.nejm.org/doi/suppl/10.1056/NEJMoa2007764/suppl_file/nejmoa2007764_appendix.pdf

GILEAD

VEKLURY® (remdesivir)

Brief summary of full Prescribing Information. Please see full Prescribing Information. Rx Only.

INDICATIONS AND USAGE

VEKLURY is indicated for the treatment of COVID-19 in adults and pediatric patients (≥28 days old and weighing ≥3 kg), with positive results of SARS-CoV-2 viral testing, who are:

- Hospitalized, or
- Not hospitalized, with mild-to-moderate COVID-19, and at high risk for progression to severe COVID-19, including hospitalization or death.

DOSAGE AND ADMINISTRATION *[Also see **Warnings and Precautions, Adverse Reactions, and Use in Specific Populations**]*:

Testing Before Initiation and During Treatment: Perform eGFR, hepatic laboratory, and prothrombin time testing prior to initiating VEKLURY and during use as clinically appropriate.

Recommended Dosage in Adults and Pediatric Patients ≥28 Days Old and Weighing ≥3 kg:

- For adults and pediatric patients weighing ≥40 kg: 200 mg on Day 1, followed by once-daily maintenance doses of 100 mg from Day 2, administered only via intravenous infusion.
- For pediatric patients ≥28 days old and weighing ≥3 kg: 5 mg/kg on Day 1, followed by once-daily maintenance doses of 2.5 mg/kg from Day 2, administered only via intravenous infusion.

Treatment Duration:

- For patients who are hospitalized and require invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 10 days. VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19.
- For patients who are hospitalized and do not require invasive mechanical ventilation and/or ECMO, the recommended treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended up to 5 additional days, for a total treatment duration of up to 10 days.
- For patients who are not hospitalized, diagnosed with mild-to-moderate COVID-19, and at high risk for progression to severe COVID-19, including hospitalization or death, the recommended total treatment duration is 3 days. VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 and within 7 days of symptom onset.

Renal Impairment: VEKLURY is not recommended in individuals with eGFR <30 mL/min.

Dose Preparation and Administration *[See full **Prescribing Information** for complete instructions on dose preparation, administration, and storage]*:

VEKLURY must be prepared and administered under supervision of a healthcare provider and must be administered via intravenous infusion only, over 30 to 120 minutes. Do not administer the prepared diluted solution simultaneously with any other medication.

- VEKLURY for injection (supplied as 100 mg lyophilized powder in vial) must be reconstituted with Sterile Water for Injection prior to diluting in a 100 mL or 250 mL 0.9% sodium chloride infusion bag.
- Care should be taken during admixture to prevent inadvertent microbial contamination; there is no preservative or bacteriostatic agent present in these products.

Dosage Preparation and Administration in Pediatric Patients ≥28 Days of Age and Weighing 3 kg to <40 kg:

The only approved dosage form of VEKLURY for pediatric patients ≥28 days of age and weighing 3 kg to <40 kg is VEKLURY for injection (supplied as 100 mg lyophilized powder in vial). Carefully follow the product-specific preparation instructions.

CONTRAINDICATIONS *[Also see **Warnings and Precautions**]*:

VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any of its components.

WARNINGS AND PRECAUTIONS *[Also see **Contraindications, Dosage and Administration, Adverse Reactions,** and **Drug Interactions**]*:

Hypersensitivity, Including Infusion-related and Anaphylactic Reactions: Hypersensitivity, including infusion-related and anaphylactic reactions, has been observed during and following administration of VEKLURY; most reactions occurred within 1 hour. Monitor patients during infusion and observe for at least 1 hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate. Symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates (maximum infusion time ≤120 minutes) can potentially prevent these signs and symptoms. If a severe infusion-related hypersensitivity reaction occurs, immediately discontinue VEKLURY and initiate appropriate treatment.

Increased Risk of Transaminase Elevations: Transaminase elevations have been observed in healthy volunteers and in patients with COVID-19 who received VEKLURY; the transaminase elevations were mild to moderate (Grades 1-2) in severity and resolved upon discontinuation. Because transaminase elevations have been reported as a clinical feature of COVID-19, and the incidence was similar in patients receiving placebo versus VEKLURY in clinical trials, discerning the contribution of VEKLURY to transaminase elevations in patients with COVID-19 can be challenging. Perform hepatic laboratory testing in all patients.

- Consider discontinuing VEKLURY if ALT levels increase to >10x ULN.
- Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation.

Risk of Reduced Antiviral Activity When Coadministered With Chloroquine or Hydroxychloroquine: Coadministration of VEKLURY with chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments, demonstrating potential antagonism which may lead to a decrease in the antiviral activity of VEKLURY.

ADVERSE REACTIONS *[Also see **Warnings and Precautions**]*:

Clinical Trials Experience: The safety of VEKLURY is based on data from three Phase 3 studies in 1,313 hospitalized adult subjects with COVID-19, four Phase 1 studies in 131 healthy adults, and from patients with COVID-19 who received VEKLURY under the Emergency Use Authorization or in a compassionate use program. The NIAID ACTT-1 study was conducted in hospitalized subjects with mild, moderate, and severe COVID-19 treated with VEKLURY (n=532) for up to 10 days. Study GS-US-540-5773 (Study 5773) included subjects hospitalized with severe COVID-19 and treated with VEKLURY for 5 (n=200) or 10 days (n=197). Study GS-US-540-5774 (Study 5774) was conducted in hospitalized subjects with moderate COVID-19 and treated with VEKLURY for 5 (n=191) or 10 days (n=193).

Adverse Reactions: The most common adverse reaction (≥5% all grades) was nausea.

Less Common Adverse Reactions: Clinically significant adverse reactions reported in <2% of subjects exposed to VEKLURY in clinical trials include hypersensitivity reactions, generalized seizures, and rash.

Laboratory Abnormalities: In a Phase 1 study in healthy adults, elevations in ALT were observed in 9 of 20 subjects receiving 10 days of VEKLURY (Grade 1, n=8; Grade 2, n=1); the elevations in ALT resolved upon discontinuation. No subjects (0 of 9) who received 5 days of VEKLURY had graded increases in ALT.

Laboratory abnormalities (Grades 3 or 4) occurring in ≥3% of subjects receiving VEKLURY in Trials NIAID ACTT-1, Study 5773, and/or Study 5774, respectively, were ALT increased (3%, ≤8%, ≤3%), AST increased (6%, ≤7%, n/a), creatinine clearance decreased, Cockcroft-Gault formula (18%, ≤19%, ≤5%), creatinine increased (15%, ≤15%, n/a), eGFR decreased (18%, n/a, n/a), glucose increased (12%, ≤11%, ≤4%), hemoglobin decreased (15%, ≤8%, ≤3%), lymphocytes decreased (11%, n/a, n/a), and prothrombin time increased (9%, n/a, n/a).

DRUG INTERACTIONS *[Also see **Warnings and Precautions**]*:

Due to potential antagonism based on data from cell culture experiments, concomitant use of VEKLURY with chloroquine phosphate or hydroxychloroquine sulfate is not recommended.

Drug-drug interaction trials of VEKLURY and other concomitant medications have not been conducted in humans. Remdesivir and its metabolites are in vitro substrates and/or inhibitors of certain drug metabolizing enzymes and transporters. The clinical relevance of these in vitro assessments has not been established.

USE IN SPECIFIC POPULATIONS *[Also see **Dosage and Administration** and **Warnings and Precautions**]*:

Pregnancy

Risk Summary: There are insufficient human data on the use of VEKLURY during pregnancy to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. COVID-19 is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Lactation

Risk Summary: There are no available data on the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, remdesivir and metabolites have been detected in the nursing pups of mothers given remdesivir, likely due to the presence of remdesivir in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VEKLURY and any potential adverse effects on the breastfed child from VEKLURY or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Pediatric Use

The safety and effectiveness of VEKLURY for the treatment of COVID-19 have been established in pediatric patients ≥28 days old and weighing ≥3 kg. Use in this age group is supported by the following:

- Trials in adults
- An open-label trial (Study GS-US-540-5823) in 53 hospitalized pediatric subjects

Geriatric Use

Dosage adjustment is not required in patients over the age of 65 years. Appropriate caution should be exercised in the administration of VEKLURY and monitoring of elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of potential concomitant disease or other drug therapy.

Renal Impairment

All patients must have an eGFR determined before starting VEKLURY and while receiving VEKLURY as clinically appropriate. VEKLURY is not recommended in patients with eGFR less than 30 mL/min.

Hepatic Impairment

Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate.

OVERDOSAGE

There is no human experience of acute overdosage with VEKLURY. Treatment of overdose with VEKLURY should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with VEKLURY.

214787-GS-006

GILEAD

ISMP identifies non-COVID-19–related vaccine errors

Ariel L. Clark, PharmD

In a recent report published by the Institute of Safe Medical Practices (ISMP), more than 1,400 vaccine-related errors were reported and analyzed within the ISMP National Vaccine Errors Reporting Program (ISMP VERP) during a 19-month period from June 2020 to December 2021. The types of errors categorized in the report—32% unrelated to the COVID-19 pandemic—can be categorized into subgroups in order to help health care providers best learn how to avoid them in practice.

Age-related non-COVID-19 vaccine errors

Analysis of age-related vaccine errors by ISMP encompassed several subgroups of error types including wrong dose and wrong vaccine. These 2 error types accounted for 33% of all the non-COVID-19–related vaccine errors during the 19-month period analyzed by ISMP.

The final age-related vaccine errors analyzed in this report were the wrong age subgroup. While this report did not detail if this meant a dose was too low or too high, both instances can have negative consequences for the patient.

Authors of the report note that receiving a dose too low can leave the patient at risk of lower-than-ideal protection from illness, while receiving a dose too high for a patient's age can lead to increased risk of adverse events and can require additional monitoring for potentially dangerous adverse effects.

Vaccinations most likely to be related to age-related errors

ISMP further analyzed the age-related vaccine errors to determine which vaccinations were connected to the errors. The most common immunizations that incurred an age-related error, according to the report, were influenza; diphtheria; tetanus; and/or pertussis combinations, hepatitis A, and hepatitis B vaccines. ISMP noted that these 4 vaccines have occurred with similar frequency as compared to earlier VERP analytic reports; namely, those from 2012, 2014, and 2017.

The root cause of the errors related to these vaccines also remained similar to previous reports. The most commonly identified reason was the struggle to differentiate between "age-dependent formulations of the same vaccine," which accounted for 44% of the errors related to the 4 previously mentioned vaccinations.

ISMP noted that similar packaging and labeling between adult and pediatric doses cause major confusion for practitioners because they can have the same or similar names, colors, etc.

Vaccine-specific errors

A second grouping of vaccine errors identified in the 2022 report were related to the wrong vaccine being administered. These errors most often occurred in age-specific formulations, including those for diphtheria, tetanus, and/or pertussis combinations as well as influenza, meningococcal, measles, mumps, rubella and/or varicella vaccines. Unsurprisingly, the same root cause associated with age-related vaccines occurred in the majority of these cases, followed by storage of vaccine products near one another, thus increasing the likelihood of administering the wrong vaccine into a patient.

Best practices for avoiding vaccine-related errors

Maximizing technology encompasses a broad span of opportunities to reduce errors. According to the report, technology can be used to produce order sets, implement barcode scanning, and coalesce generic and brand-name entries in electronic health records to help limit confusion. Ordering age-dependent vaccines from alternate manufacturers and changing storage patterns can also help minimize errors.

The ISMP report notes that this can also help ensure that sound-alike/look-alike drugs and similarly packaged drugs are not as easily confused during fulfillment. Practitioners can also help to reduce errors by preparing documentation in advance of administration, properly labeling doses pulled from multidose vials, and by engaging and educating patients and fellow providers.

As vaccinations remain of vital importance to the protection of public health, health care practitioners can reflect on the 2022 ISMP VERP reports' common findings related to vaccine errors and use the recommendations to help ensure that the right vaccine goes in the right patient, at the right time and at the right dose. ■

Analysis of age-related vaccine errors by ISMP encompassed several subgroups of error types including wrong dose and wrong vaccine.

Top 5 questions about this year's flu vaccination

Brooke Whittington, PharmD

CDC estimates that the United States will experience a high influenza disease burden for the 2022–2023 season. CDC surveillance data from late October 2022 show that there have been more than 880,000 flu infections nationwide so far this season, including 6,900 hospitalizations and 360 deaths, making for an unusually early and brutal cycle.

Pharmacists are in a unique position to screen and identify patients in need of their flu vaccine and increase immunization rates within their community. Here's what pharmacists should know about the flu vaccination this season.

Is it safe to coadminister the COVID-19 and flu vaccines?

Yes, it is safe to administer both vaccines in the same visit if it is indicated. A CDC study published in 2022 found that patients who received both the flu and COVID-19 vaccines were somewhat more likely (8%–11%) to experience reactions such as fatigue, headache, and muscle ache, but concluded that it did not pose significant safety concerns.

Additionally, a retrospective cohort analysis completed in 2021 by the University of Miami Miller School of Medicine found patients with COVID-19 that received their flu vaccine were significantly less likely to visit the emergency department and be admitted to the ICU.

How can I stay up to date on infection rates?

Flu rates are projected to increase in frequency and severity this season compared to last year. A National Foundation for Infectious Diseases survey released in October 2022 found that only 49% of adults in the United States plan to receive their flu vaccine.

CDC provides a weekly flu surveillance report (FLUView) that is available online. Pharmacists should also check their local public health department agency's website for more information.

Are there inequities in flu vaccination rates among different groups? How can pharmacists address these health disparities?

CDC has found that Black, Hispanic, and American Indian/Alaska Native individuals have low vaccination rates and are more likely to be hospitalized with the flu. Patients who experience health inequities are also more likely to be diagnosed with comorbidities such as diabetes, asthma, and other health conditions. The flu may exacerbate or worsen these conditions, leading to poor health outcomes. Pharmacists can advocate for these vaccines within these communities through motivational interviewing and cultural sensitivity.

What is motivational interviewing and how can it be incorporated into everyday practice?

Misinformation continues to spread rampantly, and pharmacists are essential at countering vaccine hesitancy.

Motivational interviewing is a technique health care providers can use to build confidence and trust with patients.

Patients who experience health inequities are also more likely to be diagnosed with comorbidities such as diabetes, asthma, and other health conditions.

This can include the pharmacist actively listening, acknowledging the patient's concerns, and then asking permission to give advice. This method serves as a discussion versus a lecture, according to CDC.

What practice and education resources does APhA provide for more information about immunizations?

APhA offers a wide multitude of immunization resources and education that includes reference guides, vaccine technique, and technician integration in pharmacy immunization services training, and much more.

Check out APhA's Immunization Center on pharmacist.com for the latest information. ■

Court holds that pharmaceutical product placement may be a representation of product quality

David B. Brushwood, BSPharm, JD

Most states have consumer protection laws that authorize lawsuits against retailers who represent their products as having characteristics that the products actually do not have. Lawsuits alleging such misrepresentations can usually be pursued against retailers either by individual product purchasers or by nongovernmental public interest groups. A recent case from the District of Columbia reviewed allegations of unfair business practices against two retailers based on their placement of homeopathic remedies near the pharmacy area of their businesses.

The placement of a product on pharmacy shelving can be legally interpreted as a representation, by the product seller to the product user, that the product has scientific value.

Background

The plaintiff was an organization with a stated mission "to foster a secular society based upon science, reason, freedom of inquiry, and humanist values." The plaintiff alleged that "homeopathy is a pseudoscience and that the concepts on which it is based contradict the most fundamental understanding of science."

According to the court, the plaintiff's lawsuit contains "numerous factual allegations and accompanying photographs to the effect that: the defendant retailers market themselves as offering products that will enable customers to get healthy; persons suffering an ailment will often turn to the pharmacy section of their neighborhood [retailer] for relief; studies and patient experience have shown that homeopathic products are not effective; [the retailers] present homeopathic products alongside FDA-approved over-the-counter products, under aisle signs indicating that the aisles contain remedies for pain, colds, heartburn, and other conditions; and the retailers do so without informing customers that there is no scientific evidence that homeopathic products have any value in treating these symptoms and diseases."

The retailers moved to dismiss the lawsuit. The trial judge granted the motion to dismiss, ruling that the plaintiff had "failed to cite any pertinent scientific studies or legal authority that placing homeopathic products next to 'science-based' medicines is misleading to a reasonable consumer."

The plaintiff appealed.

Rationale

The appellate court first noted that whether a trade practice is misleading is generally a question of fact for a jury, and not a question of law for a court.

The appellate court said, "we do not find it facially implausible that a reasonable customer could believe, based on [the retailers'] placement of homeopathic drug products alongside FDA-approved over-the-counter drugs, that homeopathic products are comparably efficacious." The court agreed with the plaintiff that "whether signage and product placement influence consumers regarding the efficacy of medical products is a question that can be answered only with evidence and is not an inherently implausible assertion that can be dismissed out of hand."

The court concluded that the plaintiff's factual allegations "plausibly support an inference that, through their product placement practices, [the retailers] misled consumers into believing that homeopathic products are equivalent alternatives to FDA-approved over-the-counter drugs."

In reversing dismissal of the plaintiff's case against the retailers, the appellate court said, "we hold as a matter of law that the placement of a product can be a representation" under consumer protection laws.

Takeaways

As a result of this reversal on appeal, the case against the retailers will continue to trial unless it is settled out of court. The case itself has not yet been resolved. Yet an important point of law has been recognized by the appellate court. The placement of a product on pharmacy shelving can be legally interpreted as a representation, by the product seller to the product user, that the product has scientific value.

The court's ruling is a significant cautionary tale for pharmacies that stock products in ways that could be interpreted as misleading to purchasers. Based on this court's ruling, it would be prudent for pharmacies to

- Stock homeopathic remedies and other alternative products separately from FDA-recognized OTC products.
- Use signage that avoids any scientifically unsupportable claim of efficacy.
- Explain to patients each product's purported mechanism of action, and facilitate patient choice based on complete understanding of the product.
- Encourage patients to read all written information on labels affixed to products and in leaflets that accompany products. ■

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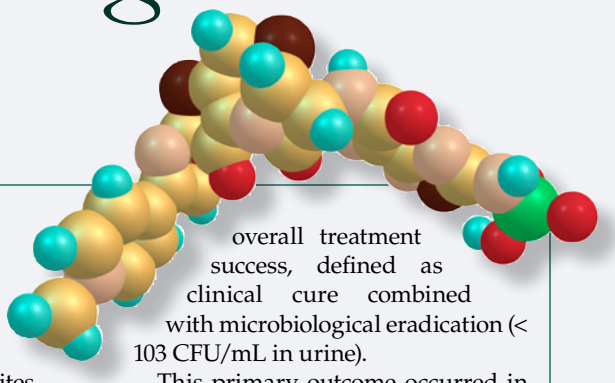

Cefepime/enmetazobactam may improve treatment for complicated UTI

Complicated UTIs are one of the most common causes of sepsis in hospitalized patients. While a simple UTI typically responds to antibiotic treatment within 24 to 48 hours, a complicated UTI doesn't respond to a single course of antibiotic treatment. These complicated UTIs often require treatment with broad-spectrum antibiotics.

In a paper published in the October 4, 2022, issue of *JAMA*, Kaye and colleagues investigated the efficacy of cefepime/enmetazobactam, a novel β-lactam/β-lactamase inhibitor combination, compared with piperacillin/tazobactam for the treatment of complicated UTI or acute pyelonephritis (a complication in which the infection spreads to the kidneys).

The researchers conducted a phase 3, randomized, double-blind, noninferiority clinical trial at 90 sites in Europe; North, Central, and South America; and South Africa.

Over 1,000 adult patients with a clinical diagnosis of complicated UTI or acute pyelonephritis caused by gram-negative urinary pathogens were randomized to receive either 2 g cefepime/0.5 g enmetazobactam or 4 g piperacillin/0.5 g tazobactam, by 2-hour infusion every 8 hours for 7 days (or up to 14 days in patients with a positive blood culture at baseline).

The primary outcome was the proportion of patients who achieved overall treatment success, defined as clinical cure combined with microbiological eradication (< 103 CFU/mL in urine).

This primary outcome occurred in 79.1% of patients receiving cefepime/enmetazobactam compared with 58.9% of patients receiving piperacillin/tazobactam. Treatment-emergent adverse events occurred in 50.0% of patients treated with cefepime/enmetazobactam and 44.0% of patients treated with piperacillin/tazobactam. Most adverse events were mild to moderate in severity.

The authors note that further research is needed to determine the potential role for cefepime/enmetazobactam in the treatment of complicated UTI and pyelonephritis. ■

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Does chronic medication use affect risk of COVID-19 death in hospitalized patients?

Among the questions raised during the pandemic is the potential association between chronic medication use and death due to COVID-19. Researchers from the Vall d'Hebron University Hospital (Barcelona) used a retrospective cross-sectional study to investigate the relationship between the use of various medications and the seriousness of COVID-19 infection.

The study, published on October 27, 2022, in the *European Journal of Hospital Pharmacy* included 978 patients hospitalized due to COVID-19 early in the pandemic. Of these patients, 4.2% were smokers, 16.7% were obese, 47.4% had hypertension, and 19.4% were diabetic; 182 patients died during the study follow up. Most patients (70.8%) were prescribed at least one medication, 32.5% used more than 5 medications, and 8.6% were prescribed more than 10 medications.

The study results suggest that hospitalized COVID-19 patients taking trimethoprim and analogues, leukotriene receptor antagonists, calcineurin inhibitors, aldosterone antagonists, selective immunosuppressants, propulsives, insulins and analogues, and benzodiazepine derivatives have a higher risk of death from COVID-19. The authors note that further research is needed to increase understanding of the impact of chronic medication use to increase understanding of the relevance of their results. ■

Simvastatin falls short in treatment of patients with Parkinson disease

Although current treatments for patients with Parkinson disease (PD) exist, there are no known treatments that slow disease progression. Preclinical and epidemiological studies support the potential use of statins as disease-modifying therapy, leading researchers from the PD STAT Study Group to investigate the efficacy of simvastatin to prevent clinical decline in patients with moderately severe Parkinson disease. The study was published in *JAMA Neurology* on October 31, 2022.

The randomized clinical trial, a double-blind, parallel-group, placebo-controlled futility trial, was conducted between March 2016 and May 2020 within 23 National Health Service Trusts in England. Participants aged 40 to 90 years with a diagnosis of idiopathic PD, with a modified Hoehn and Yahr stage of 3.0 or less while taking medication and taking dopaminergic medication with wearing-off phenomenon were included.

Participants were allocated 1:1 to simvastatin or matched placebo with patients in the simvastatin arm given 40 mg simvastatin daily for one month, followed by 23 months of 80 mg simvastatin daily and a 2-month washout period. The primary outcome was 24-month change in Movement Disorder Society Unified Parkinson Disease Rating Scale part III score measured while not taking medication,

Participants in the simvastatin group had an additional deterioration in Movement Disorder Society Unified Parkinson Disease Rating Scale part III scores while not taking medication compared with compared with the placebo group. The number of serious adverse events was similar in both groups.

The authors concluded that simvastatin was futile as a disease-modifying therapy in patients with moderately severe PD, providing no evidence to support proceeding to a Phase 3 trial. ■

Carbapenem-resistant *Klebsiella Pneumoniae* growing in U.S. hospitals

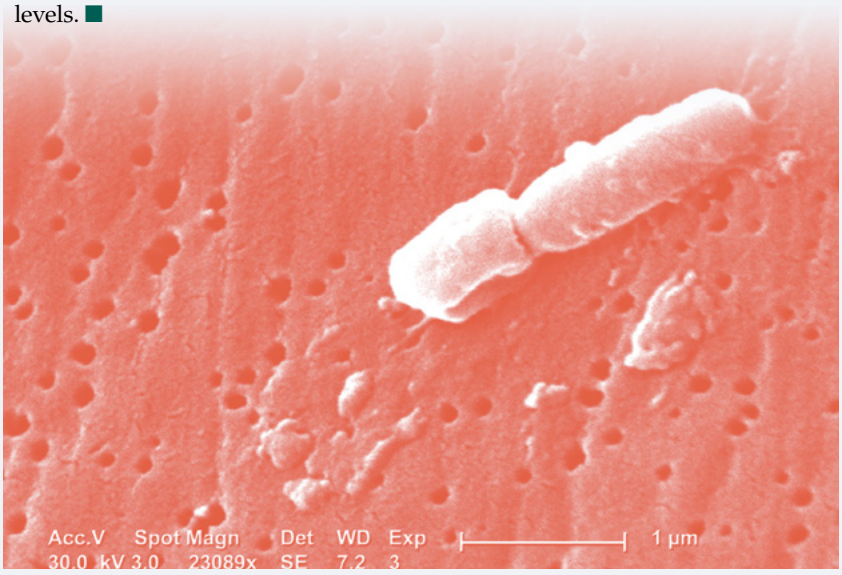
Carbapenem-resistant Enterobacterales, those that are either resistant to carbepenum antibiotics or contain a carbapenemase that make the antibiotic ineffective, are spreading within the U.S. hospital system. The genes responsible for carbapenemase production are often on mobile genetic elements, which can be easily shared between bacteria, leading to the rapid spread of resistance.

A recent study by van Duin and members of the Multi-Drug Resistant Organism Network Investigators Network Investigators and the Antibacterial Resistance Leadership Group published on September 29, 2022, in *Clinical Infectious Diseases* evaluated the spread of carbapenem-resistant Klebsiella pneumoniae (CRKp), the most prevalent carbapenem-resistant Enterobacterales in the United States. The study cohort consisted of 350 hospitalized patients with a single, positive culture for CG258 *K. pneumoniae* across 25 U.S. healthcare systems (with 42 hospitals) in 13 states and the District of Columbia from the Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacterales (CRACKLE-2) study.

The researchers evaluated samples from these hospitalized patients to better understand clustering in CRKp isolates. Their results showed evidence of extensive nosocomial transmission and spread of CG258 CRKp in U.S. hospitals.

Most patients had a CRKp isolate that could be genetically linked to an isolate of at least one other patient, regardless of the method used to assign clusters. Most patients were part of clusters with patients from the same health care system; however, about one-third of clusters showed evidence of transmission across health care systems.

The authors note that the occurrence of intersystem clusters may indicate involvement of other health care sites (e.g., skilled nursing facilities and long-term acute care hospitals) as well as the community in perpetuating CRKp spread and emphasize that successful control of multidrug-resistant organisms requires infection prevention measures at both local and regional levels. ■



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20378

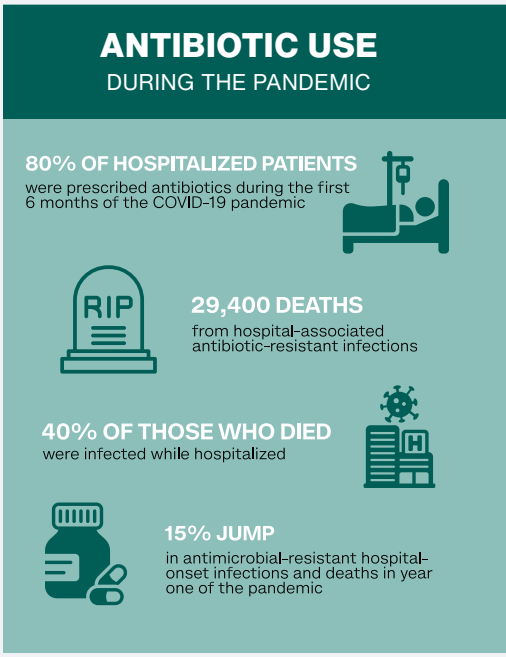
SHEA releases statement on antibiotic stewardship during public health emergencies

Sonya Collins

Eighty percent of patients hospitalized during the first 6 months of the COVID-19 pandemic were prescribed antibiotics on admission even though the antimicrobial drugs were rarely indicated at that point. The pandemic saw at least 29,400 deaths from hospital-associated antibiotic-resistant infections. Nearly 40% of those who died got the infection while hospitalized, according to CDC. The agency also reported that the antimicrobial-resistant hospital-onset infections and deaths jumped by at least 15% during the first year of the pandemic.

These findings represent major setbacks in the substantial progress made in combating antimicrobial resistance from 2012 to 2017. In response, the Society for Healthcare Epidemiology of America (SHEA) released a statement summarizing lessons learned about antimicrobial stewardship during the pandemic and offered guidance on antibiotic use in hospitals during public health emergencies.

"We just need to remember evidence-based medicine and practice from those principles," said Alan Gross, PharmD, a coauthor of the SHEA statement. "We should consider how much evidence we have for the interventions we're taking. If we don't have good evidence, we might be doing harm to the patient."



"We should consider how much evidence we have for the interventions we're taking. If we don't have good evidence, we might be doing harm to the patient."

Clinical uncertainty spurs antibiotic use

It may not come as a surprise that nonindicated antibiotic use rose in the early days of the COVID-19 pandemic.

The SHEA white paper identified several reasons for this. Among them were clinical uncertainty about signs of high-risk cases; providers' discomfort with taking no action at all for patients; and a shortage of PPE, which limited provider interaction with patients and lowered the threshold for starting and leaving patients on antibiotics.

"At the end of the day, everybody's trying to do the best thing for the patient, so it's kind of the nature of the beast," said Gross, who is a clinical associate professor in the College of Pharmacy at the University of Illinois-Chicago.

Add to that low threshold for starting antibiotics a high suspicion for co-occurring bacterial infections among patients hospitalized for COVID-19.

"There's often concomitant bacterial infections in patients with run-of-the-mill, community-acquired viruses, but with COVID, it was a shot in the dark," Gross said. In retrospect, he added, it was likely fewer than 2% of patients admitted to the hospital for COVID-19 that had concurrent bacterial infections.

The paper outlines other common triggers of antibiotic use including uncertainty about the COVID-19 diagnosis at a time when tests could be unreliable and results could be delayed, and concerns about hospital-acquired bacterial infections.

Stick to evidence, even in a pandemic

The SHEA statement offers best practices for improving antibiotic prescribing in hospitals during breakouts of new infectious diseases.

The authors recommend that providers limit the initiation of antibiotics, particularly broad-spectrum ones, in admitted patients with high likelihood of a viral infection, such as SARS-CoV-2 or influenza. They stress that providers follow this guideline even in the absence of readily available and accurate diagnostic tests.

The statement goes on to detail the circumstances in which providers might consider use of antibiotics in a respiratory viral epidemic and which tests might be necessary after initiation of antibiotics.

Importantly, the authors address the critical role of antimicrobial stewardship programs during outbreaks, epidemics, and pandemics, which should include monitoring emerging information and updates to national and international guidelines that are relevant to antibiotic prescribing; revising clinical recommendations relevant to antimicrobial use; and educating frontline health care providers on appropriate antibiotic use.

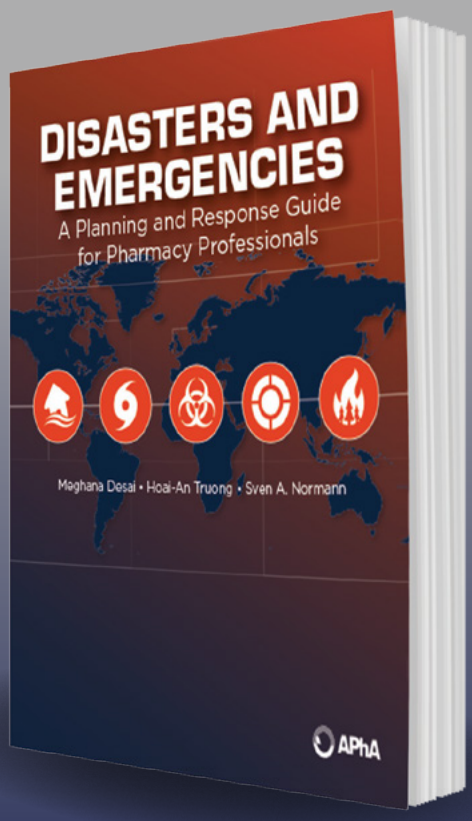
"We need to recognize the importance of antimicrobial stewardship programs and make sure that they are adequately resourced for future public health emergencies," Gross said. ■

APhA

Disasters and Emergencies:

A Planning and Response Guide for Pharmacy Professionals

By Meghana Desai, Hoai-An Truong and Sven A. Normann



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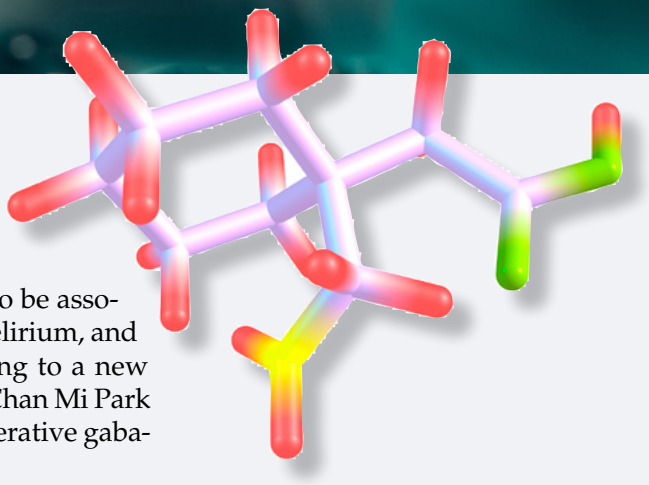

Perioperative gabapentin use associated with increased risk of adverse effects in older adults

Clarissa Chan, PharmD

Gabapentin use within 2 days postsurgery was found to be associated with increased risk of new antipsychotic use, delirium, and pneumonia as compared to no gabapentin use, according to a new study in *JAMA Internal Medicine* from September 2022 by Chan Mi Park and colleagues. They explored the safety profile of perioperative gabapentin use in patients 65 years and older.

Study significance

The investigators studied perioperative gabapentin use to better understand if nonopioid use in multimodal analgesia would be beneficial in reducing opioid use and its adverse effects to improve pain control safely.

Gabapentin exhibits its action in the same general neural space as benzodiazepines (benzos), barbiturates, some epilepsy medications, and even ethyl alcohol, which all come with their own respective baggage as well, said Mark Garofoli, PharmD, MBA, BCGP, CPE, a clinical assistant professor at West Virginia University School of Pharmacy.

"At some point, both society and health care professionals need to realize that substituting one sedative for another sedative is not exactly the 'holy grail' that it's meant to be," said Garofoli, who was not a part of the research team. "In the neverending quest for opioid-sparing or opioid-replacement pain management medications, one really needs to first consider this thought process."

This study highlights the reality that many folks will need other appropriate

alternative pain management options after surgical procedures.

"We're human, we feel pain; it keeps us away from harmful exposures, but we often need it attenuated to improve our function as well," he said.

Study design

The retrospective cohort study included adults 65 years or older who had major surgical procedures—including cardiac, gastrointestinal, genitourinary, orthopedic, neurological (excluding the brain), thoracic, and vascular surgery—at medium-sized hospitals between January 2009 to March 2018. Researchers extracted data using the Premier Healthcare Database approved by Boston's Brigham and Women's Hospital institutional review board.

Patients who died or were discharged before or on postoperative day 2 were excluded from the study, as were patients already taking gabapentin before surgery or had diagnosis codes for psychosis or for any indications that gabapentin may be prescribed—like alcohol use disorder, neuropathic pain, seizure, and social anxiety disorder—or had contraindications for the use of gabapentin like myasthenia gravis. Patients needing critical care measures who were unable to receive gabapentin orally were also excluded from the study.

Patients of various ages, sexes, races and ethnicities, insurance coverage types, hospital admission types, comorbidity diagnoses, and sources (outpatient, emergency department, transfer, or other), were included in the study.

After inclusion and exclusion criteria were applied, out of a total of 967,547 patients, 119,087 of them received gabapentin between surgery day and 2 days postsurgery.

Gabapentin is one of the "poster kids" for "start low, go slow" dosing, as dosage-related adverse effects can often cause a patient to no longer utilize the medication.

Patients receiving gabapentin were more likely to be female, younger, undergo elective surgeries, and were less likely to have comorbidities than gabapentin nonusers.

Results

While patients 65 years and older who received gabapentin were found to experience fewer adverse effects than nonusers prior to propensity score matching, afterward they were found to be at increased risk of delirium, new antipsychotic use, and pneumonia when compared to gabapentin nonusers after major surgery.

In a subgroup analysis, gabapentin users younger than 80 years were more likely to experience delirium than patients older than 80 years. No association was found with gabapentin use and hospital-related death.

"This study, of almost a million patients whittled down to just under a quarter million patients, showed that this medication works relatively similarly to benzodiazepines, barbiturates, and alcohol caused delirium compared to those not utilizing the medication," said Garofoli. "I hope that very few, if any, clinicians are surprised by that finding."

Although new atypical antipsychotic medication utilization and pneumonia were also found to be increased with statistical significance, the appreciable actual raw number difference and clinical applicability were of much less profound impact, said Garofoli.

"At some point, both society and health care professionals need to realize that substituting one sedative for another sedative is not exactly the 'holy grail' that it's meant to be."

Key limitation

"There was no detail regarding the gabapentin doses, which is extremely concerning on multiple fronts, yet primarily because, to paraphrase Paracelsus, 'It's all about the dosage, baby!'" said Garofoli.

Gabapentin exhibits saturated pharmacokinetic absorption properties, meaning that the higher the dose, the lower the percentage of absorption. Gabapentin is one of the "poster kids" for "start low, go slow" dosing, as dosage-related adverse effects can often cause a patient to no longer utilize the medication, said Garofoli.

"Thus, not discussing the observed gabapentin doses is a significant limitation of this article," he noted.

Takeaways

Pharmacists should carefully weigh the benefits versus risks of perioperative gabapentin use especially in older adults. An individualized treatment plan is advised by the authors of the study to reduce the risk of immediate harms when using multimodal analgesia to help patients improve their recovery. ■

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CGM = continuous glucose monitoring.

*Based on net promoter score Dexcom 81 vs. Abbott 27 (Medtronic 10).

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References: 1. Managed Markets Insights & Technology, LLC. MMIT Analytics, June 2022 **2.** Seagrove HCP Survey Q121, p65. **3.** dQ&A US Q1 2021 Diabetes Connections Patient Panel Report. 2021;69-72 **4.** IQVIA, February 2022

Dexcom

List of medication safety best practices grows in most recent update

Olivia C. Welter, PharmD

The Institute for Safe Medicine Practices (ISMP) updates its Targeted Medication Safety Best Practices for Hospitals list biannually. The original 6 best practices were published in 2014, with each review resulting in added guidance. The 2022–2023 edition includes 3 new best practices—highlighted below—that focus on error prevention and improving safety.

Oxytocin use

The first of the new best practices is for safeguarding against errors with oxytocin use. Oxytocin is widely used for pregnant patients in labor, and errors in its administration could cause severe medical issues. A major focus of this best practice is on process standardization. Here is what ISMP recommends for improved safety when using oxytocin:

- Standard oxytocin prescribing order sets for labor management and control of postpartum bleeding should be required, as it removes room for prescriber error when entering orders for the drug.
- Oxytocin concentration and bag size should be standardized for patients needing infusions in both antepartum and postpartum situations.
- Pharmacies should maintain stock of ready-to-use bags for oxytocin infusion in their inventory, labeling the bags boldly to differentiate them from regular hydrating infusions.
- Oxytocin infusion orders should be communicated using dose rates which are compatible with the hospital's smart infusion pump dose error-reduction system.
- Like with all medications, hospital staff should only bring oxytocin infusion bags to the patient's room or bedside when it has been prescribed and is actively needed.

When asked why ISMP decided to focus on oxytocin specifically in this best practice, Christina Michalek, RPh, FASHP, ISMP director of membership and patient safety organization, replied that "Organizations may have adopted some of the recommendations listed. However, we were seeing room for improvement. For example, some organizations adopted a standard infusion concentration, but there were some practitioners or care settings within the organization [in which cases] the standard was not used."

> "Organizations may have adopted some of the recommendations listed. However, we were seeing room for improvement."

Barcode verification

While barcoding is widely implemented in inpatient settings, other types of care areas may not be using it to its fullest potential. This added best practice encourages hospitals to incorporate barcoding to the maximum extent in areas where patient stays tend to be limited. ISMP made the following recommendations related to barcoding:

- Hospitals should specifically target clinical areas, which hold patients for short periods when implementing barcoding more universally. Such areas include EDs, perioperative areas, infusion clinics, dialysis centers, radiology areas, labor and delivery areas, catheterization laboratories, and outpatient areas.
- Reviewing compliance and other metrics, including number of bypassed or acknowledged alerts, is an additional strategy hospitals can adopt to ensure effectiveness of the safety technology.

"Although the safeguard is commonly used in inpatient care areas, adoption tends to lag in procedural settings and other areas, particularly where there is a short or limited patient encounter. Expanding barcode verification to these areas will help to prevent errors," said Michalek.

Layered medication safety strategies

The third and final addition to the best practices list suggests strategies that hospitals can implement and layer to maximize safety with high-alert medications. Here are the recommendations set forth by ISMP for layered safety strategies:

- Hospitals should outline individual procedures for managing risk of each medication on the hospital's high-alert list, being sure to confront vulnerabilities within systems at each stage of the medication use process.
- Hospital staff should focus on mid- to high-leverage risk reduction strategies to prevent errors, avoiding low-leverage strategies, which are associated with higher error rates.
- Care teams should limit use of independent double-checks when managing high-alert medications with a high risk for error, such as chemotherapy, opioid infusions, intravenous insulin, and heparin infusions.
- Hospitals should regularly assess aspects of their risk management practices by using information from internal sources and should additionally consult external sources such as The Joint Commission, ISMP, and FDA.
- Hospitals should have an ongoing commitment to maintaining risk mitigation by establishing measures that can be used for monitoring safety and collecting data to determine effectiveness of implemented strategies.

"Events continue to happen in hospitals with medications that are on the hospital's list of high-alert medications," said Michalek. "Many organizations rely primarily on midrange error-reduction strategies, such as implementing a double-check, and fail to add robust strategies throughout the entire medication use process." ■

RYLAZE®

asparaginase erwinia chrysanthemi (recombinant)-rywn

for injection
10mg/0.5mL per vial

Indication

RYLAZE is indicated as a component of a multi-agent chemotherapeutic regimen given by intramuscular injection for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.

IMPORTANT SAFETY INFORMATION

Contraindications

RYLAZE is contraindicated in patients with a history of:

- Serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis
- Serious pancreatitis during previous asparaginase therapy
- Serious thrombosis during previous asparaginase therapy
- Serious hemorrhagic events during previous asparaginase therapy

Warnings and Precautions

Hypersensitivity Reactions

Hypersensitivity reactions after the use of RYLAZE occurred in 25% of patients in clinical trials, and it was severe in 2% of patients. The median time from the first dose of RYLAZE to the onset of the first hypersensitivity event was 27 days (range 1-171 days). The most commonly observed reaction was rash (17%), and no patient experienced a severe rash. The median time from the first dose to the first onset of rash was 33.5 days (range 1-127 days).

Hypersensitivity reactions observed with L-asparaginase class products include angioedema, urticaria, lip swelling, eye swelling, rash or erythema, blood pressure decreased, bronchospasm, dyspnea, and pruritus.

Because of the risk of serious allergic reactions (e.g., life-threatening anaphylaxis), administer RYLAZE in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, oxygen, intravenous steroids, antihistamines). Discontinue RYLAZE in patients with serious hypersensitivity reactions.

Pancreatitis

Pancreatitis was reported in 14% of patients in clinical trials of RYLAZE and was severe in 6%. Clinical pancreatitis occurred in 5% of patients, and it was severe in 4% of patients. Elevated amylase or lipase without clinical diagnosis of pancreatitis was observed in 9% of patients, and it was severe in 2% of patients treated with RYLAZE. Hemorrhagic or necrotizing pancreatitis have been reported with L-asparaginase class products.

Inform patients of the signs and symptoms of pancreatitis, which, if left untreated, could be fatal. Evaluate patients with symptoms compatible with pancreatitis to establish a diagnosis. Assess serum amylase and lipase levels in patients with any signs or symptoms of pancreatitis. Discontinue RYLAZE in patients with severe or hemorrhagic pancreatitis. In the case of mild pancreatitis, withhold RYLAZE until the signs and symptoms subside and amylase and/or lipase levels return to 1.5 times the ULN. After resolution of mild pancreatitis, treatment with RYLAZE may be resumed.

Thrombosis

Serious thrombotic events, including sagittal sinus thrombosis and pulmonary embolism, have been reported following treatment with L-asparaginase class products. Discontinue RYLAZE for a thrombotic event, and administer appropriate antithrombotic therapy. Consider resumption of treatment with RYLAZE only if the patient had an uncomplicated thrombosis.

RELY ON RYLAZE

THE ONLY FDA-APPROVED *ERWINIA* ASPARAGINASE FOR THE TREATMENT OF ALL/LBL[1]

After a patient experiences an HSR, switching to an asparaginase with no immunologic crossreactivity can help protect patient outcomes.[2]

Hemorrhage
Bleeding was reported in 17% of patients treated with RYLAZE, and it was severe in 1%. Most commonly observed reactions were bruising (8%) (contusion, increased tendency to bruise and injection site bruising) and nose bleeding (6%), which was severe in 1% of patients. Other observed bleeding reactions included hematuria (2%), disseminated intravascular coagulopathy (1%), rectal bleeding (1%) and gingival bleeding (1%).

In patients treated with asparaginase class products, hemorrhage may be associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia. Consider appropriate replacement therapy in patients with severe or symptomatic coagulopathy.

Hepatotoxicity
Elevated bilirubin and/or transaminases occurred in 62% of patients treated with RYLAZE in clinical trials, and 12% had Grade ≥3 elevations.

Inform patients of the signs and symptoms of hepatotoxicity. Evaluate bilirubin and transaminases prior to treatment every 2-3 weeks and as indicated clinically during treatment with RYLAZE. In the event of serious liver toxicity, discontinue treatment with RYLAZE and provide supportive care.

Adverse Reactions
Serious adverse reactions occurred in 55% of patients who received RYLAZE. The most frequent serious adverse reactions (in ≥5% of patients) were febrile neutropenia, dehydration, pyrexia, stomatitis, diarrhea, drug hypersensitivity, infection, nausea, and viral infection.

The most common adverse reactions (incidence >20%) with RYLAZE are abnormal liver test (70%), nausea (46%), musculoskeletal pain (39%), fatigue (36%), infection (30%), headache (30%), pyrexia (27%), drug hypersensitivity (24%), febrile neutropenia (24%), decreased appetite (21%), stomatitis (21%), bleeding (21%), and hyperglycemia (21%).

Use in Specific Populations
Pregnancy and Lactation
RYLAZE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective non-hormonal contraceptive methods during treatment with RYLAZE and for 3 months after the last dose. Advise women not to breastfeed during treatment with RYLAZE and for 1 week after the last dose.

Please see following pages for Brief Summary of full Prescribing Information.

ALL=acute lymphoblastic leukemia; HSR=hypersensitivity reaction; LBL=lymphoblastic lymphoma.

References: 1. RYLAZE [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica.* 2016;101(3):279-285.

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RYLAZE™ (asparaginase erwinia chrysanthemi (recombinant)-rywn) injection, for intramuscular use

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION: Consult the full Prescribing Information for complete product information. Initial U.S. Approval: 2021

INDICATIONS AND USAGE

RYLAZE is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase.

DOSAGE AND ADMINISTRATION

Recommended Dosage

When replacing a long-acting asparaginase product, the recommended dosage of RYLAZE is 25 mg/m^2 administered intramuscularly every 48 hours.

See the full prescribing information for the long-acting asparaginase product to determine the duration of administration of RYLAZE as replacement therapy.

Recommended Monitoring and Dosage Modifications for Adverse Reactions

Monitor patient's bilirubin, transaminases, glucose, and clinical examinations prior to treatment every 2-3 weeks and as indicated clinically. If results are abnormal, monitor patients until recovery from the cycle of therapy. If an adverse reaction occurs, modify treatment according to Table 1.

CONTRAINDICATIONS

RYLAZE is contraindicated in patients with a history of:

- Serious hypersensitivity reactions to *Erwinia asparaginase*, including anaphylaxis *[see Warnings and Precautions]*;
- Serious pancreatitis during previous asparaginase therapy *[see Warnings and Precautions]*;
- Serious thrombosis during previous asparaginase therapy *[see Warnings and Precautions]*;
- Serious hemorrhagic events during previous asparaginase therapy *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions after the use of RYLAZE occurred in 25% of patients in clinical trials, and it was severe in 2% of patients *[see Adverse Reactions]*. The median time from the first dose of RYLAZE to the onset of the first hypersensitivity event was 27 days (range 1-171 days). The most commonly observed reaction was rash (17%), and no patient experienced a severe rash. The median time from the first dose to the first onset of rash was 33.5 days (range 1-127 days).

Hypersensitivity reactions observed with L-asparaginase class products include angioedema, urticaria, lip swelling, eye swelling, rash or erythema, blood pressure decreased, bronchospasm, dyspnea, and pruritus.

Because of the risk of serious allergic reactions (e.g., life-threatening anaphylaxis), administer RYLAZE in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, oxygen, intravenous steroids, antihistamines) *[see Dosage and Administration]*. Discontinue RYLAZE in patients with serious hypersensitivity reactions.

Pancreatitis

Pancreatitis was reported in 14% of patients in clinical trials of RYLAZE and was severe in 6% *[see Adverse Reactions]*. Clinical pancreatitis occurred in 5% of patients, and it was severe in 4% of patients. Elevated amylase or lipase without clinical diagnosis of pancreatitis was observed in 9% of patients, and it was severe in 2% of patients treated with RYLAZE. Hemorrhagic or necrotizing pancreatitis have been reported with L-asparaginase class products.

Inform patients of the signs and symptoms of pancreatitis, which, if left untreated, could be fatal. Evaluate patients with symptoms compatible with pancreatitis to establish a diagnosis. Assess serum amylase and lipase levels in patients with any signs or symptoms of pancreatitis. Discontinue RYLAZE in patients with severe or hemorrhagic pancreatitis. In the case of mild pancreatitis, withhold RYLAZE until the signs and symptoms subside and amylase and/or lipase levels return to 1.5 times the ULN *[see Dosage and Administration]*. After resolution of mild pancreatitis, treatment with RYLAZE may be resumed.

TABLE 1: Dosage Modifications

Adverse Reaction	Severity*	Action
Hypersensitivity Reaction *[see Warnings and Precautions]*	Grade 2	• Treat the symptoms.
	Grade 3 to 4	• Discontinue RYLAZE permanently.
Pancreatitis *[see Warnings and Precautions]*	Grade 2 to 4	• Hold RYLAZE for elevations in lipase or amylase >2 times the ULN, or for symptomatic pancreatitis. • Resume treatment when lipase and amylase are <1.5 times the ULN and symptoms are resolved. • Discontinue RYLAZE permanently if clinical necrotizing or hemorrhagic pancreatitis is confirmed.
Thrombosis *[see Warnings and Precautions]*	Uncomplicated thrombosis	• Hold RYLAZE. • Treat with appropriate antithrombotic therapy. • Upon resolution of symptoms, consider resuming RYLAZE, while continuing antithrombotic therapy.
	Severe or life-threatening thrombosis	• Discontinue RYLAZE permanently. • Treat with appropriate antithrombotic therapy.
Hemorrhage *[see Warnings and Precautions]*	Grade 3 to 4	• Hold RYLAZE. • Evaluate for coagulopathy and consider clotting factor replacement as needed. • Resume RYLAZE with the next scheduled dose if bleeding is controlled.
Hepatotoxicity *[see Warnings and Precautions]*	Total bilirubin >3 times to ≤10 times the ULN	• Hold RYLAZE until total bilirubin levels decrease to ≤1.5 times the ULN.
	Total bilirubin >10 times the ULN	• Discontinue RYLAZE and do not make up missed doses.

*Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Thrombosis

Serious thrombotic events, including sagittal sinus thrombosis and pulmonary embolism, have been reported following treatment with L-asparaginase class products. Discontinue RYLAZE for a thrombotic event, and administer appropriate antithrombotic therapy. Consider resumption of treatment with RYLAZE only if the patient had an uncomplicated thrombosis *[see Dosage and Administration]*.

Hemorrhage

Bleeding was reported in 17% of patients treated with RYLAZE, and it was severe in 1%. Most commonly observed reactions were bruising (8%) (contusion, increased tendency to bruise, and injection site bruising) and nose bleeding (6%), which was severe in 1% of patients. Other observed bleeding reactions included hematuria (2%), disseminated intravascular coagulopathy (1%), rectal bleeding (1%), and gingival bleeding (1%) *[see Adverse Reactions]*.

In patients treated with asparaginase class products, hemorrhage may be associated with increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenemia. Consider appropriate replacement therapy in patients with severe or symptomatic coagulopathy *[see Dosage and Administration]*.

Hepatotoxicity

Elevated bilirubin and/or transaminases occurred in 62% of patients treated with RYLAZE in clinical trials, and 12% had Grade ≥3 elevations *[see Adverse Reactions]*.

Inform patients of the signs and symptoms of hepatotoxicity. Evaluate bilirubin and transaminases prior to treatment every 2-3 weeks and as indicated clinically during treatment with RYLAZE. In the event of serious liver toxicity, discontinue treatment with RYLAZE and provide supportive care *[see Dosage and Administration]*.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described in greater detail in other sections of the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Pancreatic Toxicity *[see Warnings and Precautions]*
- Thrombosis *[see Warnings and Precautions]*
- Hemorrhage *[see Warnings and Precautions]*
- Hepatotoxicity *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of RYLAZE described in the WARNINGS AND PRECAUTIONS reflect exposure to RYLAZE at various dosages, including dosage other than the recommended, used in combination with chemotherapy in 102 patients in JZP458-201. These patients received a median of 3 courses of RYLAZE (range: 1-14 courses); 38% of patients received at least four courses.

The safety of RYLAZE described below was evaluated in a cohort of 33 patients from JZP458-201 who received RYLAZE 25 mg/m^2 intramuscularly on Monday, Wednesday, and Friday for 6 doses as a replacement for a single dose of pegaspargase as a component of multi-agent chemotherapy. The patients had a median age of 11 years (range: 1 to 24 years); the majority of patients were male (51%) and white (73%). The patients received a median of 4 courses of RYLAZE (range: 1-14 cycles); 48% of patients received at least four courses.

A fatal adverse reaction (infection) occurred in 1 patient treated with the RYLAZE 25 mg/m^2 dosage. Serious adverse reactions occurred in 55% of patients who received the RYLAZE 25 mg/m^2 dosage. The most frequent serious adverse reactions (in ≥5% of patients) were febrile neutropenia, dehydration, pyrexia, stomatitis, diarrhea, drug hypersensitivity, infection, nausea, and viral infection. Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received the RYLAZE 25 mg/m^2 dosage. Adverse reactions resulting in permanent discontinuation included hypersensitivity (6%) and infection (3%).

All patients treated with the RYLAZE 25 mg/m^2 dosage as a component of multi-agent chemotherapy developed neutropenia, anemia, or thrombocytopenia. The most common nonhematological adverse reactions in patients were abnormal liver test, nausea, musculoskeletal pain, fatigue, infection, headache, pyrexia, drug hypersensitivity, febrile neutropenia, decreased appetite, stomatitis, bleeding, and hyperglycemia. Table 2 shows the common adverse reactions occurring in at least 15% of the patients.

Clinically relevant adverse reactions in <15% of patients who received RYLAZE in combination with chemotherapy included:

Gastrointestinal disorders: Abdominal discomfort, abdominal distension, pancreatitis
General disorders and administration site conditions: Infusion site reaction, pain
Infections and infestations: Viral infection, bacterial infection, fungal infection
Investigations: Blood fibrinogen decreased, activated partial thromboplastin time prolonged
Metabolism and nutrition disorders: Acidosis
Musculoskeletal and connective tissue disorders: Bone pain, muscular weakness, muscle spasms
Nervous system disorders: Paresthesia
Psychiatric disorders: Agitation, anxiety, irritability

TABLE 2: Adverse Reactions (≥15% incidence) in Patients Receiving RYLAZE 25 mg/m^2 as a Component of Multi-Agent Chemotherapy in Study JZP458-201

	RYLAZE 25 mg/m^2 Dosage[a] N=33	
Adverse Reaction	**All Grades (%)**	**Grades 3-4 (%)**
Abnormal liver test*	70	12
Nausea*	46	9
Musculoskeletal pain*	39	6
Fatigue*	36	3
Infection*[b]	30	12
Headache	30	0
Pyrexia	27	6
Drug hypersensitivity*	24	6
Febrile neutropenia	24	24
Decreased appetite	21	6
Stomatitis	21	9
Bleeding*	21	0
Hyperglycemia	21	3
Abdominal pain*	18	0
Tachycardia*	18	0
Diarrhea*	18	6
Constipation	15	0
Dehydration	15	9
Neuropathy peripheral*	15	0
Cough	15	0
Insomnia	15	0

*Includes grouped terms.
Grading is based on Common Terminology Criteria for Adverse Events version 5.0.
[a]RYLAZE was administered as a component of multi-agent chemotherapy regimens.
[b]Does not include the following fatal adverse reactions: infection (N=1).
Safety data for patients treated on a Monday, Wednesday, and Friday schedule.

Renal and urinary disorders: Acute kidney injury
Skin and subcutaneous disorders: Pruritus
Vascular disorders: Hypotension

Immunogenicity
The incidence of ADA and subsequent effects on pharmacokinetics, pharmacodynamics, safety, or effectiveness have not been established.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Based on findings from animal reproduction studies, RYLAZE can cause fetal harm when administered to a pregnant woman. There are no available data on RYLAZE use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproductive and developmental toxicity studies, intramuscular administration of asparaginase *Erwinia chrysanthemi* to pregnant rats and rabbits during organogenesis resulted in structural abnormalities and embryo-fetal mortality *(see Data)* at exposures below those in patients at the recommended human dose. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Data
Animal Data
Animal reproductive and developmental toxicity studies have not been conducted with RYLAZE. In embryofetal development studies, asparaginase *Erwinia chrysanthemi* was administered intramuscularly every other day during the period of organogenesis to pregnant rats (at 3, 6, or 12 mg/m^2) and rabbits (at 0.12, 0.30, or 0.48 mg/m^2). In rats given 12 mg/m^2 (approximately 0.48 times the maximum recommended human dose), maternal toxicity of decreased body weight gain was observed, as was a fetal finding of increased incidence of partially undescended thymic tissue. In rabbits, maternal toxicity consisting of decreased body weight was observed at 0.48 mg/m^2 (approximately 0.02 times the maximum recommended human dose). Increased post-implantation loss, a decrease in the number of live fetuses, and gross abnormalities (e.g., absent kidney, absent accessory lung lobe, additional subclavian artery, and delayed ossification) were observed at doses of ≥0.12 mg/m^2 (approximately 0.005 times the maximum recommended human dose).

Lactation
Risk Summary
There are no data on the presence of asparaginase erwinia chrysanthemi (recombinant)-rywn in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for adverse reactions in the breastfed child, advise women not to breastfeed during treatment with RYLAZE and for 1 week after the last dose.

Females and Males of Reproductive Potential
RYLAZE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing
Pregnancy testing is recommended in females of reproductive potential prior to initiating RYLAZE.

Contraception
Advise females of reproductive potential to use effective non-hormonal contraceptive methods during treatment with RYLAZE and for 3 months after the last dose.

Pediatric Use
The safety and effectiveness of RYLAZE in the treatment of ALL and LBL have been established in pediatric patients 1 month to <17 years who have developed hypersensitivity to a long-acting *E. coli*-derived asparaginase. Use of RYLAZE in these age groups is supported by evidence from an adequate and well-controlled study in adults and pediatric patients. The trial included 84 pediatric patients, including 2 infants (1 month to <2 years), 62 children (2 years to <12 years old), and 20 adolescents (12 years to <17 years old). There were no clinically meaningful differences in safety or nadir serum asparaginase activity across age groups. The safety and effectiveness of RYLAZE have not been established in pediatric patients younger than 1 month of age.

Geriatric Use
Clinical studies of RYLAZE did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients.

PATIENT COUNSELING INFORMATION

- Hypersensitivity
  Inform patients of the risk of allergic reactions, including anaphylaxis. Instruct the patient on the symptoms of allergic reactions and to seek medical advice immediately if they experience such symptoms *[see Warnings and Precautions]*.
- Pancreatitis
  Instruct patients on signs and symptoms of pancreatitis and to seek medical attention if they experience severe abdominal pain *[see Warnings and Precautions]*.
- Thrombosis
  Instruct patients on the risk of thrombosis and to seek medical advice immediately if they experience headache, arm or leg swelling, shortness of breath, and chest pain *[see Warnings and Precautions]*.
- Hemorrhage
  Advise patients to report any unusual bleeding or bruising to their healthcare provider *[see Warnings and Precautions]*.
- Hepatoxicity
  Advise patients to report any jaundice, severe nausea or vomiting, or easy bleeding or bruising to their healthcare provider *[see Warnings and Precautions]*.
- Pregnancy
  Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations]*.
  Advise females of reproductive potential to use effective non-hormonal contraception during treatment with RYLAZE and for 3 months after the last dose *[see Use in Specific Populations]*.
- Lactation
  Advise women not to breastfeed during treatment with RYLAZE and for 1 week after the last dose *[see Use in Specific Populations]*.

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Jazz Pharmaceuticals

Landmark trial suggests aggressive fluid therapy in pancreatitis may cause more harm than good

Corey Diamond, PharmD

Randomized controlled trials that investigate the optimal parameters of fluid resuscitation in acute pancreatitis—such as the rate of infusion or the total volume of fluid to be infused—remain scarce. However, the newly published WATERFALL trial, published on September 15, 2022, in the *New England Journal of Medicine*, sought to answer if current guidance is too aggressive.

The study found no statistical clinical benefit in patients with acute pancreatitis treated with early aggressive fluid resuscitation versus patients treated with moderate resuscitation. Additionally, patients given early aggressive resuscitation had a much higher frequency of developed fluid overload compared to the moderate resuscitation group.

Study design

The WATERFALL trial included 249 patients from India, Italy, Mexico, and Spain. They were part of the randomized trial if they presented to the ED within 24 hours of pain onset and had been diagnosed with acute pancreatitis within 8 hours of arrival. Patients were excluded if they met criteria for moderately severe or severe pancreatic disease.

The patients were randomized in a 1:1 ratio to receive either aggressive fluid resuscitation or moderate fluid resuscitation. Aggressive resuscitation—representing the current standard of care—was defined as a bolus of lactated Ringer's solution (LR) at a dose of 20 mL/kg of body weight administered over a period of 2 hours, followed by infusion at a rate of 3 mL/kg per hour. Moderate fluid resuscitation was defined as LR at a dose of 1.5 mL/kg per hour. The protocol allowed the moderate resuscitation group to receive a 10 mL/kg bolus if the patient was also diagnosed with hypovolemia.

The trial's primary efficacy outcome was the development of moderately severe or severe acute pancreatitis during hospitalization. This was defined as meeting at least one of the Revised Atlanta Classification criteria of local complications, exacerbation of a pre-existing coexisting condition, a creatinine level of at least 1.9 mg/dL, a systolic blood pressure of > 90 mm Hg despite fluid resuscitation, or a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of no more than 300.

The main safety outcome was the occurrence of fluid overload, defined as the incidence of symptoms, physical signs, and imaging evidence of hypervolemia during hospitalization.

Results

The researchers found no significant difference between the two groups. However, roughly 17% of the patients receiving moderate fluid resuscitation progressed to moderately severe and severe pancreatitis, compared to roughly 22% in the aggressive resuscitation arm—an adjusted relative risk increase of 30%.

The trial also found a stark statistically significant difference in the rates of fluid overload between the two groups. Patients receiving the aggressive fluid treatment had a fluid overload of roughly 20%, versus roughly 6% in the moderate resuscitation arm. In fact, due to the lack of significance in the efficacy outcomes and the pronounced significance in the safety outcome, the trial was halted early

Practice implications

Acute pancreatitis is not the most pervasive disease in the acute care setting. However, it is rising globally and challenging the health care system. Nearly one-third of acute pancreatitis patients progress to severe disease, often resulting in significant morbidity and mortality.

Targeted pharmacological treatment options for acute pancreatitis are practically nonexistent currently. Consequently, most treatment strategies are derived from observational studies that have shown that aggressive fluid crystalloid resuscitation, principally with LR, reduces pancreatic necrosis and mortality by mitigating pancreatic hypoperfusion. However, this recommendation is controversial in light of recent randomized trials, some with questionable quality, that suggest overaggressive fluid resuscitation may increase the risk of sepsis and mortality.

> "These findings do not support current management guidelines, which recommend early aggressive resuscitation for the treatment of acute pancreatitis."

"These findings do not support current management guidelines, which recommend early aggressive resuscitation for the treatment of acute pancreatitis," the authors stated. They went on to detail that patients with acute pancreatitis treated with aggressive fluid resuscitation experienced a higher intensity of symptoms, a longer duration of hospital stay, and a higher incidence of necrotizing pancreatitis than those who had received moderate fluid resuscitation.

"The absence of an efficacy signal for aggressive hydration is of practical importance given that it challenges a strong predilection in many clinicians for the use of early high-volume hydration," the authors wrote. ■

A minute with ...

Jennifer Garson, 2023 PharmD candidate at Purdue University College of Pharmacy

Pharmacy Intern, Walgreens, Lafayette, IN

Member since 2019

"Being a student pharmacist member in APhA enabled me to be curious and discover the type of caregiver and leader that I want to be, regardless of the setting in which I choose to practice. My experiences as a member have given me opportunities to establish and nurture meaningful relationships, develop, and practice critical leadership skills as well as to flourish into a passionate patient care advocate."

How has APhA helped you establish meaningful connections?

Connection is why I joined APhA initially, and connection is why I choose to remain a member. An older student encouraged me to join, and she is just one of many diverse and meaningful APhA relationships that have shaped my pharmacy journey. Throughout my years of involvement, APhA has enabled me to meet current and future pharmacy leaders who are passionate about our profession.

How has APhA helped prepare you for your career as a pharmacist (e.g., experiences in patient care projects, leadership opportunities, advocacy, etc.)?

As a student, I strongly believe that our education must go beyond the classroom. While didactic coursework is crucial, experiences gained through organizations like APhA empowered me to learn about myself and who I want to be. Serving as the vice president of membership for my chapter allowed me to implement my passions for developing others, interacting with diverse groups of people, and creating excitement about pharmacy.

What excites you about the profession of pharmacy?

The opportunity for growth and impact on patient care and outcomes excites me most. Pharmacists are in a unique position to increase health care access and affordability for all patients. As health care continues to become more complex and difficult to navigate, pharmacists must be on the forefront of change and advocacy to allow for more collaborative and comprehensive care.

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

My local chapter of APhA–ASP hosts free health fairs for students and people in the community several times throughout the year.

I was volunteering at the BP station for one of these health fairs when a visibly nervous student approached me for their screening. The student explained that both his father and grandfather had suffered major heart attacks, and he was worried about his own heart health given the family history. We sat and chatted for a few minutes, as I hoped to calm some of his nerves prior to completing the BP reading. His first and second readings revealed elevated BP, and I explained that this was only a screening and that it would be best to follow up with his doctor. We also discussed some nonpharmacologic options for lowering his BP and that's when I saw a shift in the student's outlook; he had no idea that canned and frozen foods often contain large amounts of salt, which can adversely affect BP. This was an empowering discovery for the student, as he felt that it would be an easy change in his diet to consume less of those foods and make a positive difference in his health.

That student left the health fair much calmer and more confident than he had entered, and I was proud to have played a small role in making that possible. ■

Get involved in APhA

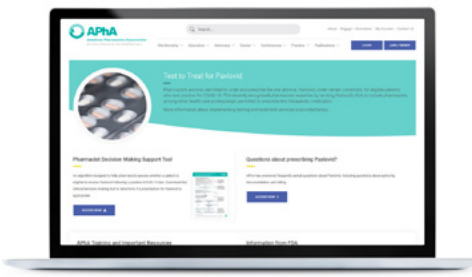
Pain, Palliative Care, and Addiction SIG

Interested in pain management? APhA's Pain, Palliative Care and Addiction Special Interest Group (SIG) supports pharmacists and student pharmacists who care for patients with all types of acute and chronic pain and for patients with life limiting illnesses who have pain and other symptoms. They also educate, collaborate with, and support pharmacists and student pharmacists interested in associated issues such as substance use disorders, medication abuse, and medication diversion.

> The Pain, Palliative Care and Addiction SIG also supports APhA's Opioid Use and Misuse Resource Center, which can be found at pharmacist.com/Practice/Patient-Care-Services/Opioid-Use-Misuse

Test to treat with Paxlovid

FDA recently revised Paxlovid's (Pfizer) EUA to allow pharmacists to prescribe this medication to eligible patients who test positive for COVID-19. To help our members, APhA has developed and collected multiple resources to help you navigate Paxlovid prescribing.



Check out our resource for testing to treat with Paxlovid at apha.us/Paxlovid, where you can find a tool to help you determine a patient's eligibility for Paxlovid treatment, answers to frequently answered questions, and more!

Pharmacists increasing access to reproductive health care

Ashley H. Meredith, PharmD, MPH, BCACP, BCPS, CDCES, FCCP, Clinical Professor, Purdue University, West Lafayette, IN; Clinical Pharmacy Specialist, Primary Care, Eskenazi Health, Indianapolis, IN

People in the United States still struggle to access sexual and reproductive health care, as evidenced by the unintended pregnancy rate of 45%.[1] Unintended pregnancies are those that are mistimed or unwanted, and they are often associated with a lack of access to or inappropriate use of contraception.

Despite evidence that shows access to contraception is the most effective way to reduce unintended pregnancies, more than 19 million patients of reproductive potential find themselves living in contraceptive deserts.[2] A contraceptive desert is a geographic area that lacks reasonable access to a health center that offers all contraceptive methods.[2]

Beyond accessing contraception, other aspects of reproductive care are also a challenge for many people. Once pregnant, more than 25% of people do not seek adequate prenatal care.[3] The existing struggle to access sexual and reproductive health care is compounded by the recent Supreme Court decision in *Dobbs v Jackson*, which removes federal protections around abortion access and returns the decision about abortion to the individual state.[4]

Increased burdens are being placed on pregnancy-capable patients that keep them from accessing the full spectrum of sexual and reproductive health care.[4]

The traditional model of health care involves scheduling an appointment with a provider, attending the scheduled provider appointment, and then often making a second stop at a community pharmacy to receive any prescribed medications. In and of itself, this model presents challenges for

Table 1. Counseling points for mifepristone and misoprostol

Patient question	Information to address
What will the bleeding be like?	• Bleeding and cramping are expected. • It will be heavier than menses.
When should I contact my provider?	You should contact your provider if you experience any of the following: • Heavy bleeding of more than 2 pads/hour for 2 consecutive hours • Any blood clots larger than a lemon • Chills and a fever of > 100.4 °F for > 4 hours • Any fever > 101 °F
What are some common adverse effects?	• Nausea, vomiting, diarrhea • Headache • Dizziness • Hot flushes and chills
What can I do for the pain?	• The most severe pain can be expected 2.5–4 hours after taking misoprostol. • NSAIDs are recommended.

Source: Adapted from References 7 and 8.

Learning objectives

At the conclusion of this knowledge-based activity, pharmacists and pharmacy technicians will be able to:

- Describe current barriers to adequate reproductive care.
- Review abortifacients commonly seen in pharmacy practice.
- Discuss available options for emergency contraception prescribing and dispensing in the pharmacy.
- Describe strategies for implementing pharmacist sexual and reproductive health services considering current legislation.
- Summarize available resources to promote safe and effective contraceptive use.

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. **How many patients of reproductive potential currently live in a contraceptive desert without access to full the spectrum of approved contraceptive methods?**
   a. 1 million
   b. 4 million
   c. 13 million
   d. 19 million
2. **What regimen is FDA-approved for medication abortion?**
   a. Misoprostol monotherapy
   b. Mifepristone monotherapy
   c. Mifepristone combined with misoprostol
   d. Methotrexate combined with misoprostol
3. **What online resource can be used to find information related to pharmacist contraception prescribing?**
   a. National Association of Boards of Pharmacy
   b. Birth Control Pharmacist
   c. Plan C Pills
   d. Power to Decide

many people who may not be able to afford to take time off work to attend provider visits; lack reliable and convenient transportation; or require other support to attend visits, such as childcare. However, approximately 90% of people in the United States live within 5 miles of a community pharmacy and 95% live within 10 miles, representing a potentially more convenient health care delivery site compared to the existing reproductive health care deserts.[5] Many community pharmacies have already created services to fill these gaps and address existing barriers to access. Pharmacy services can span the reproductive spectrum and include preconception care, contraception prescribing, and prenatal support.[6]

Pharmacists are the most easily accessible and convenient provider to answer health-related questions. Therefore, it is crucial that pharmacists have an understanding of commonly used medications for various sexual and reproductive health services along with service opportunities given the current legislation.

Medication abortion

Medication abortion can be used up to 70 days (10 weeks) of gestation.[7,8] (Gestational age is calculated based on the first day of a person's last menses.) Medication abortion should be avoided in the presence of contraindications.

The FDA-approved regimen for medication abortion includes a combination of mifepristone and misoprostol.[7] The preferred regimen and dosing is mifepristone 200 mg given orally, followed by misoprostol 800 mcg buccally 24–48 hours later.[7,8] For the buccal administration of misoprostol, the person should place 2 misoprostol 200 mcg tablets in each cheek.[7] After 30 minutes, they should swish with a small amount of water and swallow whatever misoprostol remains. Misoprostol may also be used vaginally or sublingually.[8] Higher doses of mifepristone should not be used due to higher rates of adverse effects with no difference in abortion outcome.[8] Whenever possible, the combination of mifepristone and misoprostol should be used, as monotherapy with misoprostol poses a higher risk of incomplete abortion.[8]

Contraindications to medication abortion[7]

- Current intrauterine device (IUD)
- Long term systemic corticosteroids
- Chronic adrenal failure
- Coagulopathy
- Anticoagulant therapy
- Inherited porphyria
- Intolerance or allergy to medications

Mifepristone

Mifepristone is a selective progesterone receptor modulator that competitively inhibits the actions of progesterone by binding progesterone receptors without activating them.[9]

At high doses, mifepristone is also a glucocorticoid receptor antagonist that blocks the effects of cortisol and is FDA-approved for treatment of idiopathic Cushing's syndrome for patients who have failed first-line treatment or are ineligible for surgery.[10] When used during pregnancy, mifepristone causes necrosis of the decidual uterine lining, softening of the cervix, increased uterine contractility, and increased prostaglandin sensitivity.

Mifepristone is included in a Risk Evaluation and Mitigation Strategy (REMS) program.[11] Requirements of the REMS include that prescribers must complete a prescriber agreement form and the patient must sign a patient agreement form. Initial REMS requirements also included in-person dispensing, but in December 2021, the in-person dispensing requirement was removed due to the impact of the COVID-19 pandemic on in-person provider visits. A requirement for pharmacies

Table 2. Counseling points for emergency contraception

Method	Counseling points
Levonorgestrel	• Use within 72 hours. • Efficacy is increased the sooner it is taken. • Repeat dose if vomiting occurs within 2 hours of taking. • Efficacy may be decreased with BMI > 25 kg/m^2. Common adverse effects • Nausea • Vomiting • Abdominal pain • Dizziness • Headache • Breast pain • Changes in bleeding with next menses including heavier bleeding • Fatigue
Ulipristal	• Use within 120 hours. • Efficacy is maintained across 120-hour window. • Efficacy may be decreased with BMI > 30 kg/m^2. • Wait 5 days after use to start/resume hormonal contraception and use a barrier method until next menses. • Do not use more than once per menstrual cycle. • Contact provider if vomiting occurs within 3 hours of taking it. Common adverse effects • Nausea • Dizziness • Headache • Increased pain with next menses
Copper IUD	• Insert within 120 hours. • Efficacy is maintained across 120-hour window. • Provides effective contraception for up to 10 years. • Efficacy does not decrease with increased BMI. • Requires placement by a trained health care professional. Common adverse effects • Pain or discomfort with placement • Nausea with placement • Dizziness with placement • Changes in pain and bleeding with menses • Spotting between periods

Source: Adapted from References 19, 21, 22, and 25.
Abbreviations used: IUD, intrauterine device.

dispensing mifepristone to be certified was also added in order to increase access. Pharmacies must be certified by the manufacturer; however, specific details are not yet available.

Misoprostol

Misoprostol is an analog of prostaglandin E1 that causes cervical softening and uterine contractions. It is often used off-label for the medical management of miscarriages or spontaneous abortions, labor induction, and before intrauterine device (IUD) insertion.[12] Additionally, it carries an FDA-approved indication for NSAID-induced ulcer prophylaxis.[13]

There is no REMS associated with misoprostol dispensing; therefore, any community pharmacy can stock and dispense misoprostol.

Methotrexate

Prior to the approval of mifepristone, methotrexate was used in combination with misoprostol for medication abortion based on its mechanism that interferes with DNA synthesis, repair, and cellular replication.[14,15] While it is no longer used for medication abortion, it is used for many other conditions, such as psoriasis, rheumatoid arthritis, and management of an ectopic pregnancy.[14–16]

Role of the pharmacist

While the majority of pharmacists may not be directly involved in the dispensing of mifepristone and misoprostol for medication abortions, they may be faced with questions about what to expect from a patient who has been prescribed these medications. Counseling points for mifepristone and misoprostol can be found in Table 1.

If a pharmacist is practicing in a state with restrictive medication abortion legislation, it is essential to be aware of the multiple other indications for mifepristone, misoprostol, and methotrexate. While it may not be possible to provide medications for the purpose of inducing abortion in those states, patients should not be denied access to these medications when prescribed for a reason other than medication abortion. If no diagnosis is provided, the pharmacist may call the provider to confirm the reason for use; however, significant delays in product dispensing should be avoided.

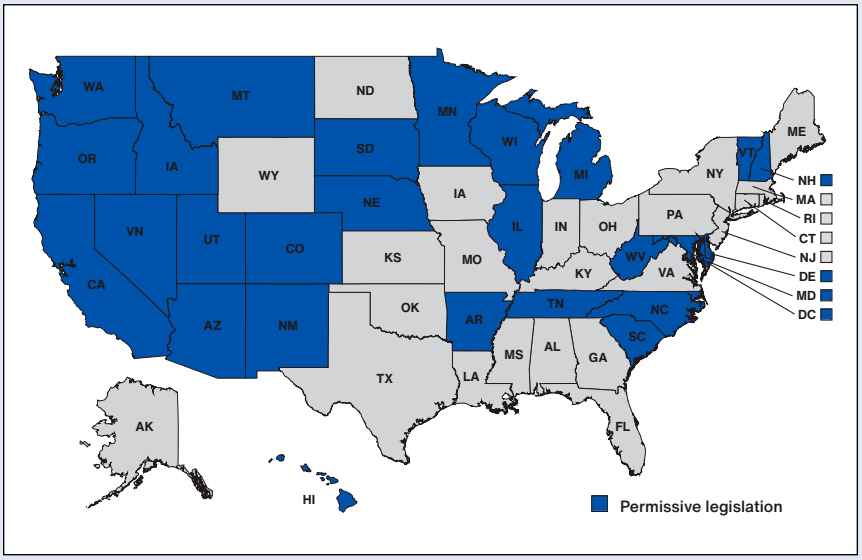
HHS issued guidance in July 2022 reminding community pharmacies of their obligation to provide discrimination-free access to medications including avoiding discrimination based on current, potential, or intended pregnancy.[17]

Emergency contraception

Emergency contraception is used after unprotected or inadequately protected vaginal intercourse to prevent pregnancy. It is effective only before a pregnancy is established and is ineffective after implantation.[18,19] Emergency contraception will not terminate an existing pregnancy and has not been shown to be harmful to a developing embryo.[19]

Three forms of emergency contraception are FDA-approved: levonorgestrel 1.5 mg, ulipristal 30 mg, and the copper IUD. It is important to

Figure 1. Status of pharmacist contraception prescribing across U.S.



Current as of October 11, 2022; for some states, while legislation has passed, the service may not yet be implemented.
Source: Adapted from References 26 and 27.

note that using combined estrogen-progestin oral contraceptive pills is no longer recommended due to a decreased efficacy compared to other methods.[19]

Levonorgestrel

Levonorgestrel was first approved as a prescription-only product in 1998. In 2006, it became available OTC for patients ≥ 18 years old, while remaining available via prescription only for those younger than 18 years.[20] As of 2013, levonorgestrel emergency contraception has been available OTC for any person of any age to purchase.[20]

A single dose of levonorgestrel 1.5 mg by mouth works to inhibit ovulation.

It should be administered within 3 days (72 hours) of unprotected vaginal intercourse, and it is more effective the sooner it is taken. Following a dose of levonorgestrel, reported pregnancy rates are 2.4%.[19]

Ulipristal

Ulipristal (Ella–HRA Pharma America) is a prescription-only oral agent that can be used for emergency contraception up to 5 days (120 hours) after vaginal intercourse with no decrease in efficacy across this timeframe.[21] It is given as a single dose of 30 mg orally and has been available in the United States since 2010.[21]

Ulipristal works by inhibiting ovulation and causing follicular rupture. It is important to educate people that they should not start or resume a hormonal contraception until 5 days after taking ulipristal, and a barrier method such as a condom should be used for any subsequent acts of vaginal intercourse for the remainder of the menstrual cycle. Phase 3 studies demonstrated a 1.9% pregnancy rate after a dose of ulipristal.[19]

Copper intrauterine device

Copper IUDs can also be used as emergency contraception if inserted within 5 days (120 hours) of unprotected vaginal intercourse.[9]

A copper IUD works through interference with sperm viability and function.[22] Reported pregnancy rates following use of the copper IUD as emergency contraception are 0.1–2.0%.[19] Once inserted, copper IUDs can provide ongoing contraception for up to 10 years.[22]

Because copper IUDs must be placed by a trained provider, their role as an emergency contraceptive may be limited due to accessibility barriers within the necessary timeframe.

Role of the pharmacist

Pharmacies began providing emergency contraception via protocol in 1998.[23] While levonorgestrel has become widely available OTC, pharmacists can still play an essential role in the provision of emergency contraception. As emergency contraceptives will not induce an abortion, dispensing and prescribing of these agents is not restricted by legislation intended to limit abortions.

Eight states specifically allow pharmacists to prescribe emergency contraception via statewide protocol or collaborative practice agreements (CPAs).[24] Table 2 includes common counseling points for available emergency contraception options.

Opportunities for pharmacists

Pharmacists are well-positioned to provide services and education related to

Accreditation information

Provider: APhA
Target audience: Pharmacists
Release date: December 1, 2022
Expiration date: December 1, 2025
Learning level: 2
ACPE Universal Activity Number: 0202-0000-22-282-H03-P
CPE credit: 1 hour (0.1 CEU)
Fee: There is no fee associated with this activity for APhA. There is a $25 fee for nonmembers.

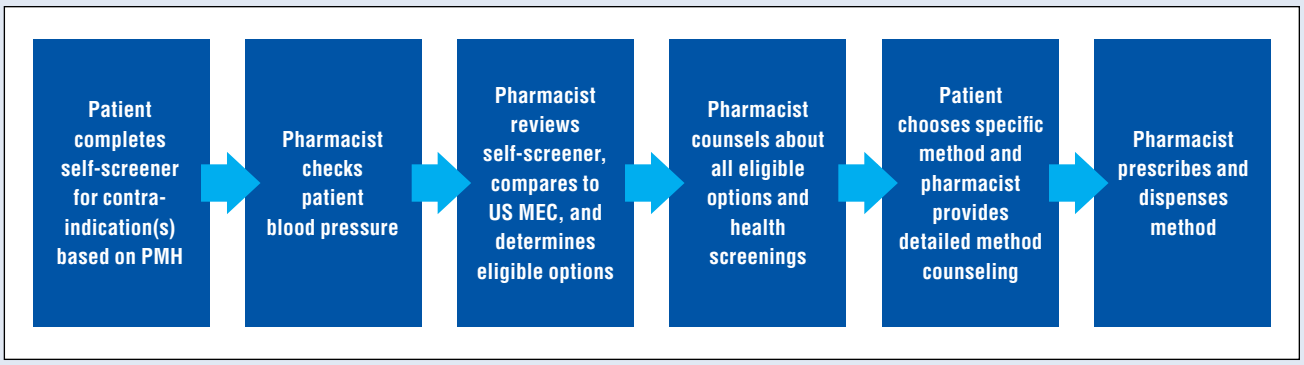
APhA is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education (CPE). The ACPE Universal Activity Number assigned to this activity by the accredited provider is 0202-0000-22-282-H03-P.

Advisory board: Katie Meyer, PharmD, BCPS, BCGP, Director, Content Creation; and Brooke Whittington, PharmD, Executive Resident APhA, Washington, DC.

Disclosures: Ashley H. Meredith, PharmD, MPH, BCACP, BCPS, CDCES, FCCP; Katie Meyer, PharmD, BCPS, BCGP; and APhA's editorial staff declare no conflicts of interest or financial interests in any product or service mentioned in this activity, including grants, employment, gifts, stock holdings, and honoraria. For complete staff disclosures, please see www.pharmacist.com/apha-disclosures.

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

Figure 2. Basic steps in pharmacist contraception prescribing



Abbreviations used: PMH, past medical history; US MEC, United States Medical Eligibility Criteria for Contraceptive Use.

sexual and reproductive health. Many opportunities have been described, and a few are highlighted below.

Contraception prescribing

As of October 2022, a total of 27 states and jurisdictions within the United States have authorized pharmacists to prescribe contraception without the need for an individual CPA.[26,27] Figure 1 illustrates the status of pharmacist contraception prescribing across the United States.

Pharmacists are empowered through statewide protocols, independent authority, and standing orders. Each state varies in the specific contraception methods that pharmacists are allowed to prescribe. Some states have limited pharmacist prescribing to only contraceptive pills, while others allow prescribing of pills, patches, vaginal rings, and injectable contraception.[27]

Differences also exist in who is eligible to utilize pharmacist prescribing services, with about half of states limiting pharmacists prescribing to those aged 18 years or older. Check your local legislation for the most accurate and up-to-date information.

In 2016, Oregon became the first state to implement pharmacist contraception prescribing, allowing pharmacists to prescribe contraceptive pills, patches, and rings.[28] Within the first 12 months of implementation, 63% of ZIP codes in the state reported at least one pharmacy offering contraception prescribing services.[28] These data from Oregon demonstrated that pharmacist contraception prescribing accounted for 10% of new oral and transdermal contraceptive prescriptions for Medicaid recipients, prevented 51 pregnancies, and saved the state an estimated $1.6 million.[29,30]

It has also been shown that people obtaining contraception from pharmacists are younger, report less education, and are more likely to be uninsured.[29-31] Additionally, patients utilizing pharmacist contraception prescribing report a higher likelihood of wanting to return to the same provider for future visits compared to those who saw other health care providers and are more likely to receive a 6-month supply or greater.[31,32]

However, despite permissive legislation and successes in some states, widespread implementation of pharmacist contraception prescribing has been limited. An often-cited barrier to implementation is the time required, with a complete appointment averaging 18–26 minutes.[28,33–35] (For a rundown of the typical process, see Figure 2). Other commonly cited barriers include reimbursement challenges, lack of private space, liability concerns, lack of patient awareness, and corporate policies.[35]

Table 3. Preconception and prenatal supplementation

Vitamin or mineral	Recommended amount
Calcium	1,000 mg daily
DHA	8–12 oz of low-mercury seafood per week
Folic acid	0.4–0.8 mg daily starting 1 month before conception
	1–4 mg daily if at high risk of having a child with neural-tube defects
Iodine	220 mcg daily
Iron	27 mg daily
	≤ 120 mg daily if iron-deficiency anemia is present
Vitamin D	600 IU daily

Abbreviations used: DHA, docosahexaenoic acid; IU, international units.
Source: Adapted from Reference 41.

While waiting for more states to approve permissive legislation, pharmacists in 49 states can explore the use of a CPA to create contraception prescribing services.[36] Some states, such as Tennessee, have a specific contraception CPA.[27] Other states (e.g., Idaho, Washington, Michigan) have implemented more broad spread pharmacist contraception prescribing via their general CPA legislation.[27] Individual community pharmacies in other states have also implemented contraception

prescribing CPAs based on the needs of their community.[33] An example CPA for contraception prescribing can be found at the website for Pharmacy Access Forms (www.pharmacyaccessforms.org/example-cdtm).

Preconception and prenatal care

In the United States, the overall infant mortality rate is 5.4 deaths per 1,000 live births.[37] The leading contributor to infant deaths is birth defects, many of which can be prevented with appropriate supplementation, avoiding harmful substances during pregnancy, controlling chronic conditions, and avoiding teratogenic medications.[38]

In the absence of permissive legislation that allows for pharmacist prescribing of sexual and reproductive health medications, many opportunities still exist to impact preconception and prenatal care through daily interactions with patients of reproductive potential.

Simple interventions as a part of everyday practice can be implemented to have a large impact on pregnancy outcomes. For example, pharmacists can screen medication lists for safety should a patient become pregnant.[38,39]

When a potentially unsafe or teratogenic medication is identified, this can be followed by a conversation with the patient about their concerns and ways to increase safety, such as use of a contraceptive method or use of an alternate medication. Recommendation of appropriate supplementation, both preconception and during pregnancy, presents another opportunity for community pharmacists.[39,40] Table 3 includes commonly recommended supplements before and during pregnancy.

Within the robust immunization services already provided at the pharmacy, specific attention can be paid to ensuring pregnant patients receive recommended vaccines, including inactivated influenza during the flu season; tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) between 27–36 weeks of gestation for each pregnancy; and COVID-19 initial series and booster dose(s).[39,40,42]

Sexual and reproductive health resources

Contraception medication information
- bedsider.org
- plannedparenthood.org/learn/birth-control

Local reproductive health providers and clinics information
- plannedparenthood.org
- opa-fpclinicdb.hhs.gov/

Medication abortion
- plancpills.org
- abortionfinder.org

Medication use during pregnancy
- mothertobaby.org
- Specific medication labeling

Pharmacist contraception prescribing process
- birthcontrolpharmacist.com
- pharmacyaccessforms.org

Sexual and reproductive health services statistics
- powertodecide.org
- guttmacher.org

Offering smoking cessation services to all patients prior to or during pregnancy may lead to improved outcomes for both the pregnant patient and the fetus.[40,42]

Available resources

As pharmacists begin expanding sexual and reproductive health services, having easy access to resources for reference and guidance is essential.

Conclusion

Despite legislation and barriers that may limit access to the full spectrum of sexual and reproductive health, pharmacists are well-positioned to fill gaps in care. Pharmacists should seek out opportunities to provide counseling, correct misinformation, and expand services to address the needs of patients of reproductive potential.

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CPE assessment

This assessment must be taken online; please see "CPE information" in the sidebar below 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. **How many patients of reproductive potential currently live in a contraceptive desert without access to full the spectrum of approved contraceptive methods?**
   a. 1 million
   b. 4 million
   c. 13 million
   d. 19 million

2. **What regimen is FDA-approved for medication abortion?**
   a. Misoprostol monotherapy
   b. Mifepristone monotherapy
   c. Mifepristone combined with misoprostol
   d. Methotrexate combined with misoprostol

3. **What online resource can be used to find information related to pharmacist contraception prescribing?**
   a. National Association of Boards of Pharmacy
   b. Birth Control Pharmacist
   c. Plan C Pills
   d. Power to Decide

4. **Following a medication abortion, when should a patient be instructed to contact their provider?**
   a. After 24 hours
   b. Passing any blood clots larger than a quarter
   c. Using more than 1 pad per hour
   d. Fever of > 101 °F

5. **Which medication used for emergency contraception is available OTC, without restrictions?**
   a. Levonorgestrel 0.75 mg
   b. Levonorgestrel 1.5 mg
   c. Ulipristal 5 mg
   d. Ulipristal 30 mg

6. **As of October 2022, how many states and jurisdictions allow pharmacist prescribing of contraception without the need for an individual collaborative practice agreement?**
   a. 7
   b. 15
   c. 27
   d. 36

7. **In addition to medication abortion, what is another clinical use of misoprostol?**
   a. Rheumatoid arthritis
   b. Emergency contraception
   c. Ectopic pregnancy
   d. Labor induction

8. **What best describes the primary role of mifepristone in a medication abortion?**
   a. Interference with cellular replication
   b. Inhibition of progesterone
   c. Prevention of ovulation
   d. Decreased sperm viability

9. **What is one sexual and reproductive health service pharmacists can incorporate into their practice today?**
   a. Access to emergency contraception
   b. Focused immunizations before and during pregnancy
   c. Counseling on prenatal supplementation
   d. All of the above

10. **What is a commonly cited barrier that limits implementation of pharmacist contraception prescribing services?**
    a. Difficult to access resources
    b. Moral concerns
    c. Lack of technician engagement
    d. Reimbursement challenges

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To obtain 1 hour of CPE credit for this activity, complete the CPE exam and submit it online at www.pharmacist.com/education. A Statement of Credit will be awarded for a passing grade of 70% or better. You have two opportunities to successfully complete the CPE exam. Pharmacists and technicians who successfully complete this activity before December 1, 2025, can receive credit. Your Statement of Credit will be available online immediately upon successful completion of the CPE exam.

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PS Form **3526**, July 2014 (Page 3 of 3)

Across

1 Depletes
5 Antibiotic produced by hay bacillis
9 Blood protein
10 Change, e.g., as a diagnosis designation
11 _____ health, e.g., fertility
13 Pops up sometimes in those with a penicillin allergy
14 Sulfur-containing diuretic
17 Common maladies for young children
18 Pure, as a liquid
20 Vocal range higher than alto
24 Absolute
25 The "A" in AIDS
26 Bacterium that doesn't need oxygen
27 Common place for a stye

Down

2 Polio vaccine inventor
3 When it affects the scalp, it causes dandruff
4 Small clumps of cells that form on the lining of the colon
5 Alprazolam, diazepam, lorazepam, or clonazepam, for short
6 Anti-inflammatory compound found in turmeric
7 Lawful, as in a drug
8 Person
12 Anticonvulsant sometimes used to treat chronic pain
15 Opaque sunscreen ingredient
16 Clinical trial that evaluates efficacy in the drug approval process
19 Language also known as Euskara
21 Democratic Republic of the Congo
22 Viruses that infect and replicate only in bacterial cells
23 Abominable Snowman, e.g.

Solution is available online at pharmacytoday.org.

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RSV MAY RAISE THE STAKES FOR OLDER ADULTS

Respiratory syncytial virus (RSV) is a common and contagious virus that typically produces mild, cold-like symptoms but can put older adults at risk for severe outcomes.[1,2,*]

Each year in the US, approximately 177,000 older adults are hospitalized and an estimated 14,000 of them die due to RSV infection.[2]

*The CDC states that adults at highest risk for severe RSV infection include older adults, especially those 65 years and older, adults with chronic heart or lung disease, and adults with weakened immune systems. Data are limited in assessing the risk of severe outcomes due to RSV infection in adults 60-64 years of age.[3,4]

CDC=Centers for Disease Control and Prevention;
CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease.

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Learn about the risks of RSV at RSVinAdults.com