MENTAL HEALTH

How to Recognize Mental Illness

MARCH 2021 | VOLUME 87 NUMBER 3 | SINCE 1897

PharmacyTimes.com
INDICATION

BIKTARVY is indicated as a complete regimen for the treatment of HIV-1 infection in adult and pediatric patients weighing ≥25 kg who have no antiretroviral (ARV) treatment history or to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 copies per mL) on a stable ARV regimen with no history of treatment failure and no known resistance to any component of BIKTARVY.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted.

Contraindications

- Coadministration: Do not use BIKTARVY with dofetilide or rifampin.

Warnings and precautions

- Drug interactions: See Contraindications and Drug Interactions sections. Consider the potential for drug interactions prior to and during BIKTARVY therapy and monitor for adverse reactions.

- Immune reconstitution syndrome, including the occurrence of autoimmune disorders with variable time to onset, has been reported.

- New onset or worsening renal impairment: Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of BIKTARVY, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Do not initiate BIKTARVY in patients with estimated creatinine clearance (CrCl) <30 mL/min. Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

  Renal monitoring: Prior to or when initiating BIKTARVY and during therapy, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, assess serum phosphorus.

- Lactic acidosis and severe hepatomegaly with steatosis: Fatal cases have been reported with the use of nucleoside analogs, including FTC and TDF. Discontinue BIKTARVY if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

Adverse reactions

- Most common adverse reactions (incidence ≥5%; all grades) in clinical studies through week 144 were diarrhea (6%), nausea (6%), and headache (5%).

Drug interactions

- Prescribing information: Consult the full prescribing information for BIKTARVY for more information on Contraindications, Warnings, and potentially significant drug interactions, including clinical comments.
The little pill that speaks for itself.

A proven high barrier to resistance

In two large clinical trials of treatment-naïve adults at Week 144\(^1\text{-}^4\)

No treatment-emergent resistance was associated with BIKTARVY—among 634 treatment-naïve adults in Studies 1489 and 1490, 8 treatment-failure subjects were tested, and no amino acid substitutions emerged that were associated with BIKTARVY resistance through Week 144.\(^1\text{-}^4\)

IMPOTANT SAFETY INFORMATION (cont’d)

Drug interactions (cont’d)

- **Enzymes/transporters:** Drugs that induce P-gp or induce both CYP3A and UGT1A1 can substantially decrease the concentration of components of BIKTARVY. Drugs that inhibit P-gp, BCRP, or inhibit both CYP3A and UGT1A1 may significantly increase the concentrations of components of BIKTARVY. BIKTARVY can increase the concentration of drugs that are substrates of OCT2 or MATE1.

- **Drugs affecting renal function:** Coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC and tenofovir and the risk of adverse reactions.

Dosage and administration

- **Dosage:** Patients weighing ≥25 kg: 1 tablet taken once daily with or without food.
- **Renal impairment:** Not recommended in patients with CrCl <30 mL/min.
- **Hepatic impairment:** Not recommended in patients with severe hepatic impairment.
- **Prior to or when initiating:** Test patients for HBV infection.
- **Prior to or when initiating, and during treatment:** As clinically appropriate, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, assess serum phosphorus.

Pregnancy and lactation

- **Pregnancy:** There is insufficient human data on the use of BIKTARVY during pregnancy. Dolutegravir, another integrase inhibitor, has been associated with neural tube defects. Discuss the benefit-risk of using BIKTARVY during pregnancy and conception. An Antiretroviral Pregnancy Registry (APR) has been established. Available data from the APR for FTC shows no difference in the rates of birth defects compared with a US reference population.

Please see Brief Summary of full Prescribing Information for BIKTARVY, including BOXED WARNING, on the following pages.
Durable power at Week 144\(^1\-\^6,\^7\)

Long-term efficacy in treatment-naïve adults—results noninferior to comparators

<table>
<thead>
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<th>Week 48</th>
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<td>HIV-1 RNA &lt;50 COPIES/ML</td>
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STUDY 1489: VIROLOGIC RESPONSE

Most common adverse reactions (incidence ≥5%; all grades) in clinical studies through Week 144 were diarrhea (6%), nausea (6%), and headache (5%).\(^2\)

Pivotal treatment-naïve study designs: The efficacy and safety of BIKTARVY\(^\circ\) for treatment-naïve adults were evaluated in Studies 1489 and 1490. In Study 1489, a phase 3, randomized, double-blind, active-controlled study, treatment-naïve adults with an eGFR\(_{\text{Cr}}\) ≥50 mL/min were randomized in a 1:1 ratio to receive either BIKTARVY (n=314) or ABC/DTG/3TC (n=315) once daily. In Study 1490, a phase 3, randomized, double-blind, active-controlled study, treatment-naïve adults with an eGFR ≥30 mL/min were randomized in a 1:1 ratio to receive either BIKTARVY (n=320) or FTC/TAF+DTG (n=325) once daily. The primary endpoint for both trials was the proportion of adults with HIV-1 RNA <50 copies/mL at Week 48. Secondary endpoints included efficacy, safety, and tolerability through Week 96 and Week 144.\(^1,\^4,\^5,\^6,\^7\)

Learn more about Study 1489 and Study 1490 at BIKTARVYhcp.com.

IMPORTANT SAFETY INFORMATION (cont’d)

Pregnancy and lactation (cont’d)

Lactation: Women infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV-1 transmission.

Please see Brief Summary of full Prescribing Information for BIKTARVY, including BOXED WARNING, on the following pages.

3TC, lamivudine; ABC, abacavir; DHHS, Department of Health and Human Services; DTG, dolutegravir; eGFR\(_{\text{Cr}}\), estimated glomerular filtration rate (Cockcroft-Gault); FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide.

BIKTARVY® (bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx only.

**WARNING:** POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of BIKTARVY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted [see Warnings and Precautions].

**INDICATIONS AND USE**

BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing ≥25 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

**DOSE AND ADMINISTRATION**

Also see Warnings and Precautions and Use in Specific Populations. Testing Prior to or When Initiating: Test patients for HBV infection. Testing Prior to or When Initiating, and During Treatment: As clinically appropriate, assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose, and urine protein in all patients. In patients with chronic kidney disease, assess serum phosphorus.

**Dosage:** One tablet taken once daily with or without food in patients weighing ≥25 kg.

- **Renal Impairment:** BIKTARVY is not recommended in patients with CrCl <30 mL/min.
- **Hepatic Impairment:** BIKTARVY is not recommended in patients with severe hepatic impairment.

**CONTRAINDICATIONS**

Also see Drug Interactions. BIKTARVY is contraindicated to be co-administered with:
- doxefilte due to the potential for increased doxefilte plasma concentrations and associated serious and/or life-threatening events
- rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY

**WARNINGS AND PRECAUTIONS**

Also see BOXED WARNING, Contraindications, Adverse Reactions, and Drug Interactions.

**Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV:** Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating ARV therapy. Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or TDF, and may occur with discontinuation of BIKTARVY. Patients coinfected with HIV-1 and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up for at least several months after discontinuation of treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

**Risk of Adverse Reactions (ARs) or Loss of Virologic Response Due to Drug Interactions:** Coadministration of BIKTARVY with certain other drugs may result in known or potentially significant drug interactions; this may lead to loss of efficacy and development of resistance to BIKTARVY or clinically significant ARs from greater exposures of concomitant drugs.

Consider the potential for drug interactions and review concomitant medications prior to and during therapy. Monitor for ARs associated with concomitant drugs.

**Immune Reconstitution Syndrome (IRS):** IRS has been reported in patients treated with combination ARV therapy. During the initial phase of treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment. Autoimmune disorders have been reported to occur in the setting of immune reconstitution; the time to onset is variable, and can occur many months after initiation of treatment.

**New Onset or Worsening Renal Impairment:** Renal impairment, including acute renal failure and Fanconi syndrome, has been reported with the use of tenofovir prodrugs in animal studies and human trials. In clinical trials of BIKTARVY in subjects with no ARV treatment history with eGFRs >30 mL/min, and in virologically suppressed subjects switched to BIKTARVY with eGFRs >50 mL/min, renal serious adverse events were encountered in <1% of subjects treated with BIKTARVY through Week 48. BIKTARVY is not recommended in patients with CrCl <30 mL/min. Patients taking tenofovir prodrugs who have renal impairment and/or are taking nephrotoxic agents including NSAIDs are at increased risk of developing renal-related ARs. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Renal Monitoring: Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, assess serum phosphorus.

**Lactic Acidosis/Severe Hepatomegaly with Steatosis:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC and TDF. Treatment with BIKTARVY should be suspended in any individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

**ADVERSE REACTIONS**

Also see BOXED WARNING and Warnings and Precautions.

In Adults with No ARV Treatment History:

The safety assessment of BIKTARVY is based on Week 48 data from two randomized, double-blind, active-controlled trials: 1489 (n=314) and 1490 (n=320), in HIV-1 infected, ARV treatment-naive adults. Through Week 48, 1% of subjects discontinued BIKTARVY due to adverse events, regardless of severity.

**Adverse Reactions:** ARs (all Grades) reported in ≥2% of subjects receiving BIKTARVY through Week 48 in Trials 1489 and 1490, respectively were: diarrhea (6%, 3%), nausea (5%, 3%), headache (5%, 4%), fatigue (3%, 2%), abnormal dreams (3%, <1%), dizziness (2%, 2%), and insomnia (2%, 2%). Additional ARs (all Grades) occurring in <2% of subjects administered BIKTARVY in Trials 1489 and 1490 included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression. Suicidal ideation, suicide attempt, and depression suicidal occurred in <1% of subjects administered BIKTARVY; all events were serious and primarily occurred in subjects with a preexisting history of depression, prior suicide attempt, or psychiatric illness.

**Laboratory Abnormalities:** Laboratory abnormalities (Grades 3-4) occurring in ≥2% of subjects receiving BIKTARVY through Week 48 in Trials 1489 or 1490, respectively were: amylase >2.0 x ULN (2%, 2%), ALT >5.0 x ULN (1%, 2%), AST >5.0 x ULN (2%, 1%), Creatine Kinase >0.0 x ULN (4%, 4%), Neutrophils <750 mm3 (2%, 2%), and fasted LDL-cholesterol >180 mg/dL (2%, 3%).

**Changes in Serum Creatinine:** Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 48. In Trials 1489 and 1490, median serum creatinine increased by 0.10 mg/dL from baseline to Week 48 in the BIKTARVY group and was similar to the comparator groups.

**Changes in Bilirubin:** In Trials 1489 and 1490, total bilirubin increases were observed in 12% of subjects administered BIKTARVY through Week 48.

In Virologically Suppressed Adults: The safety of BIKTARVY in HIV-1 infected, virologically suppressed adults is based on Week 48 data from 282 subjects in a randomized, double-blind, active-controlled trial in which virologically suppressed subjects were switched from either DTG + }
Established and Potentially Significant Drug Interactions:

Established and Potentially Significant Drug Interactions: The safety of BIKTARVY was evaluated in HIV-1 infected, virologically suppressed subjects between the ages of 12 to <18 years and weighing ≥35 kg (N=50) through Week 48, and in virologically-suppressed subjects between the ages of 6 to <12 years and weighing ≥25 kg (N=50) through Week 24 in an open label clinical trial.

DRUG INTERACTIONS

Also see Indications and Usage, Contraindications, and Warnings and Precautions.

Other Antiretroviral Medications: BIKTARVY is a complete regimen for the treatment of HIV-1 infection, BIKTARVY coadministration with other ARV medications for treatment of HIV-1 infection is not recommended. Complete information regarding potential drug interactions with other ARV medications is not provided.

Potential for BIKTARVY to Affect Other Drugs: BIKTARVY contains 3TC, FTC, and TAF. 3TC is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs, which may increase the risk of ARs.

Established and Potentially Significant Drug Interactions: The listing of established or potentially clinically significant drug interactions with recommended prevention or management strategies described are based on studies conducted with either BIKTARVY, the components of BIKTARVY (3TC, FTC, and TAF) as individual agents, or are drug interactions that may occur with BIKTARVY. An alteration in regimen may be recommended.

• Antiarhythmics: dofetilide. Coadministration is contraindicated due to potential for serious and/or life-threatening events.

• Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin. Coadministration with alternative anticonvulsants should be considered.

• Antimycobacterials: rifampin. Coadministration is contraindicated due to the effect on BIKTARVY. Rifabutin, rifapentine. Coadministration is not recommended.

• Herbal Products: St. John’s wort. Coadministration is not recommended.

• Medications/oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): Antacids containing Al/Mg: BIKTARVY can be taken at least 2 hours before or 6 hours after taking antacids containing Al/Mg. Routine administration of BIKTARVY together with, or 2 hours after, antacids containing Al/Mg is not recommended. Supplements or antacids containing Ca or Fe: BIKTARVY and supplements or antacids containing Ca or Fe can be taken together with food. Routine administration of BIKTARVY under fasting conditions together with, or 2 hours after, supplements or antacids containing Ca or Fe is not recommended.

• Metformin: Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIKTARVY and metformin.

Consult the full Prescribing Information prior to and during treatment with BIKTARVY for important drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS

Also see Dosage and Administration, Warnings and Precautions, and Adverse Reactions.

Pregnancy: Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIKTARVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263. Risk Summary: There are insufficient human data on the use of BIKTARVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Dolutegravir, another integrase inhibitor, has been associated with neural tube defects. Discuss the benefit-risk of using BIKTARVY with individuals of childbearing potential, particularly if pregnancy is being planned. BIC and TAF use in women during pregnancy has not been evaluated; however, FTC use during pregnancy has been evaluated in a limited number of women as reported to the APR. Available data from the APR show no difference in the overall risk of major birth defects for FTC compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program. The rate of miscarriage is not reported in the APR.

Lactation: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Based on published data, FTC has been detected in human milk; it is not known whether BIKTARVY or any of the components of BIKTARVY are present in human breast milk, affects human milk production, or has effects on the breastfed infant. BIC was detected in the plasma of nursing rat pups likely due to the presence of BIC in milk, and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF. It is unknown if TAF is present in animal milk. Because of the potential for HIV transmission in HIV-negative infants, developing viral resistance in HIV-positive infants, and ARs in nursing infants, mothers should be instructed not to breastfeed.

Pediatric Use: Clinical studies of BIKTARVY included 50 subjects aged 12 to <18 years and weighing ≥35 kg, and 50 subjects aged 6 to <12 years and weighing ≥25 kg. Safety and effectiveness of BIKTARVY in pediatric patients weighing ≥25 kg have not been established.

Geriatric Use: Clinical studies of BIKTARVY did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment: BIKTARVY is not recommended in patients with severe renal impairment (CrCl <30ml/min). No dosage adjustment of BIKTARVY is recommended in patients with CrCl ≥30ml/min.

Hepatic Impairment: No dosage adjustment of BIKTARVY is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. BIKTARVY is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) as BIKTARVY has not been studied in these patients.

OVERDOSE:

If overdose occurs, monitor the patient for evidence of toxicity. Treatment consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

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Pharmacists Play a Key Role in Mental Health

MIKE HENNESSY SR
Chairman & Founder
MJH Life Sciences

PHARMACISTS CAN RECOGNIZE MENTAL HEALTH disorders in patients and help guide individuals toward treatment. As trusted health care professionals, pharmacists are ideally positioned to identify symptoms and work with other colleagues to support patients with mental health disorders. This may be particularly true during the COVID-19 pandemic, when many individuals either have developed mental health issues or seen existing conditions exacerbated.¹

In this issue of Pharmacy Times®, we focus on mental health. Our cover feature, written by Kathleen Kenny, points out that even before the past year, the statistics were grim, with mental illness costing more than $1 trillion annually, about half of all conditions manifesting by aged 14 years, those with severe mental health issues dying 10 to 20 years earlier than average, and just 1 mental health professional for every 10,000 individuals globally.² In her article, Kenny shares tips on recognizing mental illness through observation and screening patients to help identify those who need treatment.

Also in this issue of Pharmacy Times® is a Patient Focus article on becoming a psychiatric pharmacist, written by Jennifer Gershman, PharmD, CPh. “This career path opens the door to a variety of opportunities for pharmacists to provide comprehensive medication management and improve health outcomes for patients with psychiatric and neurologic disorders as part of an interdisciplinary team,” Gershman says.

Other coverage includes articles on treating cardiovascular disease, OTC options for the common cold, and, for pharmacy technicians, understanding medication expiration dates.

Thanks for reading!

A Letter From the Reader

Your January note says that all Americans can soon get their vaccines at their doctors or CVS or Walgreens. Are you so tied into big corporations that you forget independent pharmacies?

I suggest you check out why West Virginia has such a great vaccination rate. They opted out of the federal government plan that uses only those chains. They let independent pharmacy and chains vaccinate nursing homes.

Please don’t forget that the big chains are not representing all of community pharmacy.—John Ochs, RPh

We’re Here to Listen

Thanks for your feedback. As you noted, independent pharmacists will be instrumental to the COVID-19 vaccine rollout, as are the larger retail chains mentioned in the January Chairman’s Letter. Our commitment to independent owners is strong, as you can see every month when we highlight independent pharmacies and the key work they do in the Independent Corner column. Thanks for reaching out, and keep reading!—Mike Hennessy Sr

March 2021 pharmacytimes.com 5
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Contents

30 Cover Feature
Recognize Mental Illness Through Observation and Screening
Kathleen Kenny, PharmD, RPh

34 Over the Counter
OTC Focus
Help Patients Treat Headaches Safely
Yvette C. Terrie, BSPharm, RPh

36 OTC Case Studies
Common Cold
Ammie J. Patel, PharmD, BCACP; and Rupal Patel Mansukhani, PharmD, FAPhA, NCTTP

38 OTC Product News

Rx Insights

40 Rx Focus
Treating Cardiovascular Disease Means Making Choices
Jeannette Y. Wick, RPh, MBA, FASCP

42 Rx Product News

Clinical Pharmacology Update
Gavreto From Blueprint Medicines Corporation
Monica Holmberg, PharmD, BCPS

Medication Safety
Safeguard Patients During COVID-19 Immunization Campaigns
Michael J. Gaunt, PharmD

Generics

48 Generic Focus
Asthma Biologics Can Improve Global Access to Treatment
Aislinn Antrim

50 Generic Product News

» Continued on page 14

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Which OTC Products Do You Recommend?

Scan the QR code or visit rb.gy/axsbvn to complete the survey.

Abbreviated Rules: NO PURCHASE NECESSARY. Void where prohibited by law and Subject to all applicable laws. Sweepstakes begins on or about November 17, 2020, at 12:01 a.m. ET and ends on March 2, 2021, at 11:59 p.m. ET. Open only to legal United States residents who are older than the age of majority in his or her state of residence at the time of entry and currently a practicing pharmacist. TO ENTER: Enter online by submitting a completed entry form, which will include your full name, e-mail address, title, employer, mailing address, phone number, and date of birth, after completing the survey available through the survey invitation e-mail sent to certain practicing pharmacists. Alternatively, any currently practicing pharmacist may enter the Sweepstakes by printing the words “2021 OTC Guide Survey,” along with his or her full name, title, date of birth, street address, city, state, zip, and phone number on a 3” by 5” white index card. Mail the card to Pharmacy and Healthcare Communications, LLC, Attn: 2021 OTC Guide Survey, 2 Clarke Drive, Suite 100, Cranbury, NJ 08512. All entries must be received no later than 11:59 p.m. ET on March 2, 2021. Limit (1) one entry per person, per mailing address, per outer mailing envelope, and per e-mail address. Total ARV of all prizes to be awarded: $2,000.00. Odds of winning depend on the number of eligible entries received. See Official Rules at www.pharmacytimes.com/otcguide/rules for additional eligibility restrictions, prize descriptions, restrictions, and complete details. Sponsor: Pharmacy and Healthcare Communications, LLC.

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The results of this survey will be published in our annual OTC Guide® and have been featured on national television.

As a thank you for your participation, you will be entered to win a $1,000 Visa gift card and two $500 Visa gift cards!*
For adult patients with type 2 diabetes, treated with diet and exercise
When pills are no longer enough
Choose Ozempic® as your preferred injectable—greater results when added on to basal insulin

**Indication and Limitations of Use**

Ozempic® (semaglutide) injection 0.5 mg or 1 mg is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular (CV) events (CV death, nonfatal myocardial infarction or nonfatal stroke) in adults with type 2 diabetes mellitus and established CV disease.

- Ozempic® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Ozempic® is not a substitute for insulin. Ozempic® is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis.

**Contraindications**

- Ozempic® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2, and in patients with known hypersensitivity to semaglutide or to any of the product components.

**Warnings and Precautions**

- **Risk of Thyroid C-Cell Tumors**: Patients should be referred to an endocrinologist for further evaluation if serum calcitonin is measured and found to be elevated or if thyroid nodules are noted on physical examination or neck imaging.
- **Pancreatitis**: Acute and chronic pancreatitis have been reported in clinical studies. Observe patients carefully for signs and symptoms of pancreatitis (persistent severe abdominal pain, sometimes radiating to the back with or without vomiting). If pancreatitis is suspected, discontinue Ozempic® promptly, and if pancreatitis is confirmed, do not restart.

**Important Safety Information**

**Warning:** RISK OF THYROID C-CELL TUMORS

- In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Ozempic® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.
- Ozempic® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Ozempic® and inform them of symptoms of thyroid tumors (eg, a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Ozempic®.

- **Diabetic Retinopathy Complications**: In a 2-year trial involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in patients treated with Ozempic® (3.0%) compared with placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline than among patients without a known history of diabetic retinopathy. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.
- **Never Share an Ozempic® Pen Between Patients**: Ozempic® pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.
- **Hypoglycemia**: The risk of hypoglycemia is increased when Ozempic® is used in combination with insulin secretagogues (eg, sulfonylureas) or insulin.

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In adult patients with type 2 diabetes on basal insulin ± metformin

**Intensify with Ozempic® when patients are not getting the glycemic results they need from basal insulin**

Primary endpoint: Mean change in A1C from baseline at Week 30
- **-1.3%** with Ozempic® 0.5 mg + basal insulin ± MET (Baseline: 8.4%) vs
- **-0.2%** with Basal insulin ± MET (Baseline: 8.4%); *P* < 0.0001
- **-1.7%** with Ozempic® 1 mg + basal insulin ± MET (Baseline: 8.3%) vs
- **-0.2%** with Basal insulin ± MET (Baseline: 8.4%); *P* < 0.0001

Secondary endpoint: Mean change in body weight from baseline at Week 30
- **-7.7 lb** with Ozempic® 0.5 mg + basal insulin ± MET (Baseline: 205 lb) vs
- **-2.6 lb** with Basal insulin ± MET (Baseline: 198 lb); ETD = −4.9 lb (95% CI; −7.5, −2.4)
- **-13.2 lb** with Ozempic® 1 mg + basal insulin ± MET (Baseline: 204 lb) vs
- **-2.6 lb** with Basal insulin ± MET (Baseline: 198 lb); ETD = −10.4 lb (95% CI; −12.8, −7.9)

In a 2-year CVOT in adult patients with type 2 diabetes and established CVD

**Significant reduction in risk of MACE**

Time to first confirmed MACE: 8.9% for standard of care (n=146 of 1649) vs 6.6% for Ozempic® + standard of care (n=108 of 1648) at 109 weeks

Composite MACE endpoints: CV death, nonfatal MI, nonfatal stroke

**SUSTAIN 5:** A 30-week, randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter trial to compare the efficacy and safety of Ozempic® in combination with basal insulin vs volume-matched placebo in combination with basal insulin. A total of 397 adult patients with type 2 diabetes inadequately controlled on basal insulin with or without metformin were randomized to once-weekly Ozempic® 0.5 mg (n=132), Ozempic® 1 mg (n=131), or placebo (n=133). Randomization was stratified according to A1C at screening. Patients with A1C ≤8.0% at screening reduced the insulin dose by 20% at start of trial to reduce the risk of hypoglycemia. The primary endpoint was mean change in A1C from baseline at Week 30. Mean change in body weight at Week 30 was a secondary endpoint.1,2

**SUSTAIN 6:** A 104-week, multicenter, multinational, placebo-controlled, double-blind CVOT designed to assess noninferiority of Ozempic® vs placebo, both in addition to standard of care, for time to first MACE using a risk margin of 1.3. A total of 3297 adult patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to once-weekly Ozempic® 0.5 mg (n=826), Ozempic® 1 mg (n=822), or placebo (n=1649), all in addition to standard of care treatments for diabetes and CVD such as oral antidiabetic treatments, insulin, antihypertensives, diuretics, lipid-lowering therapies, and antithrombotic medication at investigator discretion. The primary composite endpoint was the time from randomization to first occurrence of a 3-part composite MACE, defined as CV death, nonfatal myocardial infarction, or nonfatal stroke.1,3

Learn more about Ozempic® and the CV risk reduction indication at OzempicPro.com.

**Acute Kidney Injury:** There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of Ozempic in patients reporting severe adverse gastrointestinal reactions.

**Hypersensitivity:** Serious hypersensitivity reactions (eg, anaphylaxis, angioedema) have been reported with GLP-1 receptor agonists. If hypersensitivity reactions occur, discontinue use of Ozempic®; treat promptly per standard of care, and monitor until signs and symptoms resolve. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist.

**Drug Interactions:**
- The risk of hypoglycemia may be lowered by a reduction in the dose of the secretagogue or insulin.
- Ozempic® causes a delay of gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications, so caution should be exercised.

**Use in Specific Populations:**
- There are limited data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. Discontinue Ozempic® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

OZEMPIC® (semaglutide) injection
Rx Only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether OZEMPIC® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined (see Warnings and Precautions). OZEMPIC® is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (see Contraindications). Counseling patients regarding the potential risk for the pituitary tumors of OZEMPIC® and informing them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

INDICATIONS AND USAGE: OZEMPIC® is indicated as: an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus; to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. Limitations of Use: OZEMPIC® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic agents in patients with a history of pancreatitis (see Precautions). OZEMPIC® is not a substitute for insulin. OZEMPIC® is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis, as it would not be effective in these settings.

CONTRAINDICATIONS: OZEMPIC® is contraindicated in patients with: A personal or family history of MTC; or a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether OZEMPIC® would be associated with an increased risk of these adverse reactions. OZEMPIC® is contraindicated in patients with: a history of thyroid C-cell tumors (adenoma or carcinoma) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) (see Contraindications). Known hypersensitivity to semaglutide or to any of the product components (see Warnings and Precautions).

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-Cell Tumors: In mice and rats, semaglutide caused a dose-dependent and treatment-duration-dependent increase in incidence of rodent thyroid C-cell tumors (adenoma and carcinoma) after lifetime exposure at clinically relevant plasma exposures. It is unknown whether OZEMPIC® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined (see Warnings and Precautions). Another GLP-1 receptor agonist, liraglutide, another GLP-1 receptor agonist, has been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans. OZEMPIC® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of OZEMPIC® and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is recommended in patients evaluating the use of OZEMPIC® as monotherapy and add-on therapy to oral antidiabetic medications or insulin. In this population, a total of 3150 patients with type 2 diabetes were treated with OZEMPIC® for a mean duration of 44.9 weeks. Across the treatment arms, the mean age of patients was 56 years, 3.4% were 75 years or older and 55% were male. In these trials 71% were White, 7% were Black or African American, and 19% were Asian; 21% identified as Hispanic or Latino ethnicity. Patients had a mean HbA1c of 8.8 years and had a mean HbA1c of 8.2%. At baseline, 8.9% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m²) in 57.2%, mildly impaired (eGFR 60 to 90 mL/min/1.73m²) in 35.9% and moderately impaired (eGFR 30 to 60 mL/min/1.73m²) in 6.9% of patients. Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse events was also evaluated in a larger pool of patients with type 2 diabetes participating in 7 placebo- and active-controlled glycaemic control trials including two trials in Japanese patients evaluating the use of OZEMPIC® as monotherapy and add-on therapy to oral antidiabetic medications or insulin. In this population a total of 5159 patients with type 2 diabetes were treated with OZEMPIC® for a mean duration of 44.9 weeks. Across the treatment arms, the mean age of patients was 57 years, 3.2% were 75 years or older and 57% were male. In these trials, 60% were White, 6% were Black or African American, and 31% were Asian; 16% identified as Hispanic or Latino ethnicity. Baseline patients had type 2 diabetes for an average of 8.2 years and had a mean HbA1c of 8.2%. At baseline, 7.8% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m²) in 63.1%, mildly impaired (eGFR 60 to 90 mL/min/1.73m²) in 34.3%, and moderately impaired (eGFR 30 to 60 mL/min/1.73m²) in 2.5% of the patients. Common Adverse Reactions: Table 1 shows common adverse reactions including hypoglycemia, documented symptomatic (≤2 mmol/L glucose) and severe (≤1.5 mmol/L glucose) hypoglycemia in patients with type 2 diabetes treated with OZEMPIC® in placebo-controlled trials. These adverse reactions occurred more commonly on OZEMPIC® than on placebo, and occurred in at least 5% of patients treated with OZEMPIC®.

Table 1. Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of OZEMPIC®-Treated Patients with Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=262) %</th>
<th>OZEMPIC® 0.5 mg (N=260) %</th>
<th>OZEMPIC® 1 mg (N=251) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6.1</td>
<td>15.8</td>
<td>20.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.3</td>
<td>5.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.9</td>
<td>8.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4.8</td>
<td>7.3</td>
<td>5.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>5.0</td>
<td>1.5</td>
<td>3.1</td>
</tr>
</tbody>
</table>

In the pool of placebo- and active-controlled trials and in the 2-year cardiovascular outcomes trial, the types and frequency of common adverse reactions, including hypoglycemia, were similar to those listed in Table 1. Gastrointestinal Adverse Reactions: In the pool of placebo-controlled, gastrointestinal adverse reactions were more frequently associated with OZEMPIC® than placebo in patients treated with OZEMPIC® (15.3%, OZEMPIC® 0.5 mg 22.7%, OZEMPIC® 1 mg 36.4%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation. More patients receiving OZEMPIC® 0.5 mg (31%) and OZEMPIC® 1 mg (38%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.4%). In addition to the reactions in Table 1, the following gastrointestinal adverse reactions with a frequency of <5% were associated with OZEMPIC® (frequencies listed, respectively, as: placebo; 0.5 mg; 1 mg): dyspepsia (1.9%, 3.5%, 2.7%), eructation (0%, 2.7%, 1.1%), flatulence (0.8%, 0.4%, 1.5%), gastroesophageal reflux disease (0%, 1.9%, 1.5%), and gastritis (0.8%, 0.8%, 0.4%). Other Adverse Reactions: Hypoglycemia: Table 2 summarizes the incidence of events related to hypoglycemia by various definitions in the placebo-controlled trials.

Hepatic Impairment:
Table 2. Hypoglycemia Adverse Reactions in Placebo-Controlled Trials in Patients with Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Placebo</th>
<th>OZEMPIC® 0.5 mg</th>
<th>OZEMPIC® 1 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>(30 weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=129</td>
<td>N=127</td>
<td>N=130</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Documented symptomatic (≥5 mm/dL glucose threshold)</td>
<td>0%</td>
<td>1.6%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Severe or Blood Glucose Confirmed Symptomatic (≥55 mm/dL glucose threshold)</td>
<td>1.6%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Add-on to Basal Insulin with or without Metformin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(30 weeks)</td>
<td>N=132</td>
<td>N=132</td>
<td>N=131</td>
</tr>
<tr>
<td>Severe</td>
<td>0%</td>
<td>0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Documented symptomatic (≥50 mm/dL glucose threshold)</td>
<td>15.2%</td>
<td>16.7%</td>
<td>29.8%</td>
</tr>
<tr>
<td>Severe or Blood Glucose Confirmed Symptomatic (≥55 mm/dL glucose threshold)</td>
<td>5.3%</td>
<td>8.3%</td>
<td>10.7%</td>
</tr>
</tbody>
</table>

*Severe* hypoglycemia adverse reactions are episodes requiring the assistance of another person.

Hypoglycemia was more frequent when OZEMPIC® was used in combination with a sulfonylurea ([see Warnings and Precautions](#)). Severe hypoglycemia occurred in 0.8% and 1.2% of patients when OZEMPIC® 0.5 mg and 1 mg, respectively, was co-administered with a sulfonylurea. Documented symptomatic hypoglycemia occurred in 17.3% and 24.4% of patients when OZEMPIC® 0.5 mg and 1 mg, respectively, was co-administered with a sulfonylurea. Severe or blood glucose confirmed symptomatic hypoglycemia occurred in 6.5% and 10.4% of patients when OZEMPIC® 0.5 mg and 1 mg, respectively, was co-administered with a sulfonylurea.

### Injection Site Reactions

In placebo-controlled trials, injection site reactions (e.g., injection-site discomfort, erythema) were reported in 0.2% of OZEMPIC®-treated patients. Increases in Amylase and Lipase: In placebo-controlled trials, patients exposed to OZEMPIC® had a mean increase from baseline in amylase of 13% and lipase of 22%. These changes were not observed in placebo-controlled patients. Cholelithiasis: In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients treated with OZEMPIC® 0.5 mg and 1 mg, respectively. Cholelithiasis was not reported in placebo-treated patients. Increases in Heart Rate: In placebo-controlled trials, the mean increase in heart rate was 2.0 beats per minute in placebo-treated patients. Fatigue, Dyspepsia and Dizziness: Other adverse reactions with a frequency of ≥0.4% were associated with OZEMPIC® include fatigue, dyspepsia and dizziness.

### Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with OZEMPIC® may develop anti-semaglutide antibodies. 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, the incidence of antibodies to semaglutide in the studies described below cannot be directly compared with the incidence of antibodies in other studies or to other products. Across the OZEMPIC®- and active-controlled glycemic control trials, 32 (10.0%) OZEMPIC®-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in OZEMPIC® (i.e., semaglutide). Of the 32 semaglutide-treated patients that developed semaglutide ADAs, 19 patients (0.6% of the overall population) developed antibodies cross-reacting with native GLP-1. The in vivo activity of antibodies in this time. The in vivo activity of antibodies in this time. The in vivo activity of antibodies in this time.

### DRUG INTERACTIONS: Combinant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin: The risk of hypoglycemia is increased when OZEMPIC® is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin [see Warnings and Precautions]. Oral Medications: OZEMPIC® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, concomitantly administered oral medications were co-administered with OZEMPIC® if any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with OZEMPIC®.

### USE IN SPECIFIC POPULATIONS: Pregnancy: Risk Summary: There are limited data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy (see Clinical Considerations). Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. OZEMPIC® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In preclinical studies administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early postnatal losses and structural abnormalities were observed at below the MRHD (rabbit) and ≥5-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species ([see Data](#)). The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to be as high as 20–25% in women with a HbA1c >10. 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 fetal risk: Poorly controlled diabetes during pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity. Data: Animal Studies: OZEMPIC®-induced fetal abnormalities and reductions in body weight gain and food consumption were observed at all dose levels. In the offspring, reduced growth and fetuses with visceral (heart blood vessels) and skeletal (cranial bones, vertebra, ribs) abnormalities were observed at ≥0.0025 mg/kg/day, at clinically relevant exposures. In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.010, 0.0025 or 0.0005 mg/kg/day (≥5- and 100-fold the MRHD) were administered throughout organogenesis, from Gestation Day 6 to 19. Pharmocologically mediated reduced maternat body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at ≥0.0025 mg/kg/day, at clinically relevant exposures. In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (1.0-, 5.2-, and 14.9-fold the MRHD) were administered throughout organogenesis, from Gestation Day 16 to 50. Pharmocologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternbra, ribs) at ≥0.075 mg/kg twice weekly (≥5x human exposure). In a pre- and postnatal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (0.7-, 3.3-, and 7.2-fold the MRHD) were administered from Gestation Day 16 to 140. Pharmocologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with an increase in early pregnancy losses and led to delivery of slightly smaller offspring at ≥0.075 mg/kg twice weekly (≥5x human exposure). Life History: There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats, however, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear ([see Data](#)). The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for OZEMPIC® and any potential adverse effects on the breastfed infant from OZEMPIC® or from the underlying maternal condition. Data: In lactating rats, semaglutide was detected in milk at 0.005- and 0.015-fold the MRHD. Females and Males of Reproductive Potential: Discontinue OZEMPIC® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide ([see Use in Specific Populations](#)). Pediatric Use: Safety and efficacy of OZEMPIC® have not been established in pediatric patients (younger than 18 years).

### Geriatric Use: In the pool of placebo- and active-controlled glycemic control trials, 744 (23.6%) OZEMPIC®-treated patients were 65 years of age and over and 102 OZEMPIC®-treated patients (3.2%) were 75 years of age and over. In SUSTAIN 6, the cardiovascular outcome trial, 786 (46.0%) OZEMPIC®-treated patients were 65 years of age and over and 157 OZEMPIC®-treated patients (9.6%) patients were 75 years of age and over. No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Renal Impairment: No dose adjustment of OZEMPIC® is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed. Hepatic Impairment: No dose adjustment of OZEMPIC® is recommended for patients with hepatic impairment. In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed.

### OVERDOSAGE: In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of OZEMPIC® and its absorption over 1 week.

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For information about OZEMPIC® contact: Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, NJ 08536, 1-888-693-6742

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Date of Issue: January 2020

Version: 4

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

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Legal
52 Pharmacy Law
Pharmacy Attempts to Dispense Unwanted Prescription to Patient’s Ex-Wife
Joseph L. Fink III, BSPharm, JD, DSc (Hon), FAPhA

54 Legislative Focus
340B Assists Patients and Institutions
Sara Jo Santangelo and Joseph L. Fink III, BSPharm, JD, DSc (Hon), FAPhA

56 Independent Corner
FDA Finalizes Compounding Memorandum of Understanding
Ned Milenkovich, PharmD, JD

Consultation Counter

58 MTM Consult
Providing Support for Immunizations Is Critical
Jennifer Gershman, PharmD, CPh

62 Technician Focus
Help Patients Understand Drug Expiration Dates
Sarah Carpio, BS, and Shane P. Desselle, PhD, RPh, FAPhA

64 Patient Focus
Psychiatric Pharmacy Involves Advanced Clinical Training
Jennifer Gershman, PharmD, CPh

68 Women in Pharmacy
Female Pharmacists Are on the COVID-19 Frontlines
Suzanne Soliman, PharmD, BCMAS

70 Condition State Management
Seasonal Allergies Watch

OTC Product News

Rx Product News

Generic Product News
We’re proud to care for the hands that help care for us all.

Every day, pharmacists hold the health of others in their dependable hands. Their dedication to supporting, protecting, and caring for patients makes a daily difference… and also takes a daily toll. So whenever the hands that care for others need some care of their own, we’ve got them covered.
Continuing Education

75 Clinical Management of Allergic Conjunctivitis: Integrating Recommendations to Improve Treatment Outcomes

Educational Objectives for Pharmacists
At the completion of this activity, the participant will be able to:
• Identify the relationship between the pathophysiology and clinical presentation of allergic conjunctivitis
• Determine the role of current treatments for allergic conjunctivitis, with a focus on over-the-counter medications
• Personalize treatment recommendations for allergic conjunctivitis to optimize patient management and prevent associated complications

Educational Objectives for Pharmacy Technicians
At the completion of this activity, the participant will be able to:
• Describe allergic conjunctivitis, associated symptoms, and its impact on patients
• Outline treatment options for allergic conjunctivitis with a focus on over-the-counter medications
• Recognize the role of the pharmacy technician in referring patients who would benefit from counseling with the pharmacist and assisting patients with allergic conjunctivitis

92 Emerging Therapies in the Treatment of Central Precocious Puberty: A Review for Specialty Pharmacists
At the completion of this activity, the participant will be able to:
• At the completion of this activity, the participant will be able to:
  • Identify the epidemiology, etiology, clinical presentation, diagnosis, and clinical burden of central precocious puberty (CPP)
  • Examine the treatment landscape of CPP and compare pharmacologic therapies used for this condition
  • Explain the role of the specialty pharmacist in addressing unmet needs for patients with CPP to optimize clinical and economic outcomes

110 Advancements in Cardiovascular Disease Beyond Statins: Clinical Data and Evidence for Omega-3 Fatty Acids
At the completion of this activity, the participant will be able to:
• Examine the burden of atherosclerotic cardiovascular disease (ASCVD) and associated cardiovascular event risk
• Explore the role of omega-3 fatty acids in reducing ASCVD event risk and improving patient outcomes
• Analyze evidence-based guidelines, recent clinical trial outcomes, and cost utilization for current treatments that lower ASCVD risk in patients with elevated triglycerides
• Illustrate the role of the pharmacist in proper identification of patients at high risk for ASCVD events and provide recommendations to reduce risk and improve quality of care

« Continued from page 14
In a clinical trial a subgroup of adults with mild, age related cognitive impairment taking just one Prevagen a day, over 90 days were shown to improve in measurements related to memory.¹

- Only one capsule per day
- No known contraindications
- Safe and well-tolerated
- 30 day supply
- No common side effects
- Available in great-tasting chewable tablets

¹For more information visit www.prevagen.com/research

AGAINST THE BACKDROP OF COVID-19, the CDC reports that 81,230 deaths occurred from drug overdoses for the 12-month period ended May 2020, just a few months into the pandemic.

This increase of more than 18% from the 12 months prior represents the largest number of drug overdoses ever reported. Even more concerning are anecdotal evidence and some more recent localized data points suggesting that the drug epidemic and the pandemic and resulting economic downturn for tens of millions of Americans have created increased despair, more joblessness, and reduced social interactions.

Judicious Prescribing and Dispensing Are Now Largely in Place

Over the past decade, much effort has been made to increase opioid prescribing and dispensing stewardship. Although treatment for substance misuse itself has been historically underappreciated, a focused effort to reduce the total number of opioids dispensed has been largely successful, with multiprovider prescribing of opioids dropping by 62% in 11 states after prescription drug monitor programs were implemented. Nationwide, opioid prescribing fell about 40% from its peak in 2012 to the end of 2019.

Rates of Death Increase From Other Means of Access

Replacing many prescription-related opioid overdoses are community-acquired synthetic, illicit, and nonprescribed fentanyl drug trade) overdoses. In 2013, deaths from synthetic opioids (some prescribed but most illicit) were approximately 1 per 100,000 individuals. That skyrocketed 10-fold over the ensuing 3 years, exactly the time when judicious prescribing efforts began in earnest. This substitution effect was entirely predictable. We continue to fail at addressing the underlying issues, namely economic and social despair and lack of recognition and treatment for substance use disorder.

Our Role Will Expand to Include More Emphasis on Rescue and Treatment

The COVID-19 pandemic has brought upon pharmacy both recognition and strain through additional newsworthiness and responsibilities from activities like testing and mass vaccination efforts needing community penetration even beyond influenza vaccinations. We have done a lot as a pharmacy community to combat prescription-involved opioid overdoses. Yet, lack of access to treatment, both through formal treatment facilities and generalist health care providers, such as pharmacy or primary care, continues to plague our country.

Another Pandemic Rages on Beyond Our Consciousness

Opioid Overdoses Are Killing Nearly as Many of Our Neighbors and Patients as COVID-19 and in Much Younger Populations

By TROY TRYGSTAD, PHARMD, PHD, MBA, PHARMACY TIMES® EDITOR IN CHIEF

TROY TRYGSTAD, PHARMD, PHD, MBA, is the vice president of pharmacy provider partnerships for Community Care of North Carolina, which works collaboratively with more than 1800 medical practices to serve more than 1.6 million Medicaid, Medicare, commercially insured, and uninsured patients. He received his PharmD and MBA degrees from Drake University in Des Moines, Iowa, and his PhD in pharmaceutical outcomes and policy from the University of North Carolina at Chapel Hill. He also serves on the board of directors for the American Pharmacists Association Foundation and the Pharmacy Quality Alliance.

AUTHOR BIO
Expect a Postpandemic Renewed Focus on Overdoses

The COVID-19 pandemic may never go away (yes, we might have COVID-21 and COVID-22) and some form of the virus may become endemic worldwide over the next few years, but it will abate in our consciousness, emergency departments, and hospitals. That abatement will lead to a renewed focus on one of our leading causes of death in individuals younger than 65 years. Overdoses take away more life-years that some of our most prominent disease states and lead to more parents burying their own children than COVID-19 or any other infectious disease. And the number of overdoses is increasing, not abating.

What Health Care Providers Can Do, Including Pharmacists

The CDC recommends that health care providers engage in 3 categories of activities. For pharmacists, most of these are not new concepts, but we can aspire to more accessible and comprehensive versions of the pharmacy-based deployments we have now. Consider the following points:

Expand the provision and use of naloxone, and provide overdose prevention education.

- Co-prescribe naloxone to patients with high morphine milligram equivalents and those receiving benzodiazepines and opioids.
- Counsel patients that multiple doses of naloxone may be needed for a single overdose event because of the potency of illicitly manufactured fentanyl and fentanyl analogs and that multiple doses of naloxone may be needed over time because of the prolonged effects of opioids in some cases.
- Expand locations in which overdose prevention education and take-home naloxone are provided. These locations can include counseling and support groups, inpatient and outpatient treatment programs, primary care settings, retail pharmacies, and other community-based settings. Expanding locations may be especially important in rural areas.
- Prescribe naloxone to individuals at risk for opioid overdose, such as individuals with a prior history of overdose, patients with opioid use disorder (OUD), and those using illicit opioids and other drugs that might be mixed with illicitly manufactured fentanyl.
- Talk to patients about the changing illicit drug supply and risks for overdose and exposure to highly potent opioids, such as illicitly manufactured fentanyl.

Expand access to and the provision of treatment for substance use disorders.

- Provide medications for OUD.

Intervene early with individuals at the highest risk for overdose.

- Continue or initiate medications for OUD among individuals leaving correctional and detention facilities.
- Implement postoverdose response protocols, including in emergency departments, that incorporate links among community-based service organizations, health care and treatment providers, and public health agencies. These protocols promote linkage to care, medication for OUD, overdose education, naloxone distribution, and treatment.
- Provide active referral-to-treatment options and recovery support services.

We can assume that more will be asked of all health care providers including pharmacists in response to this continuing and growing epidemic overshadowed by the COVID-19 headlines. We should engage in new funding and programming from federal, local, and state legislation. It will soon be a good time to revisit the opioid stewardship and safety practices in place at pharmacies and broaden newly formed relationships with departments of health that resulted from the pandemic response.

REFERENCES

You recently celebrated National Pharmacist Day, and we asked what your hopes were for the pharmacy field in 2021. You answered.

Elizabeth G.: Provider status, acceptance, and respect when using the title Dr, better workplace conditions for community pharmacy, [and] reasonable reimbursement rates from [pharmacy benefit managers].

Shawn K.: I want to see pharmacists recognized as first responders, gain national provider status, and have their knowledge be utilized to their fullest capacities.

Jaclyn K.: Thank you, pharmacists! There are a handful that if it weren’t for them, I don’t think I’d be where I am today.

Kevin L.: The last couple of months have highlighted the focus and dedication of pharmacists across the nation. I look forward to seeing this continued in the new year.

Karen B.: [Pharmacists] have the COVID-19 vaccine!

Rob M.: [I hope] that retail pharmacies would get some more help.

Jenn C.: [I want] provider status.

Pharmacy Podcast Network: #NationalPharmacistDay—We want #Pharmacists to love their work, feel valued, and earn what they’re worth as health care’s most trusted providers.

Elizabeth G.: Recognize the profession and pharmacists at the national level more than it is done.

@prachi9732: Awareness in society...

@prankursaini001: 🎉🎉🎉 proud to be a pharmacist 😍

@fadia_farg: Pharmacist and extremely proud 😍
**Biologics License Applications and New Drug Applications**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Indication</th>
<th>Manufacturer</th>
<th>Date approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine (Posimir)</td>
<td>Indicated in adults for administration into the subacromial space under direct arthroscopic visualization to produce postsurgical analgesia for up to 72 hours following arthroscopic subacromial decompression</td>
<td>Durect Corporation</td>
<td>2/1/21</td>
</tr>
<tr>
<td>Tepotinib hydrochloride (Tepmetko)</td>
<td>Indicated for the treatment of adults with metastatic non–small cell lung cancer harboring MET exon 14 skipping alterations</td>
<td>EMD Seono Inc</td>
<td>2/3/21</td>
</tr>
<tr>
<td>Lisocabtagene maraleucel (Breyanzi)</td>
<td>Indicated as a chimeric antigen receptor T-cell therapy for adults with relapsed or refractory large B-cell lymphoma</td>
<td>Bristol Myers Squibb</td>
<td>2/5/21</td>
</tr>
<tr>
<td>Umbralisib tosylate (Ukoniq)</td>
<td>Indicated for the treatment of select patients with relapsed/refractory marginal zone lymphoma and relapsed/refractory follicular lymphoma</td>
<td>TG Therapeutics Inc</td>
<td>2/5/21</td>
</tr>
<tr>
<td>OnabotulinumtoxinA (Botox)</td>
<td>Indicated for the treatment of detrusor overactivity associated with a neurologic condition in pediatric patients age 5 years and older who have an inadequate response to or are intolerant of anticholinergic medication</td>
<td>Allergan</td>
<td>2/9/21</td>
</tr>
<tr>
<td>Cemiplimab-rwlc (Libtayo)</td>
<td>First immunotherapy indicated for patients with advanced basal cell carcinoma who were previously treated with a hedgehog pathway inhibitor (HHI) or when an HHI is not appropriate.</td>
<td>Regeneron Pharmaceuticals</td>
<td>2/9/21</td>
</tr>
<tr>
<td>Evinacumab-dgnb (Evkeeza)</td>
<td>Indicated as an adjunct to other low-density lipoprotein cholesterol-lowering therapies to treat patients aged 12 years and older with homozygous familial hypercholesterolemia</td>
<td>Regeneron Pharmaceuticals</td>
<td>2/11/21</td>
</tr>
<tr>
<td>Trilaciclib (Cosela)</td>
<td>Indicated to decrease the frequency of chemotherapy-induced myelosuppression in adults prior to administration of certain types of chemotherapy for extensive-stage small cell lung cancer</td>
<td>G1 Therapeutics</td>
<td>2/11/21</td>
</tr>
<tr>
<td>immune globulin intravenous [human] - ifas (Panziga)</td>
<td>Indicated for the treatment of adults with chronic inflammatory demyelinating polyneuropathy</td>
<td>Pfizer</td>
<td>2/15/21</td>
</tr>
<tr>
<td>Cemiplimab-rwlc (Libtayo)</td>
<td>Indicated as monotherapy treatment for patients with first-line advanced non–small cell lung cancer with a PD-L1 expression of 50% or more.</td>
<td>Regeneron Pharmaceuticals</td>
<td>2/22/21</td>
</tr>
<tr>
<td>Adalimumab (Humira)</td>
<td>Indicated for the treatment of moderately to severely active ulcerative colitis in pediatric patients ages 5 years and older</td>
<td>AbbVie Inc</td>
<td>2/24/21</td>
</tr>
<tr>
<td>Melphalan flufenamide (Pepaxto)</td>
<td>Indicated for use in combination with dexamethasone to treat adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy</td>
<td>Oncopeptides AB</td>
<td>2/26/21</td>
</tr>
</tbody>
</table>

FOR THE FULL FDA APPROVALS LIST, GO TO PHARMACYTIMES.COM.
Pharmacists Are Moderately Satisfied With Compensation, Job Satisfaction, Survey Shows (Part 3)

Results Show Respondents’ Top Drivers of Happiness in the Workplace Are Colleagues, Compensation, and Autonomy

By CAITLIN MOLLISON

THE FIRST PART OF THIS SERIES provided an overview of the results from the Pharmacy Times Salary and Job Satisfaction Survey; notably, when pharmacists were asked to rate their overall job satisfaction on a scale of 1 to 7 (with 1 being “not at all” and 7 being “extremely”), the average score among the 299 respondents was 4.53.

In the second part of this series, which examined pharmacists’ satisfaction with their total compensation, the average rating of the 299 respondents was 4.82.

In the third part of this series, we further explore pharmacists’ satisfaction with their jobs and the factors that contribute to their overall happiness in a position.

Pharmacy Times asked respondents to determine which 3 of the following factors are driving contributors to job satisfaction: autonomy, being a key opinion leader in the specialty, challenges, colleagues, compensation, dynamic profession, facility where they practice, frustration with providers, interactions with health insurance companies, limited scope of practice, management, work hours, work/life balance, and workload.

Of these options, the top 3 factors among 299 respondents were workload (19.7%), management (15.9%), and work/life balance (14.2%).

Pharmacists also rated how motivated they are by the potential for advancement in their organization, using the previously mentioned scale of 1 to 7. Among the 299 respondents, the average score was just 3.72.

When asked, if given the opportunity to start over, how likely they would be to choose a pharmacy career again, respondents were not particularly enthusiastic about following the same path—with an average rating of 3.78 among the 299 respondents.

Survey respondent Kent A. Purdy, RPh—a staff pharmacist at Legacy Silverton Medical Center Pharmacy in Portland, Oregon, who worked in retail pharmacies for 25 years before switching to a hospital pharmacy approximately 15 years ago—described working on the community pharmacy side as grueling.

“What started out as an enjoyable job became, with the advent of third-party billing in the late ’80s, a nightmare,” Purdy said. “By 2000, I was seriously looking for a change in careers or anything to get out of getting beat up physically, mentally, and emotionally every single day.

“I would like to see third-party billing and the problems involved with it separated from the pharmacist filling the prescription. Pharmacists need to use the knowledge they spent years learning for their patients.”
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Proprietary Zinc gluconate to shorten your cold

Homeopathic active ingredients to promote immune health*

Larger 25 count lozenges size

*Claim based on traditional homeopathic practice, not accepted medical evidence. Not FDA Evaluated.
FDA Allows More Flexible Storage, Transportation for Pfizer-BioNTech Vaccine

UNDILUTED, FROZEN VIALS OF the Pfizer-BioNTech coronavirus disease 2019 vaccine can be transported and stored at conventional temperatures commonly found in pharmaceutical freezers for up to 2 weeks, according to updated FDA guidance.1

Authorizations have required that vaccine vials be stored in freezers at temperatures between –112 °F and –76 °F, where they can be kept for up to 6 months. Before mixing with a saline solution, they could also be refrigerated for up to 5 days at standard refrigerator temperatures between 36 °F and 46 °F.2

The companies submitted new data to the FDA in February showing the stability of the vaccine at storage temperatures of –13 °F to 5 °F.2 This updated FDA guidance may make the vaccine more widely available and easier to stock.—Aislinn Antrim

Cancer Survivors Worry About Health Care Disruptions, Treatment

STUDY RESULTS SHOW THAT early in the COVID-19 pandemic, one-third of cancer survivors were concerned about potential disruptions to treatment or health care.

The impact of the pandemic on cancer survivors and the broader health care system has been widespread and exacerbated preexisting gaps in medical care, according to the study, published in the Journal of Psychosocial Oncology.

Investigators examined cancer survivor concerns around finances, infection, and treatment early in the pandemic using data from a survey taken between March 25, 2020, and April 8, 2020. Many survivors experienced disruptions in treatment, according to the study results.

A majority (77%) worried that they are at high risk for serious health effects and were concerned about intensive care unit admissions or death if they were infected with the coronavirus. Furthermore, 27% worried that the pandemic would make it difficult to afford cancer care and said that they were concerned about deciding whether food or medications would be more important.

The fear of infection and uncertainty over risk levels was pervasive for cancer survivors, leading to reported self-induced measures to reduce their risk of infection. These included strict social distancing and mask wearing. As a result, many respondents described feeling socially isolated, including feelings of isolation and loneliness.

An unanticipated theme was the concern expressed around the inability to bring a family member or friend to in-person appointments, according to the investigators.

Although participants respected and understood the limitations to protect health care staff and patients, cancer survivors seemed to be caught off-guard by the new rule, especially when receiving difficult news, such as a cancer recurrence.

“This study demonstrates the importance of clear communication between health care providers and patients experiencing concerns and uncertainties that may affect mental health during the pandemic as the care provision landscape continues to change,” study leader Corinne Leach, PhD, MPH, MS, from the American Cancer Society, said in a statement.—Aislinn Antrim

Phase 1 Trial for Intranasal, Single-Dose Vaccine Begins Enrollment

ALTIMMUNE INC HAS BEGUN enrollment for its phase 1 clinical trial of an intranasal, single-dose, coronavirus disease 2019 (COVID-19) vaccine candidate (AdCOVID), which could reduce logistical challenges for vaccine administration.

The vaccine candidate is an adenovirus-vector vaccine designed to stimulate a broad immune response, including both local and systemic immunity in the nasal cavity and respiratory tract. The trial will evaluate the immunogenicity and safety of the vaccine candidate in up to 180 healthy adult volunteers aged 18 to 55 years.

“While the roll out of currently available vaccines is an important first step in our efforts to slow the pandemic, there remains a critical need for vaccines that provide mucosal immunity,” Scot Roberts, PhD, chief scientific officer of Altimune, said in a statement.

“As pioneers in intranasal vaccine development, we believe AdCOVID has the potential for many advantages over currently available vaccines, including intranasal dosing and ease of distribution and storage, if the product is shown to have extended stability at room temperature, in addition to the potential ability to block transmission of the virus,” he said.

Trial participants will receive AdCOVID at 1 of 3 dose levels administered as a nasal spray, according to Altimune.

In addition to the primary end point of safety and tolerability, immunogenicity will be evaluated by mucosal IgA antibody from nasal samples, serum IgG binding and neutralizing antibody titers, and T-cell responses.

Vaccines delivered via intramuscular injection have not been shown to induce mucosal immunity in the nasal cavity, which may be effective in blocking transmission of SARS-CoV-2, according to Altimune.—Aislinn Antrim
Immune Response to Insulin Could Identify, Treat Those at Risk for T1D

EVALUATING IMMUNE RESPONSES TO insulin could help pinpoint individuals most at risk for developing type 1 diabetes (T1D), according to investigators from the Barbara Davis Center for Diabetes at the University of Colorado Anschutz Medical Campus.

The study measured immune responses from individuals genetically predisposed to developing T1D to naturally occurring insulin and hybrid insulin peptides. Because not all genetically predisposed individuals develop T1D, investigators sought to examine T-cell immune responses from the peripheral blood that could occur before the onset of clinical diabetes.

“We want to know why people develop T1D, and this research has helped provide a lot more information and data as to what it looks like when genetically at-risk individuals are headed towards clinical diagnosis,” investigator Aaron Michels, MD, said in a statement. “Ideally, you want to treat a disease when it’s active, so this is a need in our field to understand when people have an immune response directed against insulin producing cells.”

The research team collected blood samples from genetically at-risk adolescents every 6 months for 2 years. Inflammatory T-cell responses to hybrid insulin peptides correlated with worsening blood glucose measurements and progression to T1D development. The findings indicate an important advancement in identifying the risk of T1D early, as well as the potential for intervention.

“There are now therapies used in research studies that have delayed the onset of clinical type 1 diabetes,” Michels said. “Patients with these specific immune responses may benefit from immune intervention to delay T1D onset and possibly prevent it for years.”

Michels noted that these results can lead to research beyond T1D and into other autoimmune conditions. “Our work focused on diabetes, but this has implications for other autoimmune diseases,” he said. “Understanding how the immune system responds can be crucial in trying to prevent diseases before clinical symptoms are present.”—Jill Murphy

More US Adults Than Children Are Allergic to Peanuts

STUDY RESULTS SHOW THAT peanut allergy affect more American adults than previously thought, with about 1 in 6 adults developing the allergy after aged 18 years.

Peanut allergy affects at least 4.5 million adults in the United States but is often considered a pediatric concern, according to a statement from Northwestern University, which conducted the study.

For example, investigators pointed out that in 2020 the FDA approved a peanut allergy therapy for pediatric patients aged 4 to 17 years, but there are no FDA-approved therapies for patients with adult-onset peanut allergy.

According to Northwestern University, the study results provide the first detailed estimates of peanut allergy among adults in the United States and demonstrate that it may be more common than previously thought.

Although young adults are affected most often, peanut allergies affect adults of all ages.—Aislinn Antrim

Walking Patterns May Predict Type of Cognitive Decline in Older Adults

DIFFERENT PATTERNS IN THE way older adults walk could more accurately diagnose different types of dementia and identify Alzheimer disease, according to results of a study by London investigators from Lawson Health Research Institute (LHRI) and Canadian investigators from Western University.

Their findings were published in Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association.

The study compared step impairments across the cognitive spectrum, including individuals with Alzheimer disease, frontotemporal dementia, Lewy body dementia, mild cognitive impairment, Parkinson disease, and subjective cognitive impairment. The study also included cognitively healthy controls.

Pace, postural control, rhythm, and variability were identified as the 4 step patterns.

Only high-step variability—or stride-to-stride fluctuations in distance and timing that happen when we walk—was associated with lower cognitive performance, identifying Alzheimer disease with 70% accuracy, according to the study results.

“This is the first strong evidence showing that gait variability is an important marker for processes happening in areas of the brain that are linked to both cognitive impairment and motor control,” first author Frederico Perruccini-Faria of LHRI said in a statement.

The investigators found that when cognitive-cortical dysfunction is happening, an individual’s ability to perform multiple tasks at the same time is affected, such as chopping vegetables while talking with family members or talking while walking.—Jill Murphy
IS IT TIME FOR YOU TO START ON YOUR PATH TO PHARMACY OWNERSHIP?

Chances are, you chose your career in pharmacy because you wanted to provide quality care to patients. If that’s the case, you may be feeling frustrated in your current role, and you’re not alone. The two top complaints I hear from retail pharmacists are that they don’t have the freedom or flexibility to manage patient care their way, and that they crave more autonomy than chain pharmacy settings allow.

If you’re ready to make a change, it’s time to explore owning a Medicine Shoppe International, Inc. (MSI) franchise of your own. MSI can support you every step of the way, starting by helping you identify the right path to ownership. You can count on our team to deliver the resources you need to open your doors with confidence—and run a community pharmacy you’ll be proud of for decades to come.

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Choose from two powerful brands: The Medicine Shoppe® Pharmacy or Medicap Pharmacy®, based on the community you’ll serve. Both have strong brand recognition across the country, which you can leverage to jumpstart your pharmacy’s awareness from day one.

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When you join our elite network of independent pharmacies, we’ll get you started by:

• Performing a market analysis to help you determine the right location for your store.

<table>
<thead>
<tr>
<th>Not your typical franchise deal:</th>
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<tbody>
<tr>
<td>• $599 per month flat fee to join the network</td>
</tr>
<tr>
<td>• 5-year contract with 90-day out</td>
</tr>
<tr>
<td>• $300 credit for services that will help you succeed in a competitive industry</td>
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But we don’t stop there. We’ll also help you:

• Create a business performance plan that focuses on sound financial management.
• Implement business operations—store layout, staffing, inventory management, workflow management and more.
• Market your store with digital marketing tools that drive refills and patient engagement.
• Practice at the top of your license with patient care services like immunizations, point-of-care testing, medication therapy management and more.

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About Con Lane

Con Lane is the director of franchise development at Medicine Shoppe International, Inc. Con has more than 30 years of experience in franchise operations.
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For more than 50 years, Medicine Shoppe International, Inc. has been helping independent pharmacy owners become the healthcare destination for personalized care for families and their communities.
Orange County, Calif. — December 15, 2020 — The American Red Cross Southern California Region is proud to announce that Calmoseptine, Inc. has reached an impressive milestone: $1 million donated to the American Red Cross.

Since 2018, Calmoseptine, Inc. has been a steadfast partner of the Red Cross, making gifts in support of wildfire relief efforts, International Services, the Red Cross COVID-19 response, Canadian Red Cross preparedness efforts, Australian Bushfires response, and the Red Cross First Aid App.

Local Red Cross officials, including Glenn Maddalon, Chief Development Officer for the American Red Cross Southern California Region, and Sean Mahoney, regional chief executive officer of the American Red Cross Southern California Region, thanked Calmoseptine, Inc. for its ongoing commitment to the Red Cross mission.

Greg Dixon, founder of Calmoseptine, Inc. said “From wildfires to assisting the homeless, elderly, and underprivileged, Calmoseptine, Inc. donates to these causes and supports the Red Cross mission to help prevent and alleviate human suffering in the face of emergencies.”

Calmoseptine, Inc. also sponsors programs to teach those in need critical skills, such as health care services, to help people support themselves and their families. “This year, the Red Cross has faced unprecedented disasters, including the COVID-19 pandemic and historic western wildfires,” said Sean Mahoney, Regional CEO of American Red Cross Southern California Region. “Calmoseptine, Inc.’s ongoing support ensures the Red Cross can provide help and hope where it’s needed most.”

Each year, the American Red Cross responds to nearly 64,000 disasters across the country, including home fires, hurricanes, floods, earthquakes, tornadoes and wildfires. Red Cross services are provided to people in need of assistance at no cost and regardless of income through the generosity of Red Cross donors.

Individuals can help the American Red Cross continue to deliver its lifesaving mission by making a gift at redcross.org.

ABOUT CALMOSEPTINE, INC.

Greg Dixon, third owner of Calmoseptine® Ointment, founded Calmoseptine, Inc. in 1987.

Calmoseptine® Ointment was developed 70 years ago, by a pharmacist, as a diaper rash ointment. Since then, Calmoseptine® Ointment has been proven to be an excellent multi-purpose moisture barrier ointment, used by patients and healthcare professionals for many conditions involving the skin of both adults and children. For the second year in a row Calmoseptine® Ointment has won the US News and World Report’s survey for the #1 Pharmacist Recommended Brand in Incontinence-Related Skin Protectants.

Greg Dixon founded Calmo Manufacturing, Inc., a state-of-the-art facility dedicated exclusively to the manufacture of Calmoseptine® Ointment in 2010. This facility includes processing, robotic packaging and a Quality Control Department consisting of 3 Chemists and a Microbiologist operating under the highest standards of quality following cGMP, cGLP and ICH guidelines. Other features of Calmo Manufacturing, Inc. includes stability chambers, R&D equipment to improve product quality, and test equipment to analyze the purity of raw materials and finished product to assure conformity to USP standards.

Greg Dixon, donated over $950,000 in December 2019, to multiple children's hospitals such as CHOC (Los Angeles and Orange County), Rady Children's Hospital, and Shriner’s Children's Hospital. He also contributes over $500,000/year to pay for the utilities for women's and children's shelters, homeless shelters, and recovery centers. In addition, he donated $300,000 to Mercy House in Costa Mesa and provided the Mercy House with comfort kits. Dixon donated $350,000 to Meals on Wheels and $100,000 to Colette’s Children’s Home. Greg Dixon has supported many educational programs such as the Red Cross Nurse Assistant Training Program in the past and has donated generously to the Red Cross to help. He has many strategic ideas to help the homeless population and is consistently doing outreach to help local organizations.

ABOUT THE AMERICAN RED CROSS SOUTHERN CALIFORNIA REGION

The American Red Cross shelters, feeds and provides emotional support to victims of disasters; supplies about 40 percent of the nation’s blood; teaches skills that save lives; provides international humanitarian aid, and supports military members and their families. The Red Cross is a not-for-profit organization that depends on volunteers and the generosity of the public to perform its mission.
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Recognize Mental Illness Through Observation and Screening

Pharmacists Can Help Patients Find Appropriate Resources, Support, and Treatment

By KATHLEEN KENNY, PHARMD, RPH

Mental health is a state of well-being in which individuals can cope with life's stresses and function as civilized, productive members of society.

»
Before COVID-19 emerged, mental health statistics\(^1\) were already grim:\(^1\)

- About half of all mental health conditions begin by age 14 years.
- Depression affects 264 million people worldwide.
- Individuals with severe mental conditions die 10 to 20 years earlier than the general population.
- Mental illness costs more than $1 trillion annually.
- Suicide is the second leading cause of death in people aged 15 to 29 years.
- There is fewer than 1 mental health professional for every 10,000 people globally.

Since the lockdowns and isolation resulting from COVID-19 began a year ago, mental illnesses have increased in both intensity and number.\(^2\)

**SIGNS AND SYMPTOMS**

Mental health challenges look different for each individual affected. In fact, many individuals suffer from multiple mental illnesses. No mental health diagnosis is the same. Therefore, it can be difficult to recognize.

Let’s begin with a very basic review of several of the most common mental health disorders\(^3\):

- **Anxiety** can cause excessive fear or worry about imagined or real situations.
- **Attention deficit disorders** are some of the most common mental disorders in children. Often these disorders resolve in adulthood but not always. They are marked by a lack of focus and an inability to control impulsive behavior.
- **Bipolar disorder** is characterized by alternating episodes of depression and mania.
- **Depression** is different from normal grief and sadness, known as situational depression, and can cause anger, frustration, and/or sadness, often to the extreme.
- **Eating disorders** are driven by obsessive behaviors and thoughts surrounding body image. These disorders often involve overly indulging in calories, severely limiting calorie intake, or a combination, known as binging and purging.
- **Schizophrenia and psychotic disorders** are serious psychiatric disorders that can cause people to believe, hear, or see things that are not real.
- **Substance abuse disorders** involve excessive use of alcohol or drugs, often resulting from the attempt to self-medicate other mental health issues.

Generally, there are small changes in how individuals behave long before symptoms become serious. Some of these changes include alcohol or drug abuse; changes in eating habits, sleeping patterns, or school or work performance; decreased interest in grooming or hygiene; disorganized thoughts; disproportional fears or worries; emotional extremes; hypersensitivity to sights, smells, sounds, or touch; irritability or sadness that lasts longer than usual; isolation or withdrawal from family and friends; lack of focus; loss of interest in things that used to provide pleasure; and odd or unusual behavior.

**ASSESSING FOR MENTAL ILLNESS**

Screening tools are resources designed to help individuals or providers determine if there is a mental health issue that requires treatment. These resources can be in digital or written form. These tools use a database of standardized questions that can be different depending on the suspected diagnosis.

The answers to these questions provide valuable information on patient health and a starting point for diagnosis and treatment. This information can also be used to help both patients and providers set and measure goals during treatment.

Complete mental health assessments involve much more than just a screening questionnaire. Some possibilities include as follows\(^4\):

- **Cognitive evaluation** gauges the patient’s ability to reason, recall information, and think clearly. Questions may also be posed regarding the patient’s competence to perform daily responsibilities, such as caring for oneself or going to work.
- **Laboratory tests**, such as bloodwork, a brain scan, or a urine test, can help rule out other physical conditions. Brain tumors and substance abuse have been known to produce changes that mimic mental illness.
- **Mental evaluation** includes asking how symptoms affect daily life, if the patient has tried to treat them on his or her own, and what makes symptoms better or worse. It is also an opportunity to observe the patient’s behavior and physical appearance.
- **Mental health history** includes asking patients about how long they have had symptoms, if they ever had psychiatric treatment, and if they have a family or past history of mental illness.
- **Personal history** focuses on questions regarding the patient’s lifestyle, such marital status, what they do for a living, and their biggest sources of stress and any major traumas they have endured.
- **Physical exam** can help determine if anything else is wrong that may be manifesting as signs of mental illness, such as a neurological problem or thyroid disorder.
Screening questionnaires are often performed during an annual physical exam at a physician’s office, and pediatricians often complete a simple screening at every office visit because most mental illness surfaces early in life. These questionnaires can also be implemented at schools if school personnel feel it is necessary.

**PHARMACIST INVOLVEMENT AND RESOURCES**

Patients or parents may come to the pharmacy for advice about changing behaviors or questions about psychotropic medications. Pharmacists must take the time with patients to question them further. Below is a list of resources that pharmacists can use to print off screening questionnaires or to provide patients with resources to for more in-depth support.

**MENTAL HEALTH PROVIDERS**

Many types of providers can treat mental disorders. The most common include:

- **Licensed clinical social workers.** They have master’s degrees in social work and training in mental health and can diagnose mental disorders and provide counseling.

- **Licensed professional counselors.** Professional counselors usually have a master’s degree, but training requirements vary by state. They can diagnose mental disorders and provide counseling.

- **Psychiatrists.** These medical doctors specialize in mental health. They can diagnose and treat mental disorders and prescribe medications.

- **Psychologists.** Psychologists usually have a doctoral degree, but they are not medical doctors. They can diagnose and treat mental health disorders but cannot prescribe medications. Treatment usually includes talk-therapy either in a group or individually.

**REFERENCES**


<table>
<thead>
<tr>
<th>RESOURCES</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety and Depression Association of America</td>
<td>adaa.org</td>
</tr>
<tr>
<td>Children and Adults with Attention-Deficit/Hyperactivity Disorder (ADHD)</td>
<td>chadd.org</td>
</tr>
<tr>
<td>Depression and Bipolar Support Alliance</td>
<td>dbsalliance.org</td>
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<tr>
<td>International OCD Foundation</td>
<td>iocdf.org</td>
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<tr>
<td>National Center of Excellence for Eating Disorders</td>
<td>nceedus.org</td>
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<tr>
<td>Schizophrenia and Related Disorders Alliance of America</td>
<td>sardaa.org</td>
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<tr>
<td>Sidran Institute</td>
<td>sidran.org</td>
</tr>
<tr>
<td>Treatment and Research Advancements for Borderline Personality Disorder</td>
<td>tara4bpd.org</td>
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</table>
Help Patients Treat Headaches Safely

Prior to Making Any Recommendations, Always Screen for Possible Contraindications, Drug Interactions, and Therapeutic Duplications

By YVETTE C. TERRIE, BSPHARM, RPH

MOST INDIVIDUALS EXPERIENCE A HEADACHE from time to time, but for some it is routine, which can affect overall quality of life.

Many patients elect to use OTC analgesics for the self-treatment and management of headaches, but selecting products may be overwhelming, especially for individuals with other comorbidities and/or those taking other medications. An estimated two-thirds of OTC analgesics are used for headaches.1,2

The types of headaches most frequently amenable to self-treatment with OTC analgesics include diagnosed migraines, medication-overuse headaches, sinus headaches, and tension-type headaches, also known as stress headaches (see TABLE),1,3,4 according to the Handbook of Nonprescription Drugs.

The results of a survey showed that 24% of patients chronically overused OTC analgesics and that just 14.5% were ever advised by a health care professional to limit use of these agents for acute headaches.1,2 As frontline health care providers, pharmacists are positioned to guide patients in the proper use of these nonprescription analgesics and can encourage them to seek further medical evaluations when warranted if self-treatment is not appropriate, especially for those with recurring or severe headaches or undiagnosed migraines.

COUNSELING POINTS

Prior to making any recommendations, pharmacists should always screen for possible contraindications, drug interactions, and therapeutic duplications. Pharmacists can also identify those pharmacological agents that may cause or exacerbate headaches, make clinical recommendations accordingly and encourage patients to discuss concerns with their primary care providers.

Patients who do not find relief with the use of OTC analgesics should always be referred for further medical evaluation because effective prescription therapies are available that may be beneficial. When counseling patients about the use of OTC analgesics, pharmacists can relay the following information to them1:

1. Help Patients Treat Headaches Safely
2. Prior to Making Any Recommendations, Always Screen for Possible Contraindications, Drug Interactions, and Therapeutic Duplications
3. By Yvette C. Terrie, BSPHARM, RPH

AUTHOR BIO

Yvette C. Terrie, BSPHARM, RPH, is a consulting pharmacist and a medical writer in Haymarket, Virginia.
• Consult the primary care provider prior to using any of these products if breastfeeding or pregnant or if an individual has a preexisting medical condition or takes other medications.

• If appropriate, patients with diagnosed migraines who can predict the onset may benefit from taking an analgesic before the event known to trigger a migraine.

• Individuals with a history of hepatic disease should avoid the use of acetaminophen.

• Limit dosage of acetaminophen to no more than 4 grams per day to avoid potential liver damage.

• Take nonsteroidal anti-inflammatory drugs (NSAIDS) and salicylates with food or milk to avoid gastrointestinal (GI) upset.

In addition, caution patients not to do the following:1

• administer aspirin or other salicylates to children younger than 15 years who are recovering from chicken pox or have influenza symptoms;

• exceed recommended dosages; however, patients should discuss any concerns with a primary care provider;

• take aspirin if taking medications for arthritis, diabetes, or gout, unless directed by a primary care provider;

• take aspirin or NSAIDS if allergic to aspirin or have asthma or nasal polyps; take acetaminophen if appropriate instead;

• take aspirin or NSAIDS if there is a history of GI disorders, heart failure, kidney or liver disease, or ulcers;

• take NSAIDS if at high risk for cardiovascular disease or stroke unless under the supervision of a physician;

• take NSAIDS or salicylates if taking anticoagulants;

• take OTC analgesics for more than 3 days per week unless recommended by a health care provider;

• take products containing magnesium salicylate if an individual has renal disease;

• use naproxen for those younger than 12 years; and

• use these medications if consuming 3 or more alcoholic drinks per day. ■

### TABLE. Types of Headaches Most Amenable to OTC Treatments²,³,⁴

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tension</th>
<th>Migraine</th>
<th>Sinus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Bilateral, over the top of the head extending to neck</td>
<td>Classically unilateral</td>
<td>Discomfort, dull pain, and pressure-like sensation typically localized to the face, forehead, or periorbital or sinus area</td>
</tr>
<tr>
<td>Nature</td>
<td>Varies from diffuse ache to constricting, pressing, tight pain but not pulsing or throbbing</td>
<td>Throbbing sensation that may be preceded by an aura</td>
<td>Bilateral or dull pain that is worse in the morning or pressure behind the eyes or face</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual onset</td>
<td>Abrupt onset</td>
<td>Concurrent with sinus symptoms, including purulent nasal discharge</td>
</tr>
<tr>
<td>Causes/triggers</td>
<td>Anxiety, depression, emotional conflicts, stress, and other stimuli; eye strain from electronic device use and reading</td>
<td>Certain odors; changes in altitude, barometric pressure, eating patterns, or female hormones; fatigue; foods; irregular sleep patterns; lights; and medications, such as nitrates and oral contraceptives</td>
<td>Infection or blockage of the paranasal sinuses</td>
</tr>
<tr>
<td>Duration</td>
<td>Hours to days</td>
<td>Hours to 2 to 3 days</td>
<td>Days; typically resolves when sinus symptoms subside</td>
</tr>
<tr>
<td>Nonheadache symptoms</td>
<td>Muscle tension, neck pain, and scalp tenderness</td>
<td>Nausea and vomiting</td>
<td>Nasal congestion and discharge</td>
</tr>
</tbody>
</table>

For references, go to pharmacytimes.com/link/144.
OTC Cases

Common Cold

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

CASE 1: Rhinovirus in Children

**Q**
LS calls the pharmacy with questions regarding the rhinovirus, or the common cold, which her 2 boys contracted at school. Her children are aged 5 and 7 years and have had low-grade fevers, malaise, and nasal congestion for the past few days. What should the pharmacist recommend?

**A**
In children, the common cold is a mild viral illness, usually precipitated by rhinoviruses. Because the common cold is self-limiting and the data with OTC antihistamine, antitussives, and decongestants are lacking for children, the risks of starting OTC medications for children with rhinovirus outweigh the benefits. Nonpharmacologic treatment, including nasal saline irrigation, has been shown to relieve upper respiratory-tract infection symptoms and decrease school absences.¹² When choosing pharmacologic treatment for colds in children, data are limited to analgesics or antipyretics. If the symptoms of fever are bothersome, LS can give her children antipyretics acetaminophen or ibuprofen. Advise her to avoid combination products for the common cold in children.³

CASE 2: Common Cold During Pregnancy

**Q**
VK is a 29-year-old pregnant woman who asks about self-care for her cold symptoms, which started with a sore throat and then a runny nose. Her husband had the same symptoms a few days earlier, and Alka Seltzer Plus PowerMax helped him. VK had a low-grade fever earlier in the day and the previous night. She asks if she can use the same medication as her husband. What advice should the pharmacist give VK about Alka Seltzer Plus PowerMax?

**A**
Pharmacologic management of the common cold in pregnant patients is dependent on the availability of human data. Overall recommendations for pregnant patients are to target specific symptoms using nonpharmacologic and/or single-ingredient pharmacologic treatment. Advise to avoid combination, extra-strength, and long-acting OTC products. Alka Seltzer Plus PowerMax is a combination of dextromethorphan and phenylephrine for day and dextromethorphan, doxylamine, and phenylephrine for night. Given that VK has not reported a cough, she should avoid the cough suppressant dextromethorphan. VK should also avoid systemic decongestants, such as phenylephrine and pseudoephedrine, as they have been linked with malformations, such as abdominal wall defects, hip dislocation, and inguinal hernia.⁴ Advise her to use acetaminophen to address the fever. Intranasal cromolyn is considered a first-line treatment for a runny nose during pregnancy. Cromolyn is a mast cell stabilizer that treats rhinitis. Of note, antihistamines chlorpheniramine and diphenhydramine are also considered compatible with pregnancy.⁴ In addition to pharmacologic recommendations, VK should increase fluid intake and strive for adequate rest and a nutritious diet. Also advise her to increase humidity via humidifiers, steamy showers, or vaporizers. Hot tea with honey and lemon and salt water gargles may help ease her sore throat.⁴
CASE 3: Intranasal Spray

JP is a 24-year-old man who has a common cold and has been suffering from a headache, nasal congestion, and a sore throat for a few days. His physician recommended that he try Flonase Allergy Relief OTC nasal spray. JP brings Flonase to the pharmacy counter and asks how he should use it. How should the pharmacist counsel him?

Advise JP to first clear his nasal passages and always wash hands before and after use. If this is a new Flonase device or has not been in used in a week or more, he will need to prime the nozzle. To prime, aim the bottle away from the face, and hold the bottle with the nozzle placed between the first 2 fingers and the thumb placed on the bottom of the bottle. JP should pump until a fine mist is visible. If pumped 6 times and a mist is not visible, the Flonase spray nozzle may be clogged and would need to be cleaned. After priming, JP should prepare for use. To begin, he should gently press the opposite side of the nose with a finger to block off the passage. Next, JP should tilt his head forward and aim the tip of the Flonase delivery device away from nasal septum (center) to avoid damage. He should sniff deeply while pressing down on the pump once and repeat in the other nostril. JP should then breathe through his mouth and wait a few minutes after using the medication before blowing his nose. Remind him to avoid sharing nasal sprays and to discard the medication if discolored or expired or if contamination is suspected. Advise JP to remove caps before use and replace tightly after each use.⁵

CASE 4: Zinc

MP is a 54-year-old woman with hypertension who is asking about supplements to treat a cold and is specifically interested in zinc. Her OTC medication options are limited because she has hypertension. What information should the pharmacist provide about the use of zinc for the common cold?

Zinc has been studied in vitro for its antiviral properties, and it may provide modest antiviral efficacy. It is reported that high local concentrations of zinc block the adhesion of human rhinovirus to the nasal epithelium. It also thought that zinc inhibits viral replication by disrupting viral capsid formation. The results of a meta-analysis concluded that zinc lozenges or syrup at 75 mg or more per day are effective in decreasing cold duration or symptoms if started within 24 hours of the first symptom and administered every 2 hours. The study results applied regardless of the zinc salt. In terms of prevention, the study results showed that if zinc is used for 5 months or longer, there is a potential for decreased risk of cold. A variety of formulations of zinc are available, including capsules, chews, lozenges, oral sprays, syrups, and tablets. There was previously a nasal formulation of zinc, but it has been removed from the market due to reports of lost sense of smell with intranasal cold remedies containing zinc. Advise MP to take oral formulations of zinc with food because it may be associated with gastrointestinal adverse effects, such as bitter taste, nausea, or upset stomach if taken on an empty stomach.⁶
Banana Bag Oral Solution
Manufactured by Banana Bag Solutions, LLC
An alternative to intravenous dehydration and vitamin therapy, Banana Bag Oral Solution is pharmacist developed, contains only the necessary ingredients to treat dehydration, and has proven efficacy to bring hydration status back to baseline. It is formulated with a high-dose B-complex powder capable of achieving significant absorption of critical B vitamins into the bloodstream, making this a novel approach to treat dehydration and offer vitamin therapy concomitantly, without the needle.

FOR MORE INFORMATION:
bananabagdrink.com

Calm Sweet Calm Gummies
Manufactured by Hum Nutrition Inc
As the newest addition to Hum Nutrition’s vitamin and supplement offerings, Calm Sweet Calm is formulated with ashwagandha root and L-theanine to control and reduce symptoms of stress. Ashwagandha root extract is an adaptogen that has been studied for its stress-reducing effects when used over time, and L-theanine boosts individuals’ moods and improves relaxation without drowsiness, according to the company. Available in a sour cherry flavor, the gummies are gluten free, sustainably sourced, vegan, and do not contain artificial colors or preservatives.

FOR MORE INFORMATION:
humnutrition.com

COVID-19 Home Test
Manufactured by Ellume
Ellume’s coronavirus disease 2019 at-home test is the first FDA-approved OTC test for the disease. This product is a rapid, lateral-flow antigen test that detects fragments of proteins of the severe acute respiratory syndrome coronavirus 2 from a nasal swab. It is approved for individuals 2 years and older and offers results in as little as 15 minutes. The kit includes a Bluetooth-connected analyzer that displays the test result on the user’s smartphone. Priced at $30, the test showed an overall sensitivity of 95% and specificity of 97% when results were compared with a reverse-transcription polymerase chain reaction laboratory test.

FOR MORE INFORMATION:
ellumehealth.com

Pedialyte with Immune Support
Manufactured by Abbott
Pedialyte with Immune Support combines Pedialyte’s standard balanced electrolytes and glucose with prebiotics; vitamins B12, C, and E; and zinc to deliver advanced rehydration and promote digestive health and immune support. Especially timely with the growing interest in immune health during the COVID-19 pandemic, the product is available in 1-liter bottles and powder pack formulations and comes in fruit punch and mixed berry flavors.

FOR MORE INFORMATION:
pedialyte.com
Recommend quality you can trust

USP has tested and verified ingredients, potency and manufacturing process. USP sets official standards for dietary supplements. www.uspverified.org
MOST PHARMACISTS KNOW THAT ANTIHYPERTENSIVES, weight loss, smoking cessation, and statins are the cornerstones of treating cardiovascular disease (CVD). Other successful strategies include maintaining good dental care, identifying and treating depression early, following a low-sodium diet that includes plenty of fish and roughage, limiting alcohol, getting regular and sustained exercise, and managing stress. These facts are well known among health care providers and often promoted in public health campaigns, so why do many Americans have poor cardiovascular health? Unfortunately, many are aware of these recommendations but have trouble implementing them.

LOWDOWN ON ASPIRIN

For years, clinicians advised taking low-dose aspirin daily to prevent CVD. But healthy individuals should not take daily aspirin to prevent heart disease. Guidance on daily low-dose aspirin use changed in 2019. The American College of Cardiology (ACC) and the American Heart Association (AHA) recommend daily aspirin only for patients who have had a heart attack, open heart surgery, or a stroke. Routine low-dose aspirin use in individuals without CVD appears to lower the incidence of heart attack or stroke by 17%, which is significant. But it increases the risk of gastrointestinal bleeding by 47% and the risk of intracranial bleeding by 34%. The news that aspirin’s anticoagulation effects and the risk of major bleeding outweigh its CVD preventive benefit may not have filtered down to the millions of Americans who are not at risk and have not had CVD. In addition, individuals with risk factors for CVD who have not experienced an event benefit more from lowering blood pressure and cholesterol levels, losing weight, and quitting smoking.

Treating Cardiovascular Disease Means Making Choices

Encourage Patients to Adhere to Medication and Recommendations, but Also Deprescribe When Warranted, Ensure That Immunizations Are Up-to-Date, and Share New Information

By JEANNETTE Y. WICK, MBA, RPH, FASCP

TABLE 1. Considerations When Deprescribing Statins

Because statins’ long-term benefits are unknown, especially in older adults with comorbidities, prescribers and clinicians should consider the following:

- Actual or potential drug interactions
- Adherence and cost
- Deteriorating functional status
- Health priorities
- Hepatic and renal function
- Life expectancy < 1 year
- Outcome goals
- Presence of confirmed adverse drug reactions, such as confusion, constipation, diarrhea, falls, memory loss, muscle symptoms, and nausea

AUTHOR BIO

JEANNETTE Y. WICK, MBA, RPH, FASCP, is the assistant director of the Office of Pharmacy Professional Development at the University of Connecticut School of Pharmacy in Storrs.
STATIN THERAPY: WHEN TO STOP

As mentioned, statins are essential in CVD management in individuals with elevated low-density lipoprotein cholesterol levels (≥ 190 mg/dL), patients aged 40 to 75 years with diabetes mellitus, and those at cardiovascular risk. However, statins need not be a lifelong commitment.3 As patients age, especially past 75 years, those with no CVD symptoms may not need statins.4 This issue is receiving more attention as the proportion of individuals in this age group grows. The results of one study showed that discontinuing statins in patients older than 75 years with life expectancies of less than a year significantly improved quality of life, lowered medication costs by $3.37 per day, and reduced the medication burden.5

Although controversy surrounds the issue of discontinuing statins in older adults, evidence is accumulating. Older adults who have had a heart attack, ischemic attacks, or stroke should continue their medications. Clinicians should remember that a small increase in geriatric-specific adverse effects could offset the cardiovascular benefit. TABLE 1 lists considerations for deprescribing.6,7

LET’S TALK IMMUNIZATION

Patients with CVD need to stay up-to-date with adult immunizations (TABLE 2).8,9 They also will have questions about the coronavirus disease 2019 (COVID-19) vaccines. The message they need to hear is simple: Individuals who have CVD risk factors, had a heart attack or stroke, or have heart disease are at much greater risk from adverse effects of COVID-19 than they are from the vaccine. Patients with CVD may be concerned that their weakened immune systems are a contraindication. The vaccines for COVID-19 do not contain live virus, so patients with CVD need not worry.10

CONCLUSIONS

Although the ACC/AHA updated their joint guideline in 2019, the bulk of their recommendations remained the same.1 As pharmacists encourage patients with CVD to adhere to medications and well-known recommendations, they should also deprescribe when warranted; disseminate new information, such as stopping use of unnecessary low-dose aspirin; and ensure that adult immunizations are up-to-date. ■

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### TABLE 1. Vaccines Recommended for Adults With Cardiovascular Disease*8,9

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>Annually</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Patients younger than 65 years:</td>
</tr>
<tr>
<td></td>
<td>• PPSV23 (Pneumovax) 1 dose</td>
</tr>
<tr>
<td></td>
<td>• Asplenic and immunosuppressed patients may also need a 1-time dose of PCV13 (Prevnar).</td>
</tr>
<tr>
<td></td>
<td>Patients 65 years or older:</td>
</tr>
<tr>
<td></td>
<td>• A second dose of PPSV23, given at least 5 years after the previous dose</td>
</tr>
<tr>
<td></td>
<td>• The health care provider and the patient may also decide whether the patient would benefit from a dose of PCV13, if they have not received it. If so, space PCV13 and PPSV23 1 year apart.</td>
</tr>
<tr>
<td>Tdap</td>
<td>1 dose to start, and revaccinate every 10 years</td>
</tr>
<tr>
<td>Zoster</td>
<td>Patients 50 years or older:</td>
</tr>
<tr>
<td></td>
<td>• A 2-dose series of zoster vaccine recombinant, adjuvanted (Shingrix), even if already vaccinated with zoster vaccine live (Zostavax)</td>
</tr>
</tbody>
</table>

PCV13, pneumococcal conjugate vaccine; PPSV23, pneumococcal polysaccharide vaccine; Tdap, tetanus, diphtheria, and pertussis.
Ioteprednol etabonate ophthalmic suspension 0.25% (Eysuvis)
Marketed by Kala Pharmaceuticals

The FDA has approved Eysuvis, making it the first ocular corticosteroid for the treatment of dry eye disease and the first prescription therapeutic to specifically address short-term needs of patients with dry eye disease. Dry eye disease is a chronic condition affecting the ocular surface and tears and can cause discomfort, ocular inflammation, tear film instability, and visual disturbance. The solution is indicated for up to 2 weeks of use in patients with dry eye disease based on the results of 4 clinical trials. Kala plans to launch Eysuvis in the United States by year-end.

FOR MORE INFORMATION:
kalarx.com

Crizotinib (Xalkori)
Marketed by Pfizer Inc

Crizotinib is the first FDA-approved biomarker-driven therapy for relapsed/refractory anaplastic large cell lymphoma (ALCL) in children and young adults. The treatment is indicated for pediatric patients 1 year and older with ALK-positive relapsed/refractory ALCL. ALCL is a rare form of non-Hodgkin lymphoma (NHL) and accounts for approximately 30% of NHL cases in young people. Approximately 90% of pediatric patients and young adults with ALCL are ALK positive. The most common adverse reactions to the drug in clinical trials included decreased appetite, diarrhea, fatigue, headache, musculoskeletal pain, nausea, stomatitis, vision disorder, and vomiting.

FOR MORE INFORMATION:
pfizer.com

Darolutamide (Nubeqa)
Marketed by Bayer

The FDA has approved a supplemental new drug application to add overall survival and other secondary end point data from the phase 3 ARAMIS trial to the prescribing information for darolutamide for the treatment of patients with nonmetastatic prostate cancer (nmCRPC). Darolutamide led to a 31% reduction in the risk of death, extending survival for patients with nmCRPC. The additional findings are time to pain progression and time to the initiation of cytotoxic chemotherapy, and the prescribing information also was updated to include further guidance on drug interactions. The final analysis of the trial reinforced the safety profile of darolutamide with an extended follow-up of median 29 months for the overall study population, according to a company press release.

FOR MORE INFORMATION:
nubeqa-us.com

Anakinra (Kineret)
Marketed by Sobi

The FDA has expanded the indication for anakinra to include treatment of deficiency of IL-1 receptor antagonist (DIRA), an ultrarare, autoinflammatory disease. The FDA approved anakinra in November 2001 for treatment of moderate to severe active rheumatoid arthritis and in January 2013 for treatment of a severe form of cryopyrin-associated periodic syndromes. The efficacy and safety of anakinra for DIRA were evaluated in a long-term natural history study including 9 patients with genetically confirmed DIRA, aged 1 month to 9 years at the start of the study, who were treated with anakinra for up to 10 years. All 9 patients achieved inflammatory remission while on anakinra treatment.

FOR MORE INFORMATION:
kineretrx.com
INDICATION
EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

IMPORTANT SAFETY INFORMATION
Contraindication:
EYSUVIS, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Warnings and Precautions:
Delayed Healing and Corneal Perforation: Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. The initial prescription and each renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining.

Intraocular Pressure (IOP) Increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP.

Cataracts: Use of corticosteroids may result in posterior subcapsular cataract formation.

Bacterial Infections: Use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, corticosteroids may mask infection or enhance existing infection.

Viral Infections: Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections: Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid application. Fungus invasion must be considered in any persistent corneal ulceration where a corticosteroid has been used or is in use.

Adverse Reactions:
The most common adverse drug reaction following the use of EYSUVIS for two weeks was instillation site pain, which was reported in 5% of patients. Please see Brief Summary of Prescribing Information for EYSUVIS on the next page.
EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, for topical ophthalmic use

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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WARNINGS AND PRECAUTIONS

Delayed Healing and Corneal Perforation—Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to corneal perforation. The initial prescription and each renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining.

Intraocular Pressure (IOP) Increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP.

Cataracts—Use of corticosteroids may result in posterior subcapsular cataract formation.

Bacterial Infections—Use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, corticosteroids may mask infection or enhance existing infection.

Viral Infections—Use of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ophthalmic corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections—Fungal infections of the cornea are particularly prone to develop coincidently with long-term local corticosteroid application. Fungus invasion must be considered in any persistent corneal ulceration where a corticosteroid has been used or is in use. Fungal cultures should be taken when appropriate.

Risk of Contamination—Do not to allow the dropper tip to touch any surface, as this may contaminate the suspension.

Contact Lens Wear—The preservative in EYSUVIS may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of EYSUVIS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS

Adverse reactions associated with ophthalmic corticosteroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

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 most common adverse reaction observed in clinical trials with EYSUVIS was instillation site pain, which was reported in 5% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy—Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 1.4 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 34 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 3.4 times the RHOD. Maternal toxicity was observed in rats at doses 347 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 34 times the RHOD.

The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data—Animal Data: Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (1.4 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (5.6 times the RHOD). At 3 mg/kg (41 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (83 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day.

Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent inominate artery at 5 mg/kg (34 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (347 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (695 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (3.4 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg.

A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (3.4 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (34 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (347 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

Lactation—There are no data on the presence of loteprednol etabonate in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for EYSUVIS and any potential adverse effects on the breastfed infant from EYSUVIS.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—No overall differences in safety and effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, in a chromosome aberration test in human lymphocytes, or in vivo in the single dose mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (174 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused pre-implantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (34 times the RHOD).

For a copy of the Full Prescribing Information, please visit www.EYSUVIS.com.

Manufactured for:
Kala Pharmaceuticals, Inc.
Watertown, MA 02472
Part # 2026R02
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October 2020
Kala®
US-EYS-2000115
The FDA has approved Gavreto (pralsetinib) from Blueprint Medicines Corporation for the treatment of metastatic RET fusion–positive non–small cell lung cancer (NSCLC) as detected by an agency-approved test, advanced or metastatic RET-mutant medullary thyroid cancer (MTC) requiring systemic therapy, and advanced or metastatic RET fusion–positive thyroid cancer requiring systemic therapy in patients who are radioactive iodine refractory. RET fusions and mutations drive many types of cancer. Approximately 1% to 2% of patients with NSCLC and 10% to 20% of patients with papillary thyroid cancer cases have RET fusion–positive tumors, and approximately 90% of patients with advanced MTC harbor RET mutations. Gavreto received an accelerated approval based on the overall response rate and duration of response. Its continued approval may be contingent upon additional confirmatory trials.

**Pharmacology and Pharmacokinetics**

Gavreto is a kinase inhibitor of wild-type RET and oncogenic RET fusions and mutations.

After a single oral dose, the median time to peak concentration is 2 to 4 hours. Gavreto reaches steady-state concentrations after 3 to 5 days of treatment. Gavreto displays a mean elimination half-life of 15.7 hours after a single dose and 20 hours after multiple doses.

**Dosage and Administration**

The recommended dosage of Gavreto is 400 mg orally once daily on an empty stomach. Counsel patients to avoid food consumption for at least 2 hours before and at least 1 hour after their doses. Only patients with a gene mutation or RET gene fusion should receive treatment with Gavreto. When used for NSCLC, Gavreto is approved for adult patients only. When used for MTC or thyroid cancer, it is approved for patients 12 years and older. Gavreto is supplied as 100-mg capsules.

**Clinical Trials**

The phase 1/2 ARROW clinical trial evaluated Gavreto in patients with RET fusion–positive metastatic NSCLC. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR). In 87 patients previously treated with platinum chemotherapy, the ORR was 57% with a 5.7% complete response rate, and the median DOR was not estimable. In 27 treatment-naive patients who were ineligible for platinum-based chemotherapy, the ORR was 70%, with an 11% complete response rate, and the median DOR was 9 months.

The ARROW trial also evaluated Gavreto in patients with RET-mutant MTC and RET fusion–positive metastatic thyroid cancer. In 55 patients with RET-mutant metastatic MTC who were previously treated with cabozantinib, vandetanib, or both, the ORR was 60%, and the median DOR was not reached. In 29 patients with RET-mutant advanced MTC who were cabozantinib and vandetanib treatment-naive, the ORR was 66%, and the median DOR was not reached. In 9 patients with RET fusion–positive metastatic thyroid cancer, the ORR was 89%, and the median DOR was not reached.

**Contraindications, Warnings, and Precautions**

There are no contraindications to treatment with Gavreto. Fatal, life-threatening, or severe interstitial lung disease or pneumonitis can occur in patients using Gavreto, which may require dose reduction or permanent or temporary discontinuation of treatment. Patients with uncontrolled hypertension should have their blood pressure (BP) controlled prior to beginning Gavreto. BP should be checked after 1 week of treatment and at least monthly during treatment. Subsequent hypertensive episodes may warrant the medication to be permanently discontinued, reduced, or withheld. Because serious hepatic adverse reactions have occurred, alanine aminotransferase and aspartate aminotransferase should be monitored before beginning Gavreto, every 2 weeks during the first 3 months, and monthly thereafter. Hepatotoxicity may require discontinuation or dose reduction of Gavreto. Tumor lysis syndrome has been reported in patients with medullary thyroid carcinoma who used Gavreto. Gavreto should be permanently discontinued in patients with a life-threatening or severe hemorrhage. Gavreto should not be used for at least 5 days prior to elective surgery and for at least 2 weeks after major surgery. The medication can cause fetal harm. Women of reproductive potential should use an effective nonhormonal contraceptive during treatment and for 2 weeks after their last dose. Gavreto should not be used during breastfeeding.

Concomitant use of Gavreto with strong CYP3A inhibitors should be avoided. Gavreto should not be used concurrently with combined P-glycoprotein and strong CYP3A inhibitors, but if this combination cannot be avoided, the dose of Gavreto should be reduced. Coadministration of Gavreto with strong CYP3A inducers should be avoided, but if this is not possible, the dose of Gavreto should be increased.

The most common adverse reactions are constipation, diarrhea, fatigue, hypertension, and musculoskeletal pain.
AS OUR NATION CONDUCTS A large-scale coronavirus disease 2019 (COVID-19) immunization campaign, it is critically important for health care workers who administer the vaccine to understand proper intramuscular (IM) administration technique to avoid a disabling and preventable occurrence known as shoulder injury related to vaccine administration (SIRVA).

This is especially important because health care workers who may not normally give vaccinations may be called upon to help administer the new COVID-19 vaccines.

SIRVA is a shoulder injury triggered by the incorrect injection of a vaccine into the shoulder capsule (joint) rather than the deltoid muscle. It is caused by using an incorrect IM injection technique or improperly landmarking the IM injection site (the deltoid muscle) resulting in the unintended injection of the vaccine and/or trauma from the needle into and around the underlying bursa of the shoulder. The resulting inflammatory process causes injury to the musculoskeletal structures of the shoulder, such as bursae, ligaments, and tendons.1,2

Symptoms of SIRVA include persistent shoulder pain, limited range of motion, and weakness. These typically develop within hours to a few days after receiving a vaccination. These symptoms do not improve with OTC analgesics. The resulting chronic shoulder pain and inability to carry out daily activities that were possible prior to vaccination often lead patients to seek medical intervention. Patients are often diagnosed with inflammatory shoulder injuries, such as adhesive capsulitis, bursitis, frozen shoulder syndrome, and rotator cuff tears. These do not appear any different than routine shoulder injuries, except that the shoulder symptoms started within days of an IM deltoid vaccination.1

HOW TO PREVENT SIRVA
The key to avoiding SIRVA is to recognize the anatomical landmarks for identifying the deltoid muscle and to use proper IM administration technique. Proper landmarking of the deltoid muscle requires determining the lower and upper borders of a safe injection zone. First, the patient’s shoulder should be exposed completely. When a shirt cannot be removed, the arm should be removed from the sleeve or the sleeve should be rolled up, rather than pulling the shirt’s neck over the shoulder. To ensure the injection is given below the shoulder capsule, measure 2 to 3 finger widths from the acromion (bony prominence above the deltoid) to identify the upper border of the injection zone. The lower border can be marked by the armpit to ensure that the injection is not inserted below the deltoid muscle. Eyeballing the injection site is not acceptable. The forefinger and thumb can be used to make a V to outline the deltoid muscle and keep the injection zone visible before injecting the needle at a 90-degree angle. Injections too close to the shoulder capsule can lead to SIRVA. Injections below or too far to the side of the deltoid muscle can hit the radial or axillary nerve, respectively, which can result in neuropathy or paralysis.1

INFECTION
Safeguard Patients During COVID-19 Immunization Campaigns
Shoulder Injuries Are a Real Concern Because Some Health Care Workers May Be New to Administering Vaccines
BY MICHAEL J. GAUNT, PHARMD

AUTHOR BIO
MICHAE L J. GAUNT, PHARMD is a medication safety analyst and the editor of ISMP Medication Safety Alert! Community/Ambulatory Care newsletter at the Institute for Safe Medication Practices in Horsham, Pennsylvania.
Multiple resources related to proper vaccination techniques are provided by the Centers for Disease Control and Prevention and the Immunization Action Coalition. Many of these resources, including checklists, e-learning with continuing education credits, and videos, have been recently updated and are applicable to the COVID-19 vaccination campaign. Additionally, the University of Waterloo School of Pharmacy in Ontario, Canada, offers a helpful infographic on proper landmarking to prevent SIRVA. (www.cfp.ca/content/cfp/suppl/2019/01/18/65.1.40.DC1/SIRVA.pdf).

**ERROR REPORTING IS MANDATORY**

As noted in the fact sheets for the COVID-19 vaccine products available under an emergency use authorization (EUA) from the United States Food and Drug Administration, reporting of adverse events (AEs), including medication errors, is mandatory. Providers or their designees must report all medication errors and serious AEs using the methods noted in the specific product fact sheet and within the specified period. Errors related to the COVID-19 vaccines must be reported to the Vaccine Adverse Event Reporting System (VAERS; https://vaers.hhs.gov/). Consult the specific EUA product’s fact sheet for the required reporting method.

In addition, consider informing the Institute for Safe Medication Practices (ISMP) about any actual or potential errors involving these vaccines via email (ismpinfo@ismp.org) or the ISMP website (www.ismp.org). However, with EUA vaccines, reporting to the ISMP will not replace the need for mandatory reporting to VAERS.
Asthma Biologics Can Improve Global Access to Treatment

Patients Need Education Beforehand to Ensure the Medications Make a Significant Difference

By AISLINN ANTRIM

BECAUSE BIOLOGIC MEDICATIONS FOR ASTHMA can significantly improve the burden of the disease and reduce mortality, offering more generic options would pave the way for widespread use of these treatments.

Some investigators, however, argue that more awareness and education are necessary before this approach can be effective on a large scale.

Asthma can take a significant toll on both communities and individuals, with a current mortality estimation of 0.19 deaths per 100,000 people, according to a recent article published in World Allergy Organization Journal. Moreover, investigators have found higher mortality rates in low- and middle-income countries, where lack of access to medical resources and other socioeconomic conditions create barriers to care.

Although investigators observed a global decline in the rate of annual asthma mortality until the 1980s, that line seems to have flattened. No further reduction was registered between 2006 and 2012, but rates in the United States have continued to progressively decline since the late 1990s.

The availability of monoclonal antibodies, an important biologic treatment option for asthma, are largely limited to developed and high-income countries, and the investigators noted that “asthma management systems” in low- and middle-income countries suffer from various restrictions that limit the widespread availability of biologics for asthma.

“The availability of generic drugs in the field of biologics for severe asthma could contribute to facilitate their widespread accessibility,” the authors wrote. “But before that, awareness and expertise regarding severe asthma and proper tools to assess and manage it deserve to be shared worldwide.”

Bronchial asthma is one of the most common noncommunicable respiratory diseases, affecting more than 300 million people globally, according to the investigators. Recent epidemiological studies have found that the prevalence of bronchial asthma among the general population is 4.5% on average; although bronchial asthma is higher in developed countries, less-developed nations are seeing increasing numbers.

Severe asthma affects less than 5% of patients with asthma, according to the investigators, who defined it as a heterogeneous disease characterized by different biologic and clinical phenotypes. Although biologic drugs for asthma are a relatively recent development, they have resulted in a radical change to the therapeutic approaches to severe asthma, especially of the T2-high phenotype, the investigators wrote.

Oral corticosteroids and the monoclonal antibodies targeting IgE-, IL-4/IL-13-, and IL-5–driven inflammation have been shown to significantly reduce exacerbations and hospitalizations in patients with severe asthma, according to the article.

“In other words, biologics for severe asthma are going to have a significant impact on the burden of the disease and on its mortality rate,” the authors wrote. “However, access to these treatment options is still very limited in some areas.”

To investigate the availability of biologics, the investigators conducted a literature review of Medline and PubMed and explored marketing data of biologics, including benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab.

They found that omalizumab is the most accessible biologic drug, except in Eastern European countries, India, and many countries in the Middle East. In Africa, access to omalizumab is limited to Egypt. Mepolizumab is slightly more limited, with marketing activity in Canada, Europe, Russia, and the United States. It is not available in Africa, Central and South America, and Eastern countries.

Reslizumab is less accessible, limited to North America, Mediterranean European countries, and Northern Europe, excluding Switzerland.

Benralizumab is available only in a few European countries and in North America, according to the authors.

Finally, the authors said that dupilumab has seen a recent growth in marketing after the FDA approved it in 2018 as add-on maintenance therapy in patients with moderate to severe asthma. It has become available in the Arabian peninsula, Brazil, Brunei, Colombia, Israel, Japan, Russia, and South Korea. The European Medicines Agency approved dupilumab for the treatment of severe asthma.
in 2019, but its distribution is limited to just a handful of European countries.

The availability of biologic products globally is dynamic, with all the companies producing monoclonal antibodies for asthma committed to broadening the global market for these treatments, according to the investigators. However, they added that the gap between high-income countries and low-income countries is still substantial and predicted that the situation will not change anytime soon.

The cost of drugs is probably a major cause for this gap, with low-income countries unable to cover the costs related to biologic drugs, including acquisition, storage, and final delivery to patients. Furthermore, in many areas, the investigators noted that health care services lack the basic tools for a proper asthma assessment and physicians’ expertise regarding biologics is scarce.

Investigators said that the expenses of biologics and common treatments, such as inhaled steroids, often lead to an overuse of short-acting beta-agonists and oral corticosteroids. Although this trend has also been seen in Western countries, the investigators said that it may be more exacerbated in low-income countries and more connected with asthma morbidity and mortality.

These obstacles must be addressed before the introduction of generic biologics for asthma can make a significant difference, according to the investigators.

“However, each one of the currently recommended therapies for asthma control, including biologic drugs, should be accessible worldwide as a major strategy for reducing [oral corticosteroid] use and their costs in terms of morbidity,” the investigators said. “This should be considered a priority by the national health systems and by the stakeholders in the field....”
**Tadalafil tablets**  
**Manufactured by Glenmark Pharmaceuticals Limited**  
**Compare to:** Cialis  
The FDA has approved Glenmark Pharmaceuticals' Tadalafil Tablets USP 2.5, 5, 10, and 20 mg, indicated for erectile dysfunction and the treatment of benign prostatic hyperplasia (BPH). BPH is a common condition caused by an enlarged prostate gland, which can cause uncomfortable urinary symptoms and bladder, kidney, or urinary tract problems. The most common adverse reactions to Tadalafil Tablets include back pain, dyspepsia, flushing, headache, limb pain, myalgia, and nasal congestion. According to IQVIA sales data for the 12-month period ending November 2020, Cialis Tablets 2.5, 5, 10, and 20 mg had annual sales of approximately $125.5 million.  

**FOR MORE INFORMATION:**  
glenmarkpharma.com

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**Venlafaxine hydrochloride ER**  
**Manufactured by Camber Pharmaceuticals**  
**Compare to:** Effexor ER  
Camber’s Venlafaxine Hydrochloride ER tablets are indicated to treat major anxiety, depressive disorder, and panic disorder. By restoring the balance of norepinephrine and serotonin in the brain, the drug can improve energy levels and mood and may help restore individuals’ interest in daily living. The tablets are available in doses of 37.5, 75, 150, and 225 mg and in 30- and 90-count bottles. Adverse effects can include dizziness, drowsiness, fatigue, headache, nausea, stomach pain, and weakness.  

**FOR MORE INFORMATION:**  
camberpharma.com

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**VERTICALLY INTEGRATED**
Abiraterone acetate tablets, 500 mg
Manufactured By Amneal Pharmaceuticals, Inc

Compare to: Zytiga
The FDA has approved an additional strength of 500 mg for Amneal’s Abiraterone Acetate Tablets USP 250 mg. The tablets are used in combination with prednisone for the treatment of metastatic prostate cancer, which affects approximately 50% of men diagnosed with local prostate cancer. Abiraterone acetate can have mild or serious adverse effects, including cough, diarrhea, edema, headache, fatigue, and joint pain. Amneal immediately initiated commercialization activities upon FDA approval.

Febuxostat tablets
Manufactured by Dr Reddy’s Laboratories Ltd

Compare to: Uloric
Dr Reddy’s febuxostat tablets are indicated to lower uric acid levels in individuals with gout. Gout is a form of arthritis characterized by redness, severe and sudden pain attacks, swelling, and tenderness in joints, especially the joint at the base of the big toe. Nausea may occur when taking febuxostat, and serious liver disease or an increase in liver enzymes is a rare but serious adverse effect. The tablets are available in 40- and 80-mg strengths. The Uloric brand and generic had US sales of approximately $108 million for the 12 months ending October 2020, according to IQVIA data.

FOR MORE INFORMATION:
drreddys.com

FOR MORE INFORMATION:
amNeal.com

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Pharmacy Law

Pharmacy Attempts to Dispense Unwanted Prescription to Patient’s Ex-Wife

State Court of Appeals Allows Lawsuit for Negligence and Recovery of Punitive Damages to Proceed

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

ISSUE OF THE CASE

When an unwanted prescription for erectile dysfunction (ED) is revealed to the patient’s ex-wife, may the patient maintain a lawsuit against the pharmacy for negligence and punitive damages?

FACTS OF THE CASE

A patient in a southwestern state had a routine visit with his physician, during which the practitioner offered the patient a sample of a medication for ED. The patient accepted the sample. Later, staff members at a national pharmacy chain called the patient to let him know that the prescription medication he regularly used was ready to be picked up, along with the medication for treatment of ED. The patient told the staff member that he did not want to pick up and use the ED medication, and the staff member acknowledged the cancellation of the ED medication.

One month later, the patient called the pharmacy to check on a refill for his regular medication, and he was again told that the ED medication also was ready. Again, he informed the pharmacy staff member that he did not want to pick up the ED medication.

The following day, the patient called the pharmacy to give permission for his ex-wife to pick up his medication. He and she were attempting to reconcile at the time. Nonetheless, when she came in to get the medication for him, the pharmacy staff members offered her his regular medication along with the ED medication. She declined the latter but joked with the employee of the chain about the prescription and its use. The ex-spouse allegedly also told friends and the children of the couple about the prescription. Reconciliation efforts by the two were then halted.

The patient filed suit against the pharmacy chain alleging negligence and other tortious acts, intending to seek both compensatory and punitive damages. The attorneys for the pharmacy chain filed a motion with the trial court judge to dismiss all the claims in the lawsuit. The judge agreed with the pharmacy chain’s motion and dismissed all claims. The patient appealed that decision to the state court of appeals, arguing that all or part of the trial court judge’s decision was in error.

THE RULING

The appellate court concurred with the trial court judge as to dismissal of a number of the tort claims but differed with regard to both the basic claim of negligence and the claim that punitive damages could be recovered.

AUTHOR BIO

JOSEPH L. FINK III, BSPHARM, JD, DSC (HON), FAPHA, is a professor of pharmacy law and policy and the Kentucky Pharmacists Association Professor of Leadership at the University of Kentucky College of Pharmacy in Lexington.
THE COURT’S REASONING
The appellate court first focused on the claim by the patient/plaintiff about notifying the pharmacy staff members on 2 occasions that he did not want the ED medication; that, along with the fact that a staff member joked with his ex-spouse, may support the claim that the pharmacy chain and its employees did not act in good faith. The pretrial discovery process may shed some light on precisely what transpired in those situations, so the appellate court sent those bases of the negligence claim back to the trial court for further proceedings.

The plaintiff had argued that the federal Health Insurance Portability and Accountability Act (HIPAA) could be used at the level of the state trial court to establish or at least inform what was appropriate or not with regard to giving a patient’s information to another, such as his ex-wife.

The state appellate court acknowledged that the federal statute does not confer on an individual’s private right to sue to recover damages. The punishment for a violation of HIPAA is a federally imposed fine.

On the other hand, that federal statute does not expressly prohibit a private lawsuit for “negligent and egregious disclosure of protected health information.”

Additionally, to permit nongovernmental, state-level, private lawsuits based on a claim of negligent disclosure of protected health information using a HIPAA-derived standard would not interfere with the efforts of the federal government to enforce the statute and its mandates.

The state appellate court concluded that it would indeed be permissible for the trial court to which it was returning the matter to “inform the standard of care in a state-law negligence action” with HIPAA-derived expectations and legal duty of care.

HIPAA does not block claims for wrongful disclosure of patient information based on state law.

Punitive damages are awarded as pure and simple punishment. That contrasts with the much more commonly encountered compensatory damages designed to compensate or reimburse the plaintiff for expenses incurred.

One very important facet of punitive damages is that they may not be paid by the defendant’s liability insurance coverage like compensatory damages would be. What punishment would it be to the defendant if the insurer paid that assessment?

Public policy prohibits the insurance underwriter from paying for or reimbursing punitive damage assessments.

One argument that the plaintiff advanced to support punitive damages was that the pharmacy chain rewarded employees for the amount of pharmacy sales, thereby contributing to the failure of the pharmacy staff to cancel the ED prescription twice.

The matter was sent back to the state trial court.
CONGRESS ENACTED SECTION 340B of the Public Health Service Act in 1992, 2 years after the Medicaid Drug Rebate Program of 1990, which ensured eligible state facilities received drug products at the lowest price possible.

In 1992, Congress extended this relief beyond just Medicaid patients to any eligible health care facility treating a large volume of low-income patients. Low income is loosely defined. In some contracts, it is based on a variation of income threshold compared with the federal poverty line. Covered entities (CEs), also known as safety net facilities, must meet certain criteria to be eligible for these drastic discounts from manufacturers. Requirements include but are not limited to being operated and/or owned by the federal or state government or a private or public nonprofit organization. In 1992, hospital participation in the program was low, at just 45 facilities. In 2010, Congress expanded the program to cancer centers, rural hospitals, and rural referral centers (disproportionate share adjustment percentage greater than 8%), dramatically expanding participation. By December 2020, the number of CEs, according to the Health Resources and Services Administration, was 69,365.

Of all the parties involved in health care—community pharmacies, hospitals, insurance companies, manufacturers, patients, etc—which parties support this program? Believe it or not, insurance companies and patients see little to no change in pricing. This program is strictly between CEs and manufacturers. Patients’ co-payment do not change, and insurance underwriters are billed the same amount.

The process looks like this: Manufacturers discount a medication significantly, and the hospital then bills the insurance for the full price of the medication, maximizing their revenue on that 1 transaction. However, 340B claims cannot be explained simply by looking at 1 transaction. The next patient who is treated may come in requiring the same treatment, without insurance. In this situation, hospitals would treat the patient equally and absorb the costs. It is important to realize that most of these CEs are nonprofit and, at the end of the day, their ethical decision to take the loss on treating a patient without insurance is covered with previous encounters that earned them revenue.
Why would the manufacturers participate in this? Manufacturers do benefit. To have their drug on the Medicaid formulary, they also must participate in the 340B program. Not participating in these programs would limit access to their medication by the Medicaid population. In some socioeconomic areas, Medicaid may be the predominant insurance, affecting many patients.

Unlike some of the CEs discussed previously, drug manufacturers are profitable businesses, and they constantly try to minimize the number of eligible 340B claims to maximize their bottom dollar. But let’s not overlook the fact that these companies profit trillions of dollars. 340B claims only consist of 8% of the US drug market; 92% of the claims are not granted this program relief. The drug industry is not hurting. The 340B program is not as detrimental to the drug manufacturers as it is vital to the health care facilities that rely on it.

The 340B program is not perfect; a lot of details are constant topics of debate. To be transparent, some recent controversies with this program include contract pharmacies. A contract pharmacy is an “outside” pharmacy that is in a voluntary agreement with a CE to gain access to affordable medications for 340B eligible patients. This expands the CE’s revenue for providing health care services to patients because they obtain their prescriptions at outside pharmacies. This allows community pharmacies to get 340B pricing through CEs for eligible patients and results in splitting profits with the CE. This is controversial because community pharmacies are profiting when using this relief program that was initially designed for nonprofit facilities. Community pharmacies do profit from these contracts, but it is important to understand that through this process, CEs are increasing the revenue generated for providing care to patients, who in hindsight may not have been able to receive care without the program’s support.

In 2010, an edit was made to allow CEs to increase the number of contract pharmacies from 1 per CE to unlimited. Since then, the number of contract pharmacies has increased by 4000%. As of December 2, 2020, there were 189,920 contract pharmacies and 69,365 CEs. That means, on average, each CE has 2.74 contract pharmacies. Some CEs have agreements with upward of 400 contract pharmacies. Manufacturers are not supportive of this concept. They see it as giving discounted drugs to community pharmacies that typically would pay full price.

REFERENCES
FDA Finalizes Compounding Memorandum of Understanding
States Must Adopt Protection Within a Year and Increase Requirements, or Pharmacies Face Consequences

By NED MILENKOVICH, PHARMD, JD

IN 2012, A FUNGAL MENINGITIS OUTBREAK OCCURRED because of questionable sterile compounding methods in a Massachusetts compounding pharmacy.

After more than 750 cases, including more than 60 fatalities, the federal government forced into action new legislation known as the Drug Quality and Security Act (DQSA), which has been largely shepherded by the FDA. As a part of the DQSA under section 503A, the FDA is instructed to formulate a memorandum of understanding (MOU) with every state. The FDA has developed the MOU in close consultation with various industry stakeholders, as described in section 503A of the DQSA, and on October 26, 2020, the agency finalized the MOU. Each state now has 1 year to adopt it.

States play a vital role in reducing the risks associated with compounded drugs while ensuring appropriate patient access, according to the FDA.

For example, if a compounder distributes drugs to multiple states, the FDA has taken the position that it can be difficult to gather information about possible adverse events associated with those drugs, connect them to the compounder, and undertake coordinated action to address a potentially serious public health problem.

The FDA claims that the MOU is a key public health protection in the law and addresses certain interstate distributions of compounded drugs by traditional compounders.

The FDA views the MOU as a partnership with each state pharmacy boards to help stem any public health threat from poorly compounded drug preparations.

One key issue in the development of the standard MOU is how to define the statutory term “inordinate amounts,” which refers to compounded drugs that are distributed interstate. Pharmacy distribution of inordinate amounts of compounded drugs is a threshold for information sharing by a state and would not impose a limit on the number of compounded drugs that a compounder could distribute interstate.

The MOU also requires state investigations of complaints associated with compounded drugs that have been distributed out of state. States that enter the MOU with the FDA will investigate complaints about drugs compounded at a pharmacy within their states and distributed outside the states and advise the FDA when they receive reports of serious adverse drug experiences or product quality issues, such as drug contamination.
STAKEHOLDER CONCERNS
One area of concern raised by stakeholders throughout this process was that some states might need additional resources to collect the information requested. To address this potential resourcing issue, the FDA has entered into an agreement with the National Association of Boards of Pharmacy to make an information-sharing network available to the states. Through this network, states will be able to obtain from pharmacies in their states information and report it directly and transmit it to the FDA.

Another area of interest has been the limit on prescription orders distributed out of state. Section 503A limits distribution of compounded drugs outside the state by a pharmacist, pharmacy, or physician located in a state that has not entered the MOU to 5% of its total prescription orders dispensed or distributed.

STAKEHOLDER LAWSUIT
Just 1 day after the FDA finalized the MOU, several pharmacies sued the agency. The case, Wellness Pharmacy Inc et al v Azar et al accuses the FDA of exceeding its regulatory authority, failing to consider the administrative burden of the MOU, not properly engaging in administrative rule promulgation, and generally failing to obtain input from all the state pharmacy boards across the country.

A central issue in the lawsuit rests with the FDA’s definition of the term “distribution” to include “dispensing,” thus giving the agency regulatory authority over the act of pharmacy dispensing.

The plaintiffs claim that the FDA’s definition of distribution contradicts state laws; various model acts; the Federal Food, Drug and Cosmetic Act; and other federal laws. Although numerous stakeholders from pharmacy groups and organizations objected, the FDA thinks that dispensing and distribution are not distinguishable acts and that Congress established the inclusion of dispensing to a patient and distribution to health care practitioners, hospitals, or other entities as a single act in the DQSA.

States that signed the MOU within the 1-year period that began October 26, 2020, agreed to commit to investigating, documenting, and reporting to the FDA anytime a pharmacy ships compounded drugs to patients across state lines above threshold amounts set forth in the MOU. States also must adhere to time-sensitive reporting requirements to the FDA under certain circumstances when discovering an issue with a pharmacy.

In short, any compounding pharmacy doing business in a state that has signed the MOU will have increased regulatory burdens and requirements to share information and be subjected to additional layers of federal and state regulatory oversight.

Although it is unclear how many states are objecting to adoption of the MOU, there are rumblings that several have reservations about moving forward with it.

Pharmacies in the states that have indicated that they will not sign the MOU will be subjected to a 5% limit on interstate transactions of compounded drug products, which is otherwise commonly referred to as the 5% rule.

REFERENCE

States play a vital role in reducing the risks associated with compounded drugs while ensuring appropriate patient access.
Providing Support for Immunizations Is Critical
Pharmacists Play an Integral Role in Disease Prevention Through Vaccine Education and Administration

By Jennifer Gershman, PharmD, CPh

As the coronavirus disease 2019 (COVID-19) pandemic persists throughout the United States, pharmacists’ roles in providing immunizations continue to expand.¹

The US Department of Health & Human Services recently authorized licensed pharmacists and pharmacy interns to administer vaccines to patients aged 3 to 18 years to expand access to childhood immunizations and prevent many diseases.² Additionally, pharmacists and pharmacy interns acting under the supervision of the qualified pharmacist are authorized to administer COVID-19 vaccines to individuals 3 years and older, subject to specific requirements.³ Pharmacists play an important role in medication therapy management (MTM) services through vaccine education and administration (see FIGURE).⁴,⁵

As accessible and trusted health care professionals, pharmacists are in a great position to provide immunizations in the community setting.⁴ Pharmacies have extended business hours and efficient vaccine administration measures in place,⁴ and evidence shows that pharmacists improve immunization rates, which can lead to a reduction in vaccine-preventable diseases.⁵

In an interview, Wendy H. Updike, PharmD, BCPS, CDCES, assistant professor of pharmacy practice/ambulatory care clinical pharmacist at the University of South Florida Taneja College of Pharmacy in Tampa, discussed her role in immunizations at a family medicine department within a university setting. She administers all immunizations with a focus on diphtheria; hepatitis B; influenza; tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap); 13-valent pneumococcal conjugate vaccine; 23-valent pneumococcal polysaccharide vaccine; and tetanus.

Updike said that she listens to patients’ concerns about vaccines and provides education to counter misinformation and myths. She emphasized that vaccines do not cause autism and that individuals cannot get the flu from the influenza vaccine.

“I [also] let them know that even though there are 4 strains of the virus in the flu vaccine, they could still potentially get sick with another strain that is not covered,” Updike said. “However, having the vaccine will help reduce the severity of symptoms and length of illness.”

High-risk patients, such as older individuals or those with diabetes, receive counseling about serious complications from the flu, such as pneumonia, which can be prevented or reduced with an annual influenza vaccine.

During the COVID-19 pandemic, Updike is working remotely and seeing patients via telehealth. She reviews all patients’ immunization records and recommends that individuals visit their local pharmacies for the needed vaccines.

» Continued on page 61
Updike said that once COVID-19 vaccines are available, the goal is to administer them to patients in the family medicine clinic. “If this is not possible due to storage requirements or limitations, then we will most likely have a COVID-19 vaccine clinic set up somewhere in the building where patients will be able to make an appointment to have the vaccine administered,” she said.

**CASE STUDY AND COUNSELING PEARLS**
JM is a 70-year-old woman who is visiting the MTM clinic for a comprehensive medication review. During the review, the pharmacist discovers that JM has never received a Tdap vaccine. Additionally, JM’s daughter is pregnant, so it is especially important for her to be vaccinated before her granddaughter is born. The pharmacist explains that newborns do not have fully developed immune systems, which makes them vulnerable to infections. It is important that family members are up-to-date on all routine vaccines, such as influenza and Tdap. Pertussis is especially dangerous for newborns because they do not begin their own pertussis vaccine series until they are 2 months old. It is important for JM to get the Tdap vaccine at least 2 weeks before her granddaughter is born so that it is fully effective. Evidence shows that the efficacy of the Tdap vaccine wanes over time, so it is important to get a booster shot every 10 years with either the Tdap or the tetanus and diphtheria (Td) vaccine. Previously, only the Td vaccine was recommended for the 10-year booster; however, the Advisory Committee on Immunization Practices updated its recommendations to allow either the Td or Tdap vaccine for the 10-year booster. Common adverse effects (AEs) that may occur after Tdap administration include injection-site body aches, chills, fatigue, fever, headache, pain, redness, or swelling. Severe AEs associated with the Tdap vaccine are rare.

The proportion of adults 19 years and older reporting having received any tetanus toxoid–containing vaccine during the past 10 years is 63.4%, according to a National Health Interview Survey on vaccination coverage among adults in the United States in 2017. This demonstrates room for improvement, and pharmacists can play an important role in improving Tdap immunization rates through vaccine education.
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Most common gastrointestinal adverse reactions are: nausea, abdominal distension, vomiting and upper abdominal pain. **DRUG INTERACTIONS:** Drugs that increase risk of fluid and electrolyte imbalance.

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CONTRAINdications: Use is contraindicated in the following conditions: gastrointestinal obstruction or ileus, bowel perforation, toxic colitis or toxic megacolon, gastric retention. Warnings and Precautions: Serious Fluid and Electrolyte Abnormalities: Advise all patients to hydrate adequately before, during, and after the use of SUTAB. If a patient develops significant vomiting or signs of dehydration after taking SUTAB, consider performing post-colonoscopy lab tests (electrolytes, creatinine, and BUN). Fluid and electrolyte disturbances can lead to serious adverse events including cardiac arrhythmias, seizures and renal impairment. Correct fluid and electrolyte abnormalities before treatment with SUTAB. Use SUTAB with caution in patients with conditions, or who are using medications, that increase the risk for fluid and electrolyte disturbances or may increase the risk of adverse events of seizure, arrhythmias, and renal impairment, Cardiac arrhythmias: Use caution when prescribing SUTAB for patients at increased risk of arrhythmias (e.g., patients with a history of prolonged QT, uncontrolled arrhythmias, recent myocardial infarction, unstable angina, congestive heart failure, or cardiomyopathy). Consider pre-dose and post-colonoscopy ECGs in patients at increased risk of serious cardiac arrhythmias, Seizures: Use caution when prescribing SUTAB for patients with a history of seizures and in patients at increased risk of seizure, such as patients taking medications that lower the seizure threshold (e.g., tricyclic antidepressants), patients withdrawing from alcohol or benzodiazepines, or patients with known or suspected hyponatremia; Use in Patients with Risk of Renal Injury: Use SUTAB with caution in patients with impaired renal function or patients taking concomitant medications that may affect renal function (such as diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or non-steroidal anti-inflammatory drugs). These patients may be at risk for renal injury. Advise these patients of the importance of adequate hydration with SUTAB and consider performing baseline and post-colonoscopy laboratory tests (electrolytes, creatinine, and BUN) in these patients; Colonic Mucosal Ulcerations and Ischemic Colitis: Osmotic laxative products may produce colonic mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Concurrent use of stimulant laxatives and SUTAB may increase these risks. Consider the potential for mucosal ulcerations resulting from the bowel preparation when interpreting colonoscopy findings in patients with known or suspected inflammatory bowel disease (IBD); Use in Patients with Significant Gastrointestinal Disease: If gastrointestinal obstruction or perforation is suspected, perform appropriate diagnostic studies to rule out these conditions before administering SUTAB. Use with caution in patients with severe active ulcerative colitis. ADVERSE REACTIONS: Most common gastrointestinal adverse reactions are: nausea, abdominal distension, diarrhea, vomiting and upper abdominal pain. POTENTIAL FOR DRUG ABSORPTION: SUTAB can reduce the absorption of other co-administered drugs. Administer oral medications at least one hour before starting each dose of SUTAB. Administer tetracycline and fluoroquinolone antibiotics, iron, digoxin, chloropromazine, and penicillamine at least 2 hours before and not less than 6 hours after administration of each dose of SUTAB to avoid chelation with magnesium. Pregnancy: There are no available data on SUTAB use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. No reproduction or developmental studies in animals have been conducted with sodium sulfate, magnesium sulfate, and potassium chloride (SUTAB). Lactation: There are no available data on the presence of SUTAB in human or animal milk, the effects on the breastfed child, or the effects on milk production. Pediatric Use: Safety and effectiveness in pediatric patients has not been established. Geriatric Use: Of the 471 patients who received SUTAB in pivotal clinical trials, 150 (32%) were 65 years of age or older, and 25 (5%) were 75 years of age or older. No differences in safety or effectiveness of SUTAB were observed between geriatric patients and younger patients. Elderly patients are more likely to have decreased hepatic, renal or cardiac function and may be more susceptible to adverse reactions resulting from fluid and electrolyte abnormalities. STORAGE: Store at 20º to 25ºC (68º to 77ºF). Excursions permitted between 15º to 30ºC (59º to 86ºF). See USP controlled room temperature. Rx only. Manufactured by Braintree Laboratories, Inc. Braintree, MA 02185

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Help Patients Understand Drug Expiration Dates

Use Basic Knowledge of Medications to Be the First Line of Defense in Ensuring Safety and Maintaining Pharmacy Workflow

By SARAH CARPIO, BS, and SHANE P. DESSELLE, PHD, RPH, FAPHA

UNDERSTANDING AND KEEPING TRACK OF DRUG EXPIRATION dates can be difficult for patients.

There are times when patients may unintentionally stock up on medications and forget to check the date on their OTC medication packages or prescription bottles, which might be printed in small font and in a location that is not obvious. Patients may consistently receive their supply of maintenance prescription medications, take them as scheduled, and yet still have excess doses.

Some patients may have prescription medications that are indicated for use only as needed and thus seldom taken. These medications can be forgotten or used intermittently, only to be discovered with an expired date on the bottle. Now patients must dispose of the medication properly; however, patients might hesitate to do that if a particular medication is expensive. They may think that surely the medication is still good to use, and they may then decide to call their pharmacy and inquire.

The pharmacy technician is the most likely pharmacy staff member to answer the phone call and impart crucial information to the patient. Techs play an important role in helping patients understand medication expiration dates. Their knowledge allows them to aid the pharmacist in answering simple questions about the stability of medications past their expiry date and what to do with excess doses, including proper disposal, if required.

Thus, it is the tech who often provides information to patients about medication expiration dates and related information. The tech is the first check to ensure the medication is appropriate to dispense to the patient.

Techs should be aware of the time frame in which the patient’s medication is potent and stable. By law, the FDA requires expiration dates be displayed on medication bottles and prescriptions. Since 1979, drug expiration dates indicate to patients and pharmacy staff how potent and stable the medication is in its unopened container. Ingesting expired medications can have potentially harmful effects because it may be difficult to determine how much the medication has denatured since being removed from the original packaging. This is especially problematic for patients with compromised immune systems or impaired ability to metabolize drugs, such as those with liver or renal conditions.

It is not recommended for patients to use expired medications because it remains unclear how much potency is retained. Patients should not be tempted to use expired medications. However, if a patient happens to ingest an expired medication, which often occurs with OTC medications such as acetaminophen, there is no need for panic. There have been no published reports of human toxicity due to ingestion, injection, or topical application of a current drug formulation after its expiration.

AUTHOR BIOS

SARAH CARPIO, BS, is a PharmD candidate at Touro University California College of Pharmacy in New York, New York.

SHANE P. DESSELLE, PHD, RPH, FAPHA, is a professor of social and behavioral pharmacy at Touro University California College of Pharmacy.
Certain drug formations such as liquid drugs are less stable after expiration than solid dosage formulations.4 Some solid dosage formulations may extend their potency for at least 5 years past expiration.3,5 Techs should bring these questions of drug potency and stability past expiration dates to the pharmacist and then help facilitate honest conversations with patients.

The issue of drug expiration dates becomes that much more salient when the medication has special storage requirements, as is the case for drugs such as insulin that must be refrigerated. Typically, insulin left out at room temperature is only good for 28 days because its potency and stability degrade more rapidly than if kept refrigerated.6

It is not uncommon for a pharmacy to receive a phone call from a patient stating that he or she left a box of insulin pens on the counter, saying, “It’s unopened and unused; I just forgot.”

Techs often field these inquiries. With their basic knowledge of drug expiration dates, they can help patients understand what an expiration date for an unused and unopened box of insulin pen means and what to do next. Clear lines of communication with the pharmacist are paramount. Pharmacists and techs must work together to discern the types of information and questions that techs can field and what should be referred to a pharmacist. This comes with a mutual understanding and might be dependent on the tech’s level of certification, experience, and knowledge.

Techs are positioned to provide reminders to patients picking up medications to store them properly through a simple statement such as, “Your refrigerated prescription is ready. Make sure to place any unused medication in the fridge once you get home.”

Of course, for medications with special requirements, using the open-ended questions employed in other aspects of patient counseling might also be useful.

Making sure that patients understand drug expiration dates is part of the important role that techs play in keeping patients healthy and safe. Techs’ basic knowledge of medications allows them to be the first line of defense for patient safety and maintaining pharmacy workflow.

REFERENCES
PSYCHIATRIC PHARMACISTS SPECIALIZE IN CARING for patients with mental health disorders and illnesses through medication therapy management and can also play an important role in opioid and substance use disorders treatment.1,2

This is especially important now because the COVID-19 pandemic has taken a huge toll on mental health and wellness.3

According to results of a recent survey, 4 in 10 adults in the United States reported symptoms of anxiety or depressive disorder during the pandemic.3 The behavioral health workforce projections indicate a shortage of psychiatrists by 2030, further emphasizing the need for more psychiatric pharmacists.4 This career path opens the door to a variety of opportunities for pharmacists to provide comprehensive medication management and improve health outcomes for patients with neurologic and psychiatric disorders as part of an interdisciplinary team.5

JOURNEY TO A NEW CAREER

The number of pharmacy students interested in psychiatric pharmacy has increased 277% during the past 4 years, according to the College of Psychiatric and Neurologic Pharmacists (CPNP).6

Pharmacy students interested in pursuing a career in this specialty can take psychiatric clinical rotations and join the CPNP.6 Additionally, the number of postgraduate year 2 (PGY2) residencies has increased 158% during the past 4 years.6 Residency program directors involved in hiring psychiatric pharmacists report that the top 5 things they look for in candidates are a PGY2 psychiatric residency (67%), a board-certified psychiatric pharmacist (BCPP) credential (60%), clinical work experience (30%), postgraduate year 1 (PGY1) residency (28%), and teaching experience (18%).6 Residencies provide a variety of experiences that usually include research and teaching (see FIGURE).6 From 2016 to August 2020, PGY2 residency spots increased by 23%.6

“Psychiatric pharmacists play an essential role in improving outcomes for those living with psychiatric, neurologic, and substance use disorders,” CPNP Executive Director Brenda Schimenti wrote in an email interview. “As members of the treatment team, they impact patient outcomes for individuals who are often on complex regimens and are among the most underserved in our country.”
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“CPNP is working hard to advance the practice of psychiatric pharmacy, communicate the rewards of a career in psychiatric pharmacy, and demonstrate how psychiatric pharmacists favorably impact access, outcomes, and cost.”

The Board of Pharmacy Specialties (BPS) BCPP program also helps expand career opportunities and expertise for pharmacists,\(^1\) with the number of BCPPs increasing 23% during the past 4 years.\(^6\) There are a variety of requirements to become a BCPP (see TABLE).\(^1\)

Recertification is required every 7 years by achieving a passing score on the BPS psychiatric pharmacy recertification examination or obtaining 100 hours of continuing education credit through the BPS-approved professional development program provided by the CPNP.\(^1\)

**PHARMACIST SPOTLIGHT**

In interviews, Melissa Gorecki, PharmD, BCPP, and Abbey Krysiak, PharmD, BCPP, discussed their paths to becoming psychiatric pharmacists and their practice sites.

Gorecki said she discovered psychiatric pharmacy after transitioning into her current role of working with patients with intellectual disabilities and mental illness.

“Once I started this position and really got to know the patients, I saw what an underserved population it really was. I decided I should work to get my BCPP so that I could be on the top of my game to make sure I was giving my patients the best possible care,” said Gorecki, pharmacy manager at the South Dakota Developmental Center in Pierre.

After completing 4 years of postlicensure practice experience in the psychiatric pharmacy field, she obtained her BCPP in 2017.

Krysiak completed a PGY1 residency at Millcreek Community Hospital (MCH) in Erie, Pennsylvania, and then practiced in psychiatric pharmacy for 4 years before obtaining her BCPP. Shadowing a psychiatric pharmacist as a student was a great way for her to gain more experience and enhance her interest in this pharmacy specialty.

“I specifically rotated at MCH because they had multiple units dedicated to psychiatric patients [adult, geriatrics, and pediatrics]. After residency, I decided to stay in Erie, PA, and work as a pharmacy professor with [Lake Erie College of Osteopathic Medicine],” Krysiak said.

Her practice site is the psychiatric unit at MCH, so Krysiak obtained her BCPP to strengthen her credibility as a psychiatric pharmacist.

“As a professor, I helped students form a CPNP student chapter for our campus, and we became very involved with community service,” she said.\(^\star\)
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Submit your nomination today!
ON MARCH 8, 2021, THE world celebrated International Women’s Day, and in the wake of the coronavirus disease 2019 (COVID-19) pandemic, issues such as pay equity and recognition of the important contributions women have made take on greater importance.

This year, the United Nationals theme for International Women’s Day focused on “women in leadership and the role they’ve played in shaping a more equal future and recovery from the COVID-19 pandemic.”

Women have stood at the frontlines of the COVID-19 crisis as caregivers, health care workers, and leaders in fighting the pandemic.

In particular, the role of pharmacists has been key, particularly in terms of vaccine administration.

Consider that the majority of pharmacists (59.7%) are women, and that number continues to grow, up from about 55% in 2013. Conversely, the January jobs report from the US Bureau of Labor Statistics showed that approximately 4 times as many women versus men left the workforce. Overall, approximately 2.3 million women have left the workforce since February 2020.

Because of COVID-19, however, the demand for pharmacists has risen. Will COVID-19 change the way pharmacists are viewed? Will the long-sought provider status for which pharmacists have advocated come to pass? Combined with advances in technology, will the doors open for pharmacists, providing them expanded career options not previously in the realm of possibility? Theses change may be coming sooner than many think.

The reality is that despite efforts toward gender equality, many women shoulder most of the responsibility for childcare. Perhaps this year more than ever, it is important that employers seek to find ways to support employees as they navigate the “new normal” or remote work, particularly assisting women who may or may not have partners at home helping with childcare.

Women of color have been hardest hit by pandemic joblessness, which underscores why International Women’s Day was even more important this year.

Too many women around the world, particularly in developing countries, have fewer resources to help them through the pandemic, including getting vaccines. So, even with International Women’s Day behind us, let’s not forget how important it is that employers pay particular attention to the delicate balance many women must strike as we emerge from a pandemic that has forever changed how we see the world.

REFERENCES
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Seasonal Allergies Watch

Omalizumab Effectively Treats Allergic Rhinitis, Study Results Show

RESEARCH SHOWS THAT OMALIZUMAB, an anti-inflammatory drug commonly used to treat asthma, is effective and safe in the treatment of seasonal allergic rhinitis (SAR) in a real-world setting.

Patients with SAR who had been administered omalizumab in various doses were recruited for the study. Investigators assessed their quality of life and symptoms, and clinical outcomes were compared between post- and pretreatment conditions.

In total, 60 patients with SAR received omalizumab therapy, with a mean age of 35, just half of whom were women. The investigators found that omalizumab treatment significantly improved their nasal symptoms and quality of life. Furthermore, in 21 patients with co-existing asthma, the Asthma Control Test score significantly increased to 22.57 from 16.1 on average, indicating better-controlled asthma.

Using a threshold of 1 or more point improvement in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), investigators found that 83.3% of patients responded to omalizumab. The responder group had a higher baseline RQLQ score and a higher Total Nasal Symptoms Score, but both non-responders and responders had comparable scores after treatment.

Finally, the investigators found that a multiple linear regression analysis identified the baseline RQLQ score as a predictor of change in the score for patients with SAR who were treated with omalizumab. Based on all these findings, the investigators concluded that omalizumab is effective and safe to treat SAR.

Experts Explore Use of Multiplex Immunoassay

ALTHOUGH ALLERGIC SENSITIVITIES AND allergies are commonly diagnosed with a skin prick test or by determining immunoglobulin levels in blood samples with the ImmunoCAP assay, a research paper explores the possibility of diagnosing respiratory allergies with a high throughput method called the Meso Scale Discovery (MSD) multiplex immunoassay.

The paper authors noted that, over the past few decades, they have observed a gradual evolution from singleplex toward multiplex immunoassays. This technique has several advantages, including increased efficiency at reduced expense and a lower necessary sample volume, which could be beneficial for pediatric patients.

The MSD multiplex immunoassay requires only 25 µl of serum volume for analysis, according to the paper.

The study included 3 non-allergic controls and 15 patients, who were selected and enrolled based on their allergy symptoms. Specifically, 14 reported clinical symptoms of hay fever, including 12 who were allergic to tree pollen, 5 who were allergic to cats and dogs, and 3 who were allergic to only cats. The investigators conducted blood analyses, skin prick tests, and used the MSD multiplex immunoassay and then compared the results. They found that the MSD multiplex immunoassay was comparable to the other 2 approaches, as observed with correlations and Bland-Altman plots. They also found high sensitivity and specificity compared with the blood analyses and skin tests, as well as low inter- and intra-assay high reproducibility and variability.

Pollen Effects Cognitive Function in Children

STUDY RESULTS SHOWS THAT cognitive function was negatively affected during pollen season in children with pollen allergies, and the more symptoms the allergic children had, the longer the reaction time in cognitive tests.

Allergic rhinitis often impairs quality of life and is thought to affect cognitive function, according to the study investigators.

They examined whether this was true during grass pollen season in symptomatic allergic children and whether the degree of impairment to quality of life was related to inflammation and stress.

Forty-three children with grass pollen allergies who had unsatisfactory responses to medication in previous seasons were included in the study, and 26 non-allergic matched children were included as controls.

Both groups performed cognitive tests and completed quality-of-life questionnaires outside and during pollen season. Findings showed impaired cognitive function in spatial working memory in the allergic group, who made more errors compared with the control group during pollen season. The investigators found no differences in stress or inflammatory biomarkers between the 2 groups.

FOR REFERENCES, GO TO PHARMACYTIMES.COM/LINK/144.
Ocular allergies and dry eye can affect up to 40% and 50%, respectively, of patients in the United States.\(^1,2\) Approximately 10% of patients with ocular allergies seek medical care and 66% of dry eye patients try at least three over-the-counter (OTC) drops before consulting their eye care professional, suggesting that many patients first seek resolution to their symptoms in the pharmacy or from other health professionals before getting an ocular examination.\(^3,4\) Although the conditions can share symptoms of ocular irritation, their severity and frequency, and patient demographic can help to distinguish the conditions apart.

**OCULAR ALLERGIES**

Patients with ocular allergies often present with ocular itch and redness.\(^5\) Incidence is greatest between spring and fall, consistent with higher exposure to pollen (spring), ragweed (fall), and grass (summer), but it can occur perennially, especially when due to allergens like dust and animal hair and dander.\(^6\) Ocular allergies are often worse in the morning from higher morning pollen counts.\(^6\) While ocular allergies have been diagnosed more frequently in young patients, they can affect all age groups equally.\(^7\)

Dual-action anti-allergic agents, such as olopatadine, utilize two mechanisms of action to provide ocular allergy itch relief: antihistamine and mast cell stabilization. Pataday (olopatadine hydrochloride; Figure 1) provides rapid ocular allergy itch relief in three different strengths to last up to 8 hours (Pataday Twice Daily Relief), 16 hours (Pataday Once Daily Relief), and 24 hours (Pataday Once Daily Relief Extra Strength), offering patients the only dual-action once-daily 16- and 24-hour ophthalmic formulations OTC.

**DRY EYE**

Dry eye disease is commonly associated with complaints of dryness, grittiness, and even mild itch. Unlike ocular allergies, dry eye prevalence does not change with the season, but it increases with age.\(^8\) Symptoms are typically worse at the end of the day and can be associated with prolonged use of electronic devices, contact lens wear, environmental triggers (e.g., wind, air conditioning), and topical use of benzalkonium chloride (BAK)-preserved eye drops.\(^8\)

Systane HYDRATION Multidose Preservative-Free (MDPF) is an ocular lubricant that offers the unique combination of two demulcents (propylene glycol, polyethylene glycol), and the Systane HydroBoost Technology with hydroxypropyl guar and sodium hyaluronate, the salt form of hyaluronic acid (HA). HA is a natural lubricant with unique water-retaining and viscoelastic properties to help provide enhanced hydration and comfort to dry eye patients. The MDPF formulation is free of preservatives and ideal for dry eye patients who require frequent daily dosing of artificial tears (4 or more times per day) and who are using BAK-preserved prescription ophthalmic medications, such as in glaucoma treatment or in refractive and cataract perioperative management.\(^9,10\)

**CONCLUSION**

By understanding causes and symptoms of allergic conjunctivitis and dry eye, healthcare practitioners can recommend an appropriate over-the-counter symptom relief product for their patients.

**REFERENCES**

Pet Peeves

Slippery Slope
When my mask starts slipping off my nose when counseling a patient and they threaten to complain to management.

Misinformed
When patients ask about the dosing of random supplements needed “to prevent COVID-19.”

E-Prescribe Please
I can’t stand when physicians give patients with COVID-19 hard copy prescriptions. We don’t have a drive through, so they come in the store.

Check Online
PharmacyTimes.com will offer Pet Peeves, brought to you by the Sassy Pharmacist in coming months.

What’s Bothering You?
Bossy patients, abandoned prescriptions, drive-through demands? We want to know! Send your pet peeves to cmollison@pharmacytimes.com. We’ll share them here and online.
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Case Studies

By SINDORELA FRROKU-DIDO AND STEFANIE C. NIGRO, PHARMD, BCACP, CDE

CASE 1

TR is a 68-year-old man who was discharged from the hospital 3 days ago after being diagnosed with new onset heart failure (HF) with reduced ejection fraction. He goes to the pharmacy to fill his new prescriptions, including carvedilol. The pharmacy intern is concerned about the use of carvedilol for TR because he has a long history of chronic obstructive pulmonary disorder (COPD), although it is well controlled. The intern wonders whether she should call TR’s primary care provider (PCP) to obtain a prescription for a cardioselective β-blocker instead.

How should the pharmacist respond?

CASE 2

The ambulatory-care pharmacist in a clinic is seeing MN, a 61-year-old Black woman today. MN has a long history of hypertension (HTN), stage 3 chronic kidney disease (CKD), and type 2 diabetes (T2D). Her estimated glomerular filtration rate is 39 mL/min/1.73 m² and has been stable over the past year. Despite excellent control of her HTN (average blood pressure < 120/70 mmHg) and T2D (A₁c 6.8%), her urine albumin:creatinine ratio remains elevated at 280 mg/g, MN takes losartan 100 mg daily for her CKD. She does not smoke and does not take any drugs known to be nephrotoxic. MN’s primary care provider wants to know if adding a sodium-glucose cotransporter 2 (SGLT2) inhibitor would be beneficial for MN.

How should the pharmacist respond?

For References, Go To PharmacyTimes.com/Link/144.
Clinical Management of Allergic Conjunctivitis: Integrating Recommendations to Improve Treatment Outcomes

EDUCATIONAL OBJECTIVES FOR PHARMACISTS
At the completion of this activity, the participant will be able to:
• Identify the relationship between the pathophysiology and clinical presentation of allergic conjunctivitis
• Determine the role of current treatments for allergic conjunctivitis, with a focus on over-the-counter medications
• Personalize treatment recommendations for allergic conjunctivitis to optimize patient management and prevent associated complications

EDUCATIONAL OBJECTIVES FOR PHARMACY TECHNICIANS
At the completion of this activity, the participant will be able to:
• Review allergic conjunctivitis, associated symptoms, and its impact on patients
• Outline treatment options for allergic conjunctivitis with a focus on over-the-counter medications
• Recognize the role of the pharmacy technician in referring patients who would benefit from counseling with the pharmacist and assisting patients with allergic conjunctivitis

TARGET AUDIENCE: Community pharmacists and pharmacy technicians
ACTIVITY TYPE: Application for pharmacists; Knowledge for pharmacy technicians
RELEASE DATE: March 15, 2021
EXPIRATION DATE: March 15, 2022
ESTIMATED TIME TO COMPLETE ACTIVITY: 2.0 hours
FEE: This lesson is offered for free at www.pharmacytimes.org.

Introduction to Allergic Conjunctivitis
Ocular allergy, or allergic conjunctivitis (AC), is a common inflammatory immunologic process that is estimated to affect 20% to 40% of the US population and has been increasing in prevalence.1,2 A concern with AC diagnosis and treatment is that it is often either self-diagnosed by patients, or it is misdiagnosed or underdiagnosed by health care providers.3 Patients with AC also have decreased quality of life for various reasons (including bothersome symptoms and emotional effects), and the economic burden due to health care costs, medications, missed work, etc, is substantial.4,5 Patients presenting with AC will typically experience bilateral tearing, ocular redness, swelling, and the hallmark, and most bothersome, symptom of pruritus (itching).1,2,3 Many patients with AC will also present with allergic rhinitis (nasal symptoms).4,5 It is estimated that up to 3 of 4 patients with allergic rhinitis present with symptoms of AC.8 There is also a correlation with AC and patients with a predisposition to atopy (allergic disorders), such as asthma, eczema, and food allergies.6,8

Taking a well-detailed history is particularly important when considering a diagnosis of AC in a patient. Specifically, asking about exposure to allergens and determining a timeline associated with exposure and symptoms is important. Whether the allergen is indoor or outdoor

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Video vignettes featuring a pharmacist providing education and recommendations to patients about management of allergic conjunctivitis symptoms are highlighted at pharmacytimes.org/go/conjunctivitis.

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can indicate the type of AC as well as the best course of treatment. Allergens that commonly cause AC include pollen, grass, pet dander, mold, and dust mites.6,8

**Etiology and Pathophysiology of AC**

There are several different subtypes of AC; **TABLE 1** provides a brief comparison. The most common immunologic process taking place in AC is a type I immunoglobulin E (IgE)-mediated hypersensitivity with mast cell activation with histamine release occurring immediately.9 Essentially, an allergen is identified by the immune system, and the body’s response is to release histamine from mast cells to try to rid the body of the allergen.6,9 More severe forms of AC occur due to a delayed type IV cell-mediated hypersensitivity with T-cell involvement.6 Benign cases can be treated with nonpharmacologic measures, as well as with both nonprescription, or over-the-counter (OTC) and prescription items. These cases are often self-diagnosed by patients, or diagnosis and treatment are managed by general practitioners such as primary care physicians.3 More severe cases, however, require diagnosis and treatment by specialty practitioners such as ophthalmologists.9

Seasonal allergic conjunctivitis (SAC) is the most common form of AC and is considered benign. Patients typically present with ocular itching, redness, tearing, and swelling in response to outdoor allergens such as pollen and grass.6,9 Rhinitis often accompanies the ocular symptoms and patients with SAC often have a history of atopy.6 The immune process of SAC is an IgE-mediated type I hypersensitivity reaction that causes an increase in mast cell presence and degranulation, as well as the subsequent release of histamine, which causes the typical AC symptoms.3,9

Perennial allergic conjunctivitis (PAC) is similar to SAC but is considered persistent (or chronic), with symptoms lasting more than 4 to 6 weeks.3,9 PAC is most often triggered by indoor allergens, such as dust mites, pet dander, mold, or pests such as cockroaches, and patients may have some additional symptoms such as foreign body sensation (eg, sand in the eye) as well as some burning of the conjunctiva.6,9 Like SAC, PAC is also associated with a history of atopy, is an IgE-mediated type I hypersensitivity reaction, and is considered benign.3,6,9

Giant papillary conjunctivitis (GPC) is a chronic form of AC but is due to the constant exposure of the conjunctiva to a foreign body, most commonly contact lenses or a prosthetic eye and is considered moderate to severe.3,10 It is a T cell-mediated response, although a type I IgE-mediated hypersensitivity response can also occur if allergens attach to the contact lenses.6 Giant papillae (or round protuberances) of greater than 1 mm develop on the conjunctiva of both the upper and lower eyelids.3 Patients will also experience symptoms such as discharge, blurred vision, and photophobia.8

Vernal keratoconjunctivitis (VKC) is a severe form of AC that can lead to structural changes of the epithelium, development of
giant papillae, and vision loss.\textsuperscript{5,9} VKC occurs most often in male children before 10 years of age with a history of atopy living in warmer countries surrounding the Mediterranean Sea and equatorial areas.\textsuperscript{3,8,9} Presentation of VKC includes intense tearing, itching, redness, papillae, edema of the eyelid, and photophobia that can have a profound impact on a patient’s quality of life.\textsuperscript{9} The immunology of VKC has characteristics of both type I IgE-mediated hypersensitivity as well as type IV T cell-mediated hypersensitivity that becomes a chronic lymphocyte-predominant condition.\textsuperscript{3,8}

Atopic keratoconjunctivitis (AKC) is similar to VKC but is extremely rare and typically occurs in adults with a history of severe atopy.\textsuperscript{3,9} Like VKC, AKC is a combination of type I and type IV hypersensitivity processes and has a similar presentation and associated complications as VKC, with the addition of eczema, scarring, and corneal involvement.\textsuperscript{3,9}

Contact blepharoconjunctivitis (CBC) is a type IV T cell-mediated hypersensitivity that consists of an antigen complex formation that develops between the eye and a foreign body or substance.\textsuperscript{8,9} This can occur as a result of products applied around (but not directly to) the eye as well.\textsuperscript{7} There is no background of atopy associated with CBC, but symptoms can include contact dermatitis of the eyelid and conjunctival follicles in addition to the standard AC symptoms of tearing, itching, redness, and inflammation.\textsuperscript{9,12}

**Burden of AC**

AC, especially SAC and PAC, is very common. It is estimated that worldwide, AC affects 15% to 20% of the population, with up to 40% of the US population impacted.\textsuperscript{1,2,12} SAC and PAC have a tremendous burden on individuals for various reasons. Quality of life is decreased with the presence of ocular symptoms in addition to frequent concurrent rhinitis.\textsuperscript{6,9} Patients report that these uncomfortable symptoms affect concentration and focus, cause emotional distress due to perception of AC, and can impair activities of daily living.\textsuperscript{1,12} SAC and PAC are most frequently self-diagnosed by patients because the symptoms are more bothersome than alarming.\textsuperscript{5} In addition, SAC and PAC are often inadequately treated or mistreated, which results in further decrease in quality of life, productivity, and increased financial burden.\textsuperscript{3,6}

The financial burden of AC is estimated to be more than $2 billion yearly for prescription items with expected nonprescription costs being far higher.\textsuperscript{3,13} In addition, there are indirect costs such as decreased productivity at work, absenteeism, and out-of-pocket expenses.\textsuperscript{3,6} The combined costs, both direct and indirect, are estimated to be approximately $6 billion and are increasing yearly.\textsuperscript{11}

**Clinical Presentation**

Patients presenting with AC have symptoms of itching, tearing, redness, and swelling. Patients often experience concurrent rhinitis.\textsuperscript{3,6} AC is typically bilateral as unilateral presentation often indicates bacterial or viral conjunctivitis.\textsuperscript{3,11} Less common symptoms include burning, irritation, or foreign body sensation.\textsuperscript{9} SAC occurs intermittently with season and outdoor allergen exposure changes while PAC is persistent or chronic due to continuous indoor allergen exposure. These are considered the most common forms of AC and are benign with minimal damage and only local sequelae.\textsuperscript{11}

Patients with more severe forms of AC, such as GPC, VKC, AKC, and CBC, will also experience itching, tearing, redness, and swelling but symptoms will likely be more intense. In addition, these patients will also present with more severe symptoms such as papillae, photosensitivity, and eyelid swelling or eczema.\textsuperscript{9} Patients with GPC will likely be contact lens wearers (soft lenses specifically) or will have protheses, exposed sutures, or ocular surface abnormalities.\textsuperscript{3,9}

**Diagnosis of AC**

To appropriately diagnose AC, a complete patient history, including evaluating the temporal relationship of symptoms and exposure to allergens (or identification of triggers), is imperative.\textsuperscript{9} Patients should be asked about their symptoms, environmental exposures, aggravating and remitting factors (including nonpharmacologic and pharmacologic treatments tried), and ocular history including changes in vision or recent trauma.\textsuperscript{5} A complete history of medication use is also necessary as several OTC medications can contribute to or worsen AC symptoms if overused or if used inappropriately.\textsuperscript{6} Based on the severity and duration of symptoms, a physical examination and/or allergen sensitivity tests may be required by a physician, ophthalmologist, allergist, or immunologist.\textsuperscript{3,6} Patients with AC often present with rhinitis, asthma, and symptoms of dry eye, which can make diagnosis more complicated, although ocular itching is the key symptom in all patients with AC.\textsuperscript{8,10} In addition, some patients may actually present with symptoms that are more alarming and require immediate referral to a physician. Examples of symptoms requiring medical referral include mucus or discharge other than tearing, which may indicate infection (including viral or bacterial conjunctivitis), bleeding or other signs of trauma or injury, growths, recent exposure to chemicals, suspected foreign substance trapped or embedded in the eye, or if there is uncertainty that the cause of symptoms is exposure to an allergen.\textsuperscript{7}
**What are nonpharmacologic recommendations for the treatment of AC?**

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

### Treatment Goals

The goals of treatment for AC are improving quality of life, removing or avoiding the allergen, relieving symptoms, and ultimately minimizing inflammation to maintain the integrity of the ocular surface.

### Nonpharmacologic Recommendations

Nonpharmacologic measures represent the foundation of treatment for AC. The first step is to identify potential allergens via patient interview and develop a care plan for avoidance or reduced exposure. Once allergens are identified, avoidance is optimal but may be difficult to achieve; reduced exposure may be a more reasonable approach. Other nonpharmacologic recommendations include application of cool compresses and use of ophthalmic lubricants. Patients should be advised to resist the urge to rub their eyes as this may lead to degranulation of mast cells and worsening of symptoms. Contact lens wearers should consider switching to glasses when symptoms are at their peak or switching to disposable, daily wear contact lenses. While nonpharmacologic recommendations alone provide minimal benefit, they provide an additive effect when used in combination with pharmacologic interventions.

### Allergen Avoidance

Common outdoor allergens include pollen, molds, ragweed, and pollutants; indoor allergens include pets, molds, and dust mites. Recommendations concerning allergen avoidance are summarized in **TABLE 2**. Exposure to outdoor allergens can be reduced by keeping doors and windows closed and by monitoring pollen counts when planning outdoor activities. Indoor allergens can be minimized with regular cleaning, dusting, and vacuuming. Pets should be washed weekly and should not be allowed in the bedroom. House dust mites can be minimized by regular cleaning and using pillow and mattress covers. If possible, carpet should be removed or vacuumed regularly using a vacuum bag equipped with a high-efficiency particulate air (HEPA) filter. HEPA filters should also be installed in heating and air conditioning ducts.

### Ocular Lubricants

Ophthalmic lubricants, or artificial tears, work to dilute and potentially rinse away the allergen and other inflammatory mediators that may have accumulated on the eye surface. In addition to cleansing the eye surface of allergens, ocular lubricants act as a barrier to allergens and help to treat any comorbid dry eye disease. **TABLE 3** features select common ocular lubricants that are available in drops, gels, and ointment dosage forms and contain a variety of thickening agents. For this table and all other medication-specific tables, please refer to individual prescribing information, labeling, and/or package insert for additional information including age-specific recommendations. Lipid-containing ocular lubricants are typically more expensive but may be more effective for patients with evaporative dry eye as they help to prevent evaporation and improve the tear film stability. Ocular lubricant drops provide temporary relief and must be used several times throughout the day for maximal benefit. Adverse effects (AEs) associated with ocular lubricants are limited and are typically related to the preservative rather than the active ingredient. Benzalkonium chloride (BAK) is a common preservative in numerous ophthalmic products but has been associated with corneal damage. If artificial tears are used frequently (>4-6 times per day) or if use is prolonged, a preservative-free formulation should be recommended. Ointment formulations offer a longer lasting effect but cause blurry vision and should be reserved for use at bedtime.

### Cool Compresses

Cool compresses may be helpful in reducing symptoms of...
eye and eyelid swelling. Using a clean cloth dampened with cold water or a frozen gel pack, cool compresses should be applied to closed eyelids for 5 to 10 minutes 3 or 4 times daily. The cooling effect leads to vasoconstriction and reduces itching and inflammation.  

**STAR**

What are examples of available OTC products that have both antihistamine and mast cell-stabilizing activity?

Pharmacologic Treatments

Based on pathophysiology and immunology, there are several medications that can be used for the treatment of AC. Specifically, SAC and PAC can often be managed by patients, as well as their pharmacists and primary care providers or pediatricians, while patients with more severe forms of AC, such as VKC or AKC, should be followed by ocular specialists.  

First-line therapy should always be nonpharmacologic treatment. The preferred second-line therapy is initiation of dual-activity agents that have both antihistamine and mast cell-stabilizing activity. If symptoms are still not managed, a course of topical corticosteroids can be used as well as topical nonsteroidal anti-inflammatory drugs (NSAIDs), second-generation oral antihistamines, and nasal corticosteroids for additional symptom relief. If appropriate use of the aforementioned therapies does not yield sufficient relief, immunotherapy can be considered.  

**Dual-activity Agents (Antihistamines With Mast Cell-stabilizing Properties)**

Ophthalmic agents that have both antihistamine and mast cell-stabilizing activity are the preferred pharmacologic treatment for AC and are found to be better than antihistamines or mast cell stabilizers by themselves. They are the ocular agents most frequently prescribed by ophthalmic professionals and allergists. In SAC and PAC, the immune response to allergens is IgE mediated, which means that mast cell degranulation and subsequent release of histamine and other inflammatory mediators occurs, causing the bothersome symptoms of ocular allergy. Therefore, working to both stabilize the mast cells (and subsequently decrease the release of histamine) and block histamine receptors would relieve the symptoms of AC and prevent or stop the hypersensitivity reaction from occurring. An additional benefit of the combination is the rapid relief of symptoms within minutes (due to antihistamine activity), as well as long-term efficacy due to regulation of the inflammatory response in the late phase of the hypersensitivity reaction.

Select common dual-activity agents are outlined in **TABLE 4**. There are 2 available OTC dual-activity agents that are considered to have comparable efficacy for mild AC: olopatadine 0.1%, 0.2%, and 0.7% and ketotifen 0.025% ophthalmic solutions. Olopatadine, the first dual-activity agent on the market, was prescription only for many years. This agent is considered to be the gold standard across all dual-activity OTC and prescription products. Olopatadine was first available as a 0.1% solution, dosed as 1 drop in each affected eye twice daily, and has since been approved for once-daily 0.2% solution and once-daily 0.7% solution (extra strength formulation). The primary difference between the 2 once-daily formulations is that the 0.2% is found to relieve ocular itching for
approximately 18 hours, whereas the 0.7% relieves symptoms for upwards of 24 hours. All formulations are for patients aged 2 years or older.

Ketotifen is available OTC under 2 different brand names as well as generic formulations. For patients aged 3 years or older, it is dosed 1 drop in the affected eye(s) twice daily with 8 to 12 hours between doses. The only preservative-free dual-activity agent is ketotifen 0.035%, which will be made available OTC in spring 2021. All other products contain BAK, which can cause damage to the corneas and worsen ocular symptoms over time, so long-term use should be carefully evaluated. With both olopatadine and ketotifen eye drops, patients should stop use and ask a doctor if they experience eye pain, vision changes, increased eye redness, or itching that worsens or lasts for more than 72 hours.

The prescription-only dual-activity agents include alcaftadine 0.25%, azelastine 0.05%, bepotastine 1.5%, and epinastine 0.05%. Alcaftadine is dosed once daily in patients aged 2 years or older, has minor ocular AEs, and has proven to be more beneficial for ocular itching than the other dual-activity agents. 

**Mast Cell Stabilizers**

Select common additional topical and ocular agents are summarized in TABLE 5. Mast cell stabilizers are seldom used as monotherapy but remain an option for the treatment of all IgE-mediated forms of AC: SAC, PAC, VKC, AKC, and possibly GPC. Mast cell stabilizers have specific administration requirements that may negatively affect patient adherence and result in subtherapeutic patient outcomes. Specifically, the mast cell stabilizer ophthalmic solutions must be instilled frequently throughout the day and must be used for days to weeks before benefit can be observed. The available mast cell stabilizers are cromolyn, lodoxamide, nedocromil, and pemirolast. In general, they have similar ocular AEs such as burning and stinging, and they differ only slightly in dosing frequency and approved age.

**Topical Ocular Antihistamine (Single Acting)**

Topical ocular antihistamines work directly to block histamine-1 (H₁) receptors in the eye. Given the ophthalmic dosage form, topical antihistamines have a quick onset (within 15 minutes) with minimal systemic AEs but are associated with burning and stinging upon administration. Of note, these agents are contraindicated in patients at risk of
developing closed angle glaucoma. The topical ocular anti-
histamines emedastine (Emadine) and levocabastine (Livos-
stin) have been discontinued. A topical version of cetirizine
(Zerviate 0.24%) ophthalmic solution launched in March
2020.\textsuperscript{57,58} Ophthalmic cetirizine has been shown to relieve
ocular symptoms (pruritus, erythema, and swelling) as well
as nasal symptoms including rhinorrhea, nasal pruritus, and
nasal congestion.\textsuperscript{72,73} The duration of action of cetirizine
ophthalmic solution is approximately 8 to 12 hours; dosing is
twice daily approximately 8 hours apart.\textsuperscript{58}

\textbf{Topical Ocular Decongestants}
The role of the topical ocular decongestants, tetrahydrozoline
and naphazoline, for the treatment of allergic conjunctivitis
is limited.\textsuperscript{3} These agents work to reduce ocular erythema and
chemosis via vasoconstriction but do not relieve pruritus and
do not provide additional symptomatic relief. Further, when
used for more than a few days, ocular decongestants are asso-
ciated with tachyphylaxis (diminished response to successive
administrations of a drug) and rebound ocular hyperemia
(redness) known as conjunctivitis medicamentosa.\textsuperscript{74} Product

<table>
<thead>
<tr>
<th>TABLE 5. ADDITIONAL TOPICAL AND OCULAR AGENTS\textsuperscript{3,6,55-71}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic name</strong></td>
</tr>
<tr>
<td>Mast cell stabilizers</td>
</tr>
<tr>
<td>Cromolyn 4%</td>
</tr>
<tr>
<td>Lodoxamine 0.1%</td>
</tr>
<tr>
<td>Nedocromil 2%</td>
</tr>
<tr>
<td>Pemirolast 0.1%</td>
</tr>
<tr>
<td>Single-acting antihistamine</td>
</tr>
<tr>
<td>Cetirizine 0.24%</td>
</tr>
<tr>
<td>Decongestants</td>
</tr>
<tr>
<td>Naphazoline 0.012%</td>
</tr>
<tr>
<td>Tetrahydrozoline 0.05%</td>
</tr>
<tr>
<td>Antihistamine/decongestant combination</td>
</tr>
<tr>
<td>Pheniramine/naphazoline • 0.3%/0.025% • 0.315%/0.02675%</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Fluorometholone acetate 0.1%</td>
</tr>
<tr>
<td>Loteprednol etabonate • 0.2% • 0.5%</td>
</tr>
<tr>
<td>Prednisolone acetate 1%</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>Diclofenac 0.1%</td>
</tr>
<tr>
<td>Ketorolac 0.45%</td>
</tr>
<tr>
<td>Ketorolac 0.5%</td>
</tr>
<tr>
<td>Nepafenac 0.1%</td>
</tr>
</tbody>
</table>
labeling indicates these agents should not be used for more than 72 hours without referral for further evaluation.60,61 These agents are contraindicated during pregnancy and in patients with closed angle glaucoma; use in patients with cardiovascular disease and hyperthyroidism should be avoided due to their activity as adrenergic agonists.3,10

A longer acting alpha-2 agonist, brimonidine 0.025% (Lumify), is available OTC, but is just labeled for use to treat general ocular redness (it is not intended for treatment of AC).6,75 The 0.025% OTC concentration is lower than the 0.15% and 0.2% that is indicated for glaucoma. The alpha-2 selectivity is associated with lower risk of tachyphylaxis and rebound hyperemia.8

**Topical Ocular Antihistamine/Decongestant Combinations**
The topical ocular antihistamine pheniramine is available OTC in combination with ocular decongestants.6 Of note, the antihistamine antazoline, previously available in combination with naphazoline, is no longer commercially available. Although this combination works quickly (within 3-15 minutes) to treat both the itching and redness associated with AC, the duration of relief is short, so this product must be dosed frequently (up to 4 times daily). The rebound congestion associated with the decongestant limits the duration of use. As previously described, product labeling for these agents also specifies that they should not be used for more than 72 hours without referral for further evaluation.61 Thus, the overall utility of these agents in the treatment of AC is limited. The precautions and contraindications to individual antihistamine and decongestant agents previously mentioned apply to the combination as well.

**Topical Corticosteroids**
Topical corticosteroids are extremely effective for all forms of AC and all levels of severity. They are, however, associated with a great deal of potential ocular damage, such as cataracts, increased intraocular pressure (IOP), and increased risk of infections.2 Therefore, topical corticosteroids are used only intermittently, and their duration of use is typically limited to 1 to 2 weeks.5,11 Some of the commonly used topical corticosteroids are fluorometholone, loteprednol, and prednisolone.6 The topical corticosteroids typically contain the preservative BAK, which also limits their use in AC.

**Topical NSAIDs**
Although topical NSAIDs are not used frequently, they are an option if patients continue to have symptoms while using a dual-activity product.6 Topical NSAIDs can be considered

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**TABLE 6. OTC ORAL ANTIHISTAMINES AND INTRANASAL CORTICOSTEROIDS**66-89

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Typical adult dosing</th>
<th>Clinical pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second-generation oral antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine</td>
<td>Zyrtec</td>
<td>One 10-mg tablet once daily (5 mg for less severe symptoms)</td>
<td>May cause sedation for some patients.</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Allegra</td>
<td>One 180-mg tablet once daily or 60 mg BID</td>
<td>Unlikely to cause sedation. Absorption is decreased if taken with fruit juices.</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>Xyzal</td>
<td>One 5-mg tablet once daily (2.5 mg for less severe symptoms)</td>
<td>May cause drowsiness for some patients. Active isomer of cetirizine, not proven more effective or better tolerated.</td>
</tr>
<tr>
<td>Loratadine</td>
<td>Claritin</td>
<td>One 10-mg tablet once daily</td>
<td>Unlikely to cause sedation.</td>
</tr>
<tr>
<td><strong>Intranasal corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>Rhinocort</td>
<td>1 or 2 sprays in each nostril once daily as recommended</td>
<td>≥6 years of age</td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>Flonase Sensimist</td>
<td></td>
<td>≥2 years of age</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Flonase</td>
<td></td>
<td>≥4 years of age</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Nasacort</td>
<td></td>
<td>≥2 years of age</td>
</tr>
</tbody>
</table>

*Labeling for most products states that patients aged ≥65 years consult a doctor before use.
during severe exacerbations of symptoms and in more severe forms of AC, such as VKC and AKC, or if topical corticosteroid therapy is not preferred for a patient. The agents often used include diclofenac, ketorolac, and nepafenac. The AEs associated with topical NSAID use include substantial irritation, burning, and stinging, which can limit their use, and in rare cases, corneal ulceration or keratitis can occur. The topical NSAIDs typically contain BAK as a preservative, which also limits their use. They are typically only used short term (for approximately 1 week) and are not considered a mainstay of therapy.

**Oral Antihistamines**
Select common OTC oral antihistamines and intranasal corticosteroids are covered in Table 6. Oral antihistamines are effective in treating both nasal and ocular allergy symptoms. Although effective, first-generation antihistamines such as diphenhydramine and chlorpheniramine are rarely used due to central nervous system-related AEs, including sedation and confusion as well as anticholinergic AEs (urinary retention, dry eyes, and dry mouth). Second-generation antihistamines cetirizine, fexofenadine, levocetirizine, and loratadine, are available OTC and are preferred due to their favorable AE profile (minimal sedation). The average onset of action with these agents is 150 minutes; therefore, topical ocular antihistamines may be preferred. For added benefit, oral antihistamines may be used in combination with topical ocular agents that do not include an antihistamine.

**Intranasal Corticosteroids**
Intranasal corticosteroids are often considered the most effective treatment option for allergic rhinitis, owing to their ability to address multiple components of the allergic response; corticosteroids suppress the immune response, are anti-inflammatory, and reduce mast cell proliferation. Intranasal corticosteroids are effective for both nasal and ocular symptoms. Given that the majority (>80%) of patients with AC also have comorbid allergic rhinitis, intranasal corticosteroids may be the most effective treatment option using one agent to treat all symptoms. The onset of action of intranasal corticosteroids is generally delayed with maximal improvement taking up to 2 weeks; however, ocular symptoms including pruritus, redness, and tearing have been shown to improve in 2 to 5 days. AEs with intranasal corticosteroids are typically limited to local irritation and epistaxis. Patients with glaucoma or at risk of glaucoma should be monitored for increased IOP; patients should also be monitored for cataracts. Pediatric patients should be monitored for growth suppression. Proper administration technique is important; patients should be counseled to spray away from the septum. Although rare, repeatedly spraying at the septum may lead to nasal septal perforation.

**STAR**
What are helpful educational points for patients who need to administer medications for the eye?

---

**Optimizing Patient Care**
**The Role of the Pharmacist**
Patients experiencing AC typically self-diagnose and self-treat with OTC treatment options to relieve their ocular symptoms of itching, redness, tearing, swelling, photophobia, and general discomfort. Unfortunately, patients may not truly understand their condition or how to appropriately treat it. Patients may inappropriately believe they have dry eye, red eye, an eye infection, or may fail to recognize that their nasal and ocular symptoms are related. Most recently, the novel COVID-19 illness may also include ocular symptoms such as discharge and congestion. Therefore, it is imperative that pharmacists are prepared to evaluate and assess patients who present with symptoms. This means that they should be able to identify patients with mild AC who can be treated with OTC medications as well as identify the potentially more severe forms of AC (or if something other than AC is suspected) that require referral to a primary care physician, allergist, ophthalmologist, or other health care professional. Patients who report eye pain, changes in vision, or trauma to the eye (including exposures to chemicals) are not appropriate candidates for OTC recommendations and should be referred to their provider for further evaluation.

During the patient interview, pharmacists must identify when symptoms began and what new exposures to allergens may have occurred, and try to determine the cause of the patient’s allergic reaction. When mild SAC or PAC is suspected, pharmacists should counsel patients regarding the various nonpharmacologic, or foundational, treatments first and foremost. This includes allergen avoidance with appropriate recommendations to minimize exposure. When symptoms are moderate or if they do not respond to nonpharmacologic recommendations, pharmacists should be prepared to assist patients in selecting the most appropriate OTC product. Product selection should be based on patient preferences (eg, patients may prefer an oral dosage form...
versus an eye drop); the indication of the product and symptoms the product is likely to relieve; as well as the pharmacokinetic properties of the drug, including onset and duration of therapy. As the duration of therapy of several ophthalmic products is limited in order to minimize potential severe AEs, pharmacists should monitor patients who may be overusing or inappropriately refilling ophthalmic products.

Pharmacists must counsel patients on proper use of their treatment recommendation. Patients should be educated on proper instillation of both ophthalmic drops and ophthalmic ointments as well as appropriate contact lens care. Patient treatment expectations should be addressed, including potential AEs, the onset of symptom relief, as well as duration. Most ocular agents cause some degree of local irritation; patients should be reassured that these AEs are typically transient. If the irritation or any additional AEs become intolerable, patients should be referred to their provider. Pharmacists should also counsel patients on the importance of adherence to scheduled medication such as the dual-activity agents. If a dose is missed, patients should be instructed to use their medication as soon as they remember, unless it is too close to their next dose. Then, patients should skip their dose and resume with their next scheduled dose; patients should not use 2 doses at once. Finally, pharmacists can provide information on when to follow up; for example, if patients experience an inadequate response to the recommended treatment, patients should contact the pharmacist for further evaluation and potential referral to a provider for prescription options. For instance, a patient who is experiencing control of symptoms during the day after initiating an OTC ophthalmic medication but continues to experience symptoms throughout the night may benefit from switching to a product that provides more long-lasting relief.
**Contact Lens Care**

Patients who wear contact lenses are at increased risk of infection and further complications. It is imperative that contact lens wearers disinfect their lenses daily (or dispose of their lenses if the patient has daily wear contacts). Patients should also be reminded to always wash their hands when inserting and removing contact lenses to avoid introduction of microorganisms, allergens, or other contaminants to the eye. When counseling contact lens wearers with AC, they should be advised to wear their glasses or switch to daily wear contacts if possible. These patients should also be aware that most ophthalmic products require lens removal for use and a wait time of at least 5 minutes before reinserting. Specific products may recommend waiting an additional amount of time or advise not to wear contact lenses at all when using the product.

**How to Administer an Ophthalmic Medication**

Best practices on how to properly administer ophthalmic products are discussed in the FIGURE. Before using any ophthalmic product, patients should wash their hands. If the product is a suspension, they should be instructed to shake the product before use. Once the product is open, patients should be mindful not to contaminate the product by touching the tip of the bottle or tube; it is prudent to place the cap of the product on its side on a clean tissue. When ready to instill the ophthalmic product, patients should tilt their head back slightly and pull the lower eyelid down to create a pouch for the drop, gel, or ointment.

When using ophthalmic drops, the bottle should be held upside down above the eye, and the bottle should be squeezed lightly to release a drop of the medication. Again, patients should be cognizant not to touch the tip of the applicator to their eye to avoid potential contamination. Once the drop has been instilled into the eye, the patient should release their lower eyelid and gently close their eye. They should not blink or “squeeze shut” their eye as this may cause the drop to be expelled. The patient should then block the nasolacrimal duct by gently pressing on the inner eye for 1-2 minutes; this will prevent medication from draining through the duct and will maximize medication contact time.

When using ophthalmic ointments, patients should squeeze the tube gently to dispense a thin ribbon, approximately 0.25 to 0.5 inches in length, into the pouch created by pulling down the lower eyelid. Then the patient should release the lid, blink gently, and keep the eye closed for 1 to 2 minutes. Ophthalmic ointments are likely to cause blurry vision and if possible, should be administered at bedtime. After using either drops or ointments, patients should wash their hands and be sure to put the cap back on the product to minimize contamination.

If patients are using multiple ophthalmic products, they should apply the least viscous product first (drops first, followed by gels, then ointments). Patients should wait 5 minutes between products if administering 2 different drop formulations. If using an ointment and drops, patients should wait for 10 minutes after drops to apply the ointment. ADDITIONAL RESOURCES included at the end of this activity also provide further guidance for administration of eye drops, ointments, and gels.

**Role of the Pharmacy Technician**

Pharmacy technicians play an essential role in patient care by assisting the pharmacist. Pharmacy technicians can help to identify patients who appear to be experiencing AC and referring these patients to the pharmacist when appropriate. There are numerous medications in multiple dosage forms available for the treatment of AC. Technicians should become familiar with products available to treat AC and remain updated as new products become available. OTC products in particular are updated frequently; technicians should also be aware of new product packaging and new brand name extensions as well as any products that have been discontinued. Most importantly, pharmacy technicians can play a key role in assisting patients to locate OTC products as recommended by the pharmacist. Technicians can also provide handouts on appropriate administration techniques when dispensing eye drops or eye ointments or when a patient purchases an OTC ophthalmic product.
Patient Counseling Video Vignettes

Video vignettes featuring a pharmacist providing education and recommendations to patients about management of allergic conjunctivitis symptoms are highlighted at pharmacytimes.org/go/conjunctivitis.

Conclusion

AC is a very common condition that affects millions of people every year. Specifically, SAC and PAC are mild, but can have bothersome symptoms that can heavily impact quality of life, especially when improperly diagnosed or treated. Fortunately, there are nonpharmacologic as well as OTC and prescription treatment options available. With the help of the pharmacist and pharmacy technician, patients are better able to select safe and proper products, review proper eye care administration technique, and successfully manage the symptoms of AC.

REFERENCES


ADDITIONAL RESOURCES

Asthma and Allergy Foundation of America (AAFA): Overview of allergic conjunctivitis for patients who may be experiencing ocular allergy
American Academy of Ophthalmology (AAO): Instructions for preparation and administration of eye drops
American Society of Health-System Pharmacists (ASHP): Instructions for administration of eye ointments and gels
American College of Allergy, Asthma, and Immunology (ACAAI): Discussion of eye allergies and opportunity to ask an allergist via chat or find an allergist near you

acaai.org/allergies/overview-of-allergic-conjunctivitis
aao.org/eye-health/treatments/how-to-put-in-eye-drops
safemedication.com/safemed/docs/Eye-Ointments-and-Gels-Flyers.pdf
acaai.org/allergies/types/eye-allergy
redness-relief/clear-eyes-redness-relief-eye-drops#ingredients
INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

For pharmacists, go to www.pharmacytimes.org/go/conjunctivitis to access the online version of this activity.

For pharmacy technicians, go to www.pharmacytimes.org/go/conjunctivitis-techs.

Click “Proceed,” then complete the online pretest.

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

Complete the online posttest and activity evaluation form.

After successfully completing the posttest and evaluation form, this information will be uploaded to CPE Monitor.

You must complete these steps before the activity expires in order to receive your credit.

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

NOTE: Your CE credit will be automatically uploaded to CPE Monitor. Please ensure that your Pharmacy Times® account is updated with your NABP e-profile ID number and your date of birth. Participation data will not be uploaded into CPE Monitor if you do not have your NABP e-profile ID number and date of birth entered into your profile on www.pharmacytimes.org.

SYSTEM REQUIREMENTS FOR COMPLETION:
Computer or smartphone with internet-access web browser (IE7.0+ or Webkit-/Mozilla-compatible) with JavaScript enabled.

FOR QUESTIONS ABOUT THIS INTERNET CPE ACTIVITY, PLEASE CONTACT: ceinfo@pharmacytimes.com.

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PHARMACIST POSTTEST QUESTIONS*

1. Jessica is an 18-year-old woman who states that she has been having daily itchy, watery, and red eyes for the past 6 months since moving into a new apartment. She does not wear contact lenses or other eyewear, but she says she also has allergic rhinitis. Which type of allergic conjunctivitis (AC) is Jessica most likely experiencing?
   A. Atopic keratoconjunctivitis (AKC)
   B. Perennial allergic conjunctivitis (PAC)
   C. Seasonal allergic conjunctivitis (SAC)
   D. Vernal keratoconjunctivitis (VKC)

2. Based on immunology, which of the following best describes why dual-activity agents with antihistamine and mast cell-stabilizing activity are beneficial for the treatment of SAC and PAC?
   A. SAC and PAC are immunoglobulin E (IgE)-mediated reactions that involve degranulation of mast cells and subsequent release of histamine, which causes AC symptoms.
   B. SAC and PAC are IgE-mediated reactions that involve antagonism of histamine receptors and subsequent degranulation of mast cells.
   C. SAC and PAC are T cell-mediated reactions that involve degranulation of mast cells and subsequent release of histamine, which causes AC symptoms.
   D. SAC and PAC are T cell-mediated reactions that involve antagonism of histamine receptors and subsequent degranulation of mast cells.

3. Miguel is a 32-year-old man who presents to the pharmacy with eye allergies. He states that he uses olopatadine 0.2% as directed. He says that his symptoms are well controlled during the day, but he continues to have some ocular itching throughout the night. Which recommendation is the most appropriate to make for Miguel?
   A. Change the medication to olopatadine 0.7% 1 drop once daily.
   B. Increase dose of olopatadine 0.2% to 1 drop every 6 to 8 hours (maximum 2 doses per day).
   C. Continue olopatadine 0.2% and add tetrahydrozoline 1 or 2 drops at bedtime.
   D. Contact Miguel’s provider to request a prescription for loteprednol 0.5% 1 or 2 drops 4 times daily.

4. Which statement best describes why mast cell stabilizers are typically not used as monotherapy?
   A. They are only available over-the-counter (OTC) and may be used inappropriately and result in treatment failure.
   B. They must be used 2 to 6 times daily, and it may take weeks before they become effective.
   C. They are not effective for the swelling and redness associated with AC.
   D. They are only formulated in combination with other medications.

5. Which statement is true regarding the use of topical nonsteroidal anti-inflammatory drugs and topical corticosteroids for AC?
   A. Their adverse effect profiles are favorable over mast cell stabilizers and antihistamines.
   B. They are prescription only, so they do not contain the preservative benzalkonium chloride.
   C. Once-daily formulations should be reserved for VKC and AKC.
   D. Due to serious adverse effects, use is limited to a short duration to relieve severe symptoms.

6. Which of the following best describes the mechanism of action of olopatadine?
   A. It works by blocking ocular histamine receptors.
   B. It prevents the degranulation of mast cells.
   C. It acts as a vasoconstrictor to decrease AC symptoms.
   D. It works to both stabilize mast cells and block histamine receptors.

7. Rebecca is a 32-year-old woman presenting to the pharmacy with a new prescription for cetirizine 0.24% ophthalmic solution to treat her SAC. Her prescriber also recommended that she buy an OTC lubricant eye ointment to help with her complaints of ocular dryness. Rebecca has never used topical ophthalmic products and requests advice on how to administer these agents. Which of the following is an appropriate recommendation for Rebecca?
   A. Rebecca should squeeze her eye shut after administering the lubricant eye ointment and keep her eye closed for 30 seconds.
   B. Rebecca should administer the lubricant eye ointment in the morning upon awakening.
   C. Rebecca should administer the lubricant eye ointment first, then wait 1 to 2 minutes before administering the cetirizine 0.24% ophthalmic solution.
   D. Rebecca should block the nasolacrimal duct by gently pressing on the inner corner of her eye after administering cetirizine 0.24% ophthalmic solution.
PHARMACIST POSTTEST QUESTIONS* (continued)

8. Sam is a 26-year-old man with SAC during the spring. His symptoms include ocular dryness, itchiness, and redness. You determine his symptoms are mild and he may benefit from a short trial of nonpharmacologic therapy. Which of the following is an appropriate nonpharmacologic recommendation for Sam?
   A. Recommend propylene glycol lubricant eye drops several times a day to rinse away allergens.
   B. Shower and wash hair first thing in the morning to minimize daytime symptoms.
   C. Apply warm compresses to soothe ocular irritation.
   D. Sam is unlikely to benefit from nonpharmacologic recommendations; initiate treatment with a pheniramine/naphazoline eye drop.

9. Which of the following is an appropriate counseling point regarding the use of intranasal corticosteroids?
   A. Use should be limited to 2 weeks.
   B. Role in ocular symptoms is limited to pruritus; there is no benefit in ocular erythema.
   C. Ocular symptoms typically improve in 2 to 5 days.
   D. Use should be avoided in children younger than 12 years.

10. Sally is an 18-year-old college student who has recently developed SAC. She reports that her eyes are very itchy, and both eyes are visibly red and tearing; she states she wants something that will work quickly to treat her symptoms. Sally has a package of tetrahydrozoline eye drops and is asking if it is appropriate for her symptoms. Which of the following is an appropriate recommendation for Sally?
   A. Tetrahydrozoline eye drops is an appropriate recommendation; counsel Sally not to use it for more than 2 weeks.
   B. Tetrahydrozoline eye drops is not an appropriate recommendation; recommend Sally use pheniramine/naphazoline eye drops instead.
   C. Tetrahydrozoline eye drops is not an appropriate recommendation; recommend Sally use oral loratadine instead.
   D. Tetrahydrozoline eye drops is not the most appropriate recommendation; recommend that Sally use olopatadine eye drops instead.

*Pharmacy technician posttest questions can be found at www.pharmacytimes.org
Emerging Therapies in the Treatment of Central Precocious Puberty: A Review for Specialty Pharmacists

EDUCATIONAL OBJECTIVES

At the completion of this activity, the participant will be able to:
• Identify the epidemiology, etiology, clinical presentation, diagnosis, and clinical burden of central precocious puberty (CPP)
• Examine the treatment landscape of CPP and compare pharmacologic therapies used for this condition
• Explain the role of the specialty pharmacist in addressing unmet needs for patients with CPP to optimize clinical and economic outcomes

TARGET AUDIENCE: Specialty pharmacists

ACTIVITY TYPE: Application

RELEASE DATE: February 26, 2021

EXPIRATION DATE: June 15, 2022

ESTIMATED TIME TO COMPLETE ACTIVITY: 2.0 hours

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

Introduction

Puberty is a transitional stage in which a child experiences endocrine, physical, and psychological changes.1 Increased linear growth, the development of secondary sex characteristics, and the attainment of reproductive function accompany this transition into adulthood. It occurs due to complex biological events regulated by genetic, endocrine, environmental, social/economic, and geographic factors, resulting in increased hypothalamic-pituitary-gonadal (HPG) axis activity.

Sexual precocity is a medical condition in which puberty begins early.1 Parental concerns about potential premature pubertal development are a leading cause of referrals to pediatric endocrinologists. The timing of the onset of puberty has changed according to the historical record. Recent studies demonstrate an earlier mean age of onset of secondary sex characteristics, such as breast development, pubic hair, and menarche, than formerly reported.

Differentiating patients with benign normal variants of puberty and patients requiring testing and treatment may sometimes be quite challenging.

Epidemiology

Normal Puberty: Endocrine Changes

In 2005, the journal Science stated there was limited information as to the reason for childhood to end and classified the control of the onset of puberty as one of the 125 unsolved questions of science.2,3 Progress since then has not uncovered the exact control mechanism of the biological clock that starts the process of puberty, but much has been learned about the components of the process. It involves a plethora of neurotransmitters and neuromodulators, which will be simplified in the following sections.

Gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus into the pituitary portal system occurs as low amplitude pulses at a slow frequency before
Puberty. During the progression of puberty, the production of kisspeptin from the hypothalamic neurons changes the pattern of release of GnRH from the hypothalamus. Kisspeptin is a peptide hormone produced in the hypothalamus, pancreas, and adrenal glands. The neurons secreting kisspeptin are thought to be the site of the pulse generator, which leads to the episodic secretion of GnRH, that in turn results in the episodic pulses of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. Kisspeptin binds to the kisspeptin receptor (KISS1R), which is present on the GnRH-producing neurons. Increased kisspeptin levels augment the amplitude and rate of GnRH pulsatility. Neurokinin B, a neuropeptide that binds to the neurokinin 3 receptor (NK3R), is produced in the hypothalamic kisspeptin, neurokinin B, and dynorphin (KNDy) neurons that coexpress NK3R. Neurokinin B with kisspeptin stimulates GnRH secretion, whereas dynorphin, another neurotransmitter emanating from the KNDy neurons, inhibits GnRH secretion, leading to a balance that affects pulsatility of GnRH secretion. Furthermore, insulin and leptin play a role in modulating the timing of the onset of puberty as they interact with other neurotransmitters sensitive to the nutritional status of the developing body.

The GnRH pulsatility rate increases predominantly in the evening during the early stages of puberty. As puberty progresses, the changes in GnRH release continue into the daytime until there is no longer a diurnal variation in late puberty. Pulsatile GnRH secretion stimulates the anterior pituitary to release LH and FSH in a pulsatile manner. LH stimulates the testes to produce testosterone. FSH promotes follicular development in girls, which leads to gradually increasing estradiol production in the ovaries. Gonadarche, the awakening of the gonads, is the initiation of the production of sex steroids from the ovary or testes. At a later stage in puberty, when the ovary has been appropriately prepared, estradiol exerts positive feedback, which leads to the LH surge resulting in ovulation. The timing of this process is complex, and many initial menstrual periods after menarche are anovulatory, even in normal girls. FSH fosters sperm development in boys in puberty. Estradiol causes thelarche (ie, breast development) as well as rapid linear growth and bone age advancement. Testosterone causes pubic hair and penile growth in boys and, through conversion to estradiol, also stimulates the male growth spurt and advances bone age. An increase in adrenal androgens production during adrenarche, the awakening of the adrenal gland, causes the development of pubic hair in girls and body odor in boys and girls, a process called pubarche. Adrenarche is unrelated to the HPG axis activation, and some children develop pubic hair or axillary odor well before the onset of puberty.

Normal Puberty: Physical Changes

Although the exact age of onset, rate, or particular order may vary, puberty usually occurs in a specific pattern. The sexual maturation ratings, commonly called the Tanner stages of sexual maturation, provide an objective way to classify the degree of pubertal development and monitor a patient’s progress through puberty. At the time of initial evaluation, it is important to note whether the patient has no pubertal development (stage I) or some pubertal development (stage II). Tanner stage II breast development in girls is evaluated by inspection and palpation and signals the most common first indication of pubertal onset in girls, thelarche. Tanner stage II genital development in boys, measured by testicular volume greater than 4 mL or testicular length greater than 2.5 cm, indicates pubertal development. Further stages extend up to stage V and show more breast and pubic hair development in girls and more genital and pubic hair development in boys. A well-treated child with precocious puberty (PP) should not be advancing through these stages.

Pubertal Timing

The classically accepted age of normal puberty occurs between 8 and 13 years in girls and 9 and 14 years in boys. However, the onset of puberty may vary depending on various factors besides genetics; thus, nutrition, psychological stress, and environmental factors can play a role. Race and ethnicity may also influence pubertal onset. A study conducted in the states of New York, Ohio, and California found that at 7 and 8 years of age, 10.4% and 18.3% of White, 23.4% and 42.9% of Black non-Hispanic, and 14.9% and 30.9% of Hispanic girls, respectively, attained greater than Tanner stage II breast development. The mean age for Tanner stage II genital development in boys reported by the Pediatric Research in Office Setting network was 10.14 years in non-Hispanic Whites, 9.14 years in Blacks, and 10.04 years in Hispanics. Tanner stage II pubic hair development in boys occurred at the average ages of 11.47 years in non-Hispanic Whites, 10.25 years in Blacks, and 11.43 years in Hispanics.

Puberty may occur earlier in girls after international adoption or with exposure to estrogenic endocrine-disrupting chemicals. Excessive weight gain or obesity in childhood, especially in girls, plays a role in early development; there is a
correlation between pubertal onset and body mass index. On the other hand, low birthweight has also been associated with early pubertal development.  

Benign Early Pubertal Development Variants

Two common benign variants of early pubertal development include premature thelarche (PT) and premature adrenarche (PA). PT is the isolated growth of breast tissue. Accelerated linear growth and advanced skeletal development characteristic of the onset of central puberty in girls, as well as rapid breast development progression, do not occur with PT. PT does not progress significantly and usually subsides over several months. PA is an early pubertal variant accompanied by mildly increased adrenal androgens levels, which causes gradual progressive pubic and/or axillary hair growth but no activation of the HPG axis. Mildly advanced bone development may accompany PA, but breast development is absent in girls. However, PT may present as the first sign of PP, and PA could present as the first sign of an adrenal tumor. Even after a consideration of these conditions, the patient must be observed longitudinally. The evaluation of children with early pubertal development is essential to differentiate between PT, PA, and PP.

Central Precocious Puberty Versus Normal Puberty

Many biological processes, including the age of onset of puberty, are defined by 2 standard deviations above and below the mean encompassing 95% of the population. Thus, 2.5% of children will be expected to enter puberty below the normal standards. Many children will be just slightly outside of the normal range, while those with pathologic disorders that qualify as PP will likely be farther below the cutoff age. Although the lower limits of normal pubertal development are controversial, the current consensus defines PP as the development of progressive thelarche before 8 years of age in girls and increased testicular volume before 9 years of age in boys.

Many different conditions can cause PP. Causes of PP can be either GnRH dependent or GnRH independent. When it is due to an early onset of the central mechanism that normally controls puberty, it is called central precocious puberty (CPP). CPP occurs due to an abnormally early activation of the HPG axis (GnRH dependent), resulting in the same physical features and biochemical processes of puberty at an unusually early age. When sexual precocity is due to the autonomous production of sex steroids from the adrenal gland, ovaries, or testes, or from exogenous sources of sex steroids, it is called peripheral precocious puberty (PPP). PPP occurs due to GnRH-independent causes. Some etiologies of PPP include sex hormone production by extragonadal tissue (eg, congenital adrenal hyperplasia, androgen-secreting adrenal tumor), unregulated sex steroid secretion by gonads (eg, McCune-Albright syndrome or familial male-limited PP), human chorionic gonadotropin-secreting tumor, sex steroid tumor (eg, Leydig cell tumor), and exposure to exogenous sex steroids.

Prevalence

Few epidemiologic studies estimate the true prevalence of PP, particularly CPP. Reasons for the sparsity of data may be due to the fact that diagnosis of CPP relies on multiple factors, including nonuniform criteria for age cutoff for CPP diagnosis, ambiguous terminology, different biochemical and radiological criteria, and a variety of national data registration models. However, it is clear that girls have PP more frequently than boys.

In a Danish study using national registries, approximately 0.2% of girls younger than 9 years and less than 0.05% of boys younger than 10 years had precocious pubertal development. The prevalence of PP was 5 times lower in boys (<5 per 10,000) than in girls (~20-30 per 10,000). In this study, 46% of patients had PP, with the remaining children having PT, PA, or early normal puberty.

An observational study conducted in Spain reported the incidence rate of CPP from 1997 to 2009 to be 5.66 cases per million person-years at risk, with 11.21 times greater relative risk (95% CI, 7.52-17.53) in girls than in boys. The annual incidence rate for new cases was 0.02 and 1.07 per 100,000 in boys and girls, respectively. This study excluded patients in whom puberty began at 8 years or older in girls or 9 years or older in boys as well as those with PT, unlike the Danish study.

A recent longitudinal national registry-based study in Korea in patients with newly diagnosed CPP from 2008 to 2014 found the overall incidence of CPP was 122.8 per 100,000, with an incidence of 262.8 per 100,000 for girls and 10.9 for boys. The overall prevalence of CPP was 193.2 per 100,000 persons (410.6 girls and 10.9 boys). The study included children who had an ICD-10 diagnosis code of CPP (girls before 9 years old and boys before 10 years old) and who were treated with GnRH analog (GnRHa) therapy. Overestimation of prevalence and incidence rates could be due to the inclusion of girls aged 8 to 9 years and boys aged 9 to 10 years with early puberty who developed secondary sexual characteristics and the inability to determine if proper observation before treatment occurred in cases of slowly progressing CPP.
Etiology

Idiopathic versus Pathologic

There are both idiopathic and pathologic etiologies of CPP (refer to TABLE 1 for pathologic causes of CPP). Older studies estimated the prevalence of central nervous system (CNS) pathology to be 10% in girls and between 30% and 70% in boys, but recent studies suggest a much lower incidence of pathogenic CNS lesions in girls. In the past 10 years, there has been progress in identifying genetic-related causes.

CNS Lesions/Disorders Causes

The principal risk factors for a physical CNS cause for CPP include male sex and younger age. A hypothalamic hamartoma (HH) is the most common CNS lesion linked to CPP. It is a congenital nonneoplastic collection of neural tissue located at the base of the third ventricle. HH can be considered a congenital defect that does not enlarge. Unless it causes associated morbidity, such as intractable seizures, HH does not cause a threat to life and requires no surgical treatment. GnRH agonists are the treatment of choice for CPP due to this etiology. The estimated prevalence of HH is 1 in 50,000 to 1 in 100,000 children, with most cases diagnosed before 4 years of age.

CNS tumors located in the posterior hypothalamus may cause CPP. Medulloblastomas, pineal tumors, cerebellar astrocytomas, craniopharyngiomas, germinomas, low-grade gliomas, and ependymomas have been associated with CPP. Patients with type 1 neurofibromatosis commonly have juvenile pilocytic astrocytomas (low-grade gliomas), which may cause seizures, headaches, and PP. A CNS tumor can cause CPP in both boys and girls, but it is much more common in boys as an etiology of early puberty.

Cranial irradiation used to treat childhood malignancy, including CNS tumors, may lead to premature activation of GnRH neurons. The risk for CPP increases with irradiation 18 Gy or greater, younger age, and female sex. A patient with such radiation treatment might be left with growth hormone deficiency, which would ordinarily cause poor growth but, if coexisting CPP occurs, the growth may increase, thus masking the growth hormone deficiency.

Genetic Causes

There are currently 4 different gene mutations identified as causes of CPP. The Makorin RING-finger protein 3 (MKRN3) gene appears to normally inhibit puberty in children and has been considered the “brake” on puberty. MKRN3 mutation is the most common genetic cause of CPP. The prevalence of MKRN3 mutations ranges from 0.4% to 5% and 33% to 46% in sporadic and familial cases, respectively. The Delta-like homolog (DLK1) gene regulates pituitary cell differentiation, and its mutation has recently been identified as a cause of CPP. Gain of function mutations in the
kisspeptin gene (KISS1) and kisspeptin receptor (KISS1R) account for rare cases of CPP.

Some syndromes caused by chromosomal abnormalities rarely linked to CPP include Williams-Beuren syndrome, Temple syndrome, Prader-Willi syndrome, and Rett syndrome. Other genetic syndromes associated with CPP include neurofibromatosis type 1, tuberous sclerosis, and Sturge-Weber syndrome.

Clinical Presentation and Diagnosis

Patient History and Family History

When PP progresses, worries include unfavorable psychosocial outcomes in boys and girls, short adult stature due to premature epiphyseal closure, and early menarche in girls. The age of pubertal onset is inversely related to height loss in untreated PP. Taking a complete patient and family history is the first step in the differential diagnosis of CPP. The patient history should include growth velocity, the age of pubertal onset, progression of pubertal development, sex steroid exposure, and symptoms of CNS disorder (ie, vomiting, visual changes, seizures, excessive thirst and urination due to diabetes insipidus and headache). The health care provider should also collect information about birth (eg, gestational age, length, weight, birth complications, maternal illness during gestation), concomitant chronic diseases, and psychomotor development. Family history regarding the presence of elevated testosterone in boys and estradiol and symptoms of CNS disorder (eg, seizures, excessive thirst and urination due to diabetes insipidus and headache) is necessary.

TABLE 1

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams-Beuren syndrome</td>
<td>Short stature, developmental delay, cognitive impairment, seizures</td>
</tr>
<tr>
<td>Temple syndrome</td>
<td>Short stature, developmental delay, cognitive impairment, seizures</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>Short stature, developmental delay, cognitive impairment, seizures</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>Microcephaly, developmental delay, seizures, speech delay, seizures</td>
</tr>
</tbody>
</table>

Biochemical Measurements

Preliminary laboratory workup for CPP involves obtaining gonadotropin, serum testosterone, and 17-β-estradiol levels, all in a specialty laboratory with pediatric standards. A laboratory dealing with adult disorders will not necessarily have sensitive methods appropriate for children. In recent years, measuring total testosterone and estradiol using high-performance liquid chromatography tandem mass spectrometry shows higher accuracy, precision, and sensitivity than previous assays and is now the standard. Serum testosterone measured with this appropriate assay is sensitive to diagnose sexual precocity in boys but insufficient to distinguish precocious pubarche from CPP in boys as adrenal androgens production, they may occur through the benign condition PA rather than CPP.

Clinical Signs/Symptoms

A physical examination will evaluate the progression of secondary sex characteristics (refer to TABLE 1). Careful examination of breast development by inspection and palpation and determination of clinical signs of estrogen effect, including nipple and areolae maturation and vaginal mucus discharge in girls, is necessary. The development of breast buds (Tanner stage II) marks the onset of puberty in girls; however, with the epidemic of obesity this becomes difficult. In boys, the health care provider should examine the testicles to determine size and symmetry. A testicular volume of 4 mL or greater than 2.5 cm excluding the epididymis usually indicates HPG axis activation. Workup should also include evaluation of the skin for the presence of acne, oily skin, excess body hair, and pigmented lesions (café au lait spots seen in neurofibromatosis type 1). Body odor, axillary hair, and pubic hair in both girls and boys can be helpful as a sign of CPP but, because they are due to adrenal androgens production, they may occur through the benign condition PA rather than CPP.

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GNRHa stimulation testing, with GnRH being unavailable. The stimulating agent predominantly used in the United States for GnRH stimulation testing. Currently, leuprolide is the peak threshold indicating the onset of puberty depends on the protocols using GnRH and GnRHa as the stimuli exist. The LH peak threshold indicating the onset of puberty is typically drawn 18 to 24 hours after leuprolide dosing may enhance stimulation testing sensitivity. Baseline LH levels are higher in children younger than 2 years, so discretion in interpreting results is needed to avoid CPP misdiagnosis. An LH/FSH ratio greater than 0.66 after stimulation may also indicate puberty, although it has less sensitivity and specificity than the stimulated LH peak.

Imaging
A bone age x-ray is a complementary test used in the evaluation of PP. Compared with normal early pubertal variants, the bone age of patients with PP is usually significantly advanced (>2 standard deviations above the mean) compared with their chronological age. Providers may use bone age to predict adult height potential, but this test has low predictive reliability. Bone age readings must be provided by an experienced radiologist, though in areas where they are rarely ordered, accuracy may be adversely affected.

A pelvic ultrasound may detect ovarian cysts or tumors that may increase estradiol in girls. This evaluation is useful in difficult cases when differentiating between girls with suspected PT and PPP and, on occasion, those with CPP. For girls up to 8 years, measurement of uterine and ovarian dimension through pelvic ultrasounds is helpful to support the diagnosis of CPP. After the age of 8 years, there is a more significant overlap in uterine and ovarian measurement, making pelvic ultrasounds less useful. The normal pubertal ovary has many cysts and, sometimes, the diagnosis of polycystic ovarian syndrome is incorrectly applied to a normal ovarian ultrasound.

Providers should perform routine brain magnetic resonance imaging (MRI) studies for all girls younger than 6 years and boys younger than 9 years with documented CPP; boys are more likely than girls to have a CNS pathology. The role of routine MRI in the workup for CPP is less defined for girls aged 6 to 8 years. Some studies have revealed that girls diagnosed with CPP undergoing brain MRI discovered unsuspected pathological findings. A review examining the frequency of occult intracranial lesions in girls aged 6 to 8 years with CPP revealed that although brain MRI detected abnormalities in 8% to 15%, up to 2% of brain MRIs uncovered previously unknown findings requiring intervention. For asymptomatic girls aged 6 to 8 years with CPP, the provider must assess the benefits of an MRI.

Burden of Disease and Impact on Quality of Life
Psychological and Social Impact
PP may cause psychological and social issues for children, including increased incidence of depression, social withdrawal, behavior issues, obsessive behavior, stress, aggression, and sleeping problems. Compared with girls who do not experience early puberty, girls with PP may experience lower self-esteem, increased absenteeism at school, increased risk for suicide, and more substance use disorders. Sexual abuse is associated with earlier onset of puberty and earlier menarche compared with a control population in a large US national study. Other studies, however, have suggested that girls with CPP do not experience significant adverse psychological consequences compared with control children.

Impact on Health-Related Quality of Life
There is mixed evidence on the effect of CPP on quality of life. A recent survey of 142 caregivers of children with CPP and 300 without CPP evaluated health-related quality of life. There were significantly lower adjusted mean scores in children with CPP for Pediatric Quality of Life Inventory, Psychosocial Health Summary, and Physical Health Scores than in children without CPP. Emotional functioning scores were significantly lower in the CPP than the non-CPP group. Caregivers of children in the CPP group reported that their child experienced more sleep issues; more worry; more problems feeling scared, sad, or angry; and more teasing. They also noted more trouble completing tasks, forgetfulness, aches, lower energy, and less sports participation. The study reported a nonsignificant decrease in Patient-Reported Outcomes Measurement Information System peer relationship T scores. Overall, results demonstrated that CPP significantly impacts a child’s physical, emotional, and social functioning. Other studies, however, have suggested that girls with CPP do not experience significant adverse psychological conse-
quences compared with control children, showing significant variation in views of quality of life in this condition.21

### Treatment Landscape

#### Goals of Therapy

The treatment goals in children with CPP are to slow the progression of puberty and physical development and preserve or recover adult height potential.15 Although treatment can significantly increase adult height if started early enough, the effectiveness of treatment to alleviate psychological stress is inconclusive and requires more research.5

#### Treatment With GnRHa

Since the 1980s, the mainstay of CPP treatment has involved the use of GnRHa.18,14 GnRHa is a synthetic decapeptide that binds to the GnRH receptor in the anterior pituitary,
competing with endogenous GnRH. GnRHa is resistant to breakdown by proteases, which increases its stability and half-life over the native molecule. Initially, GnRHa stimulates LH and FSH secretion over a period of days. However, following this, GnRHa therapy causes desensitization of GnRH receptors and downregulation of their number. Thus, GnRHa treatment suppresses LH and FSH secretion, resulting in decreased production of sex hormones by the gonads. These effects are reversible upon discontinuation of treatment. Still, the time to recover to the basal state may be lengthy as the child will, in fact, be progressing through puberty once again. Originally, GnRHa therapy was available as a 4-week depot injection, but 12-week and 24-week depot formulations and subcutaneous (SC) implants have become available over time.

Overview of Currently FDA-Approved GnRHa Therapies

Leuprolide Acetate

Initially approved as the 1-month intramuscular (IM) depot formulation, leuprolide acetate has long been a CPP treatment option. Subsequently, the FDA approved the 3-month IM depot injection for children aged 2 years and older. Although both formulations require supervision of administration by a physician, the 3-month formulation was highly advantageous to patients because it reduced the frequency of injections from 12 to 4 per year. The recommended starting dose for the 1-month formulation is weight-based at 7.5 mg (≤25 kg), 11.25 mg (>25 to 37.5 kg), and 15 mg (>37.5 kg). The manufacturer recommends monitoring of basal or stimulated LH levels and sex steroid levels 1 to 2 months after starting treatment and after each dose change to ensure adequate suppression. The 3-month formulation is available as an 11.25-mg or 30-mg dose. Regardless of the dose chosen to initiate therapy, the manufacturer recommends basal or stimulated LH levels or sex steroid levels at months 2 to 3, month 6, and afterward as clinically appropriate to ensure suppression. For either formulation, providers should also measure height velocity quarterly and bone age every 12 months. The treatment-emergent adverse effects (AEs) occurring in at least 2% of patients receiving the leuprolide 1-month depot formulation were injection-site reactions including abscess, pain, headache, vasodilation, acne/seborrhea, rash, emotional lability, and vaginal bleeding/discharge or vaginitis. The most frequent AEs in the 3-month depot study were increased weight, injection-site pain, headache, altered mood, and injection-site swelling (TABLE 2). However, weight gain has not been a consistent finding in treatment of CPP.

In a clinical study with 55 treatment-naïve patients (49 girls and 6 boys with a mean age of 7 ± 2 years) using the 1-month formulation, treatment resulted in suppressing peak stimulated LH concentrations up to 1.75 mIU/mL in 96% of study participants at month 1. In total, 5 participants required increased doses to achieve or sustain LH suppression. Treatment suppressed breast development in 66.7% to 90.6% of girls and genitalia development in 60% to 100% of boys during the first 5 years of treatment. In 19.4% of girls without menses at baseline, transient vaginal bleeding and spotting were reported during the first 4 weeks of treatment. Mean stimulated estradiol and testosterone levels decreased to prepuberal levels consistently during the first 5 years of treatment. The mean ratio of bone age to chronological age decreased from 1.5 to 1.1 years, the mean growth rate declined to 3.4 to 5.6 cm/year, and the mean height standard deviation score decreased from 1.6 to 0.7 by the end of treatment.

In a randomized, open-label trial, 84 participants (76 girls, 8 boys) aged between 1 and 11 years received either 11.25 mg or 30 mg leuprolide depot injection every 3 months. Each dose group had an equal number of treatment-experienced and treatment-naïve patients. In 78.6% of the participants receiving the 11.25-mg dose and 95.2% receiving the 30-mg dose, suppressed peak-stimulated LH level up to 4.0 mIU/mL after 6 months was experienced. The 11.25-mg formulation and the 30-mg 3-month formulations suppressed sex steroid production to prepubertal levels in 93% and 100% of participants, respectively. The trial reported a clinical pubertal suppression rate of 90.6% in the 11.25-mg and 82.4% in the 30-mg group in girls at 6 months. The study demonstrated clinical suppression of puberty in 50% and 40% in boys in the 11.25-mg and 30-mg groups at 6 months, respectively. In 87.9% of participants in the 11.2-mg group and in 75% in the 30-mg group, a decrease in the ratio of bone age to chronological age at 6 months was reported.

In May 2020, the FDA approved a 6-month SC leuprolide acetate formulation for children aged 2 years and older to treat CPP. Similar to the other leuprolide products, this formulation also requires administration by a health care professional. Still, the 6-month formulation has the advantage of reducing dosing frequency to only 2 injections per year, which may help improve adherence in patients with CPP. It also can be given SC in a small volume unlike other injectable formulations, which may improve tolerability. The manufacturer recommends monitoring stimulated or basal LH levels or sex steroids for 1 to 2 months following initiation and periodically after confirming adequate suppression. The manufacturer also recommends periodic bone
age monitoring and monitoring of height velocity every 3 to 6 months. The most common AEs occurring in at least 5% of patients in the clinical trial were injection-site pain, injection-site redness, upper respiratory tract infection, nasopharyngitis, productive cough, bronchospasm, pyrexia, headache, cough, abdominal pain, nausea, constipation, vomiting, and hot flush (TABLE 223-26). With the exception of injection-site reactions, the other AEs were not thought to be drug related.

A 12-month, open-label, uncontrolled trial of 64 treatment-naïve pediatric patients with CPP (62 girls and 2 boys with a mean age of 7.5 years) received at least 1 SC 45-mg dose every 24 weeks for 1 year.24 The 6-month leuprolide formulation suppressed peak stimulated LH concentrations to below 4 IU/L in 87% and 86% of participants by months 6 and 12, respectively. Treatment decreased estradiol or testosterone to prepubertal levels in 97% and 100% of participants at month 6, respectively, with maintained suppression in 98% of girls and 50% of boys at month 12. Mean growth velocity declined from 8.9 (± 13.1) cm/year, 6.9 (± 3.1) cm/year, and 6.4 (± 1.9) cm/year at 1 month, 6 months, and 12 months, respectively.

Histrelin Acetate Implant

The FDA approved histrelin acetate implant, a treatment option for CPP in children 2 years and older, in May 2007.25,27 Histrelin acetate implant is available as a 50-mg SC implant, delivering 65 mcg histrelin per day. It requires surgical insertion into the inner aspect of the upper arm and removal by a physician every 12 to 24 months. Although it is FDA approved for 12-month use, the histrelin implant usually lasts at least 2 years.28 The manufacturer recommends monitoring gonadotropins and sex steroids for 1 month post-implantation, then every 6 months going forward. Additionally, the manufacturer recommends assessment of height velocity every 6 months and bone age every 12 months. The most common adverse reaction occurring in 51.1% of patients was implant-site reaction, which included implant insertion or removal complications. Post-marketing experience reported occasional implant breakage during attempts at removal. Also reported were adverse reactions related to the suppression of endogenous sex steroid production.

The FDA evaluated the efficacy of histrelin acetate implant in 16 pretreated and 20 treatment-naïve children (33 girls and 3 boys) with CPP aged 4.5 to 11.6 years.29 Suppression of LH peak below 4 mIU/mL occurred in all treatment-naïve and treatment-experienced patients after 1 month and continued through month 12. Estradiol suppression occurred in 100% of girls at month 9 and 97% at month 12. Histrelin treatment maintained testosterone suppression in all 3 treatment-experienced boys in the study.

Triptorelin

The FDA added triptorelin to the CPP treatment armamentarium in 2017 for children 2 years and older.26,29 Triptorelin is available as a 22.5-mg extended-release injectable suspension to be administered IM once every 24 weeks by a health care provider. The manufacturer recommends monitoring stimulated or basal LH levels or sex steroids beginning 1 to 2 months after initiation and periodically after ensuring suppression. Additionally, providers should monitor growth velocity every 3 to 6 months and bone age periodically per the manufacturer. The most common AEs (≥4.5%) reported are injection-site reactions, vaginal bleeding, headache, hot flush, cough, and infections (see TABLE 223-26).

In a noncontrolled, open-label study, 44 treatment-naïve children (39 girls and 5 boys) with CPP aged 2 to 9 years received 22.5 mg of triptorelin every 24 weeks for 12 months.26 In at least 93% of children, LH suppression (≤5 IU/L) to prepubertal levels was achieved. In at least 79% of girls and 80% of boys, suppression of estradiol and testosterone was achieved, respectively. Additionally, the study demonstrated no increase in bone age/chronological age ratio in 95% of children, as well as stabilized sexual maturation at 12 months in 89% of children. After the first injection, 1 girl who previously achieved prepubertal hormonal suppression experienced an increase in basal LH above 5 IU/L or serum estradiol greater than 20 picograms/mL 48 hours after the second triptorelin injection.

STAR

Think about the different GnRHa medications approved to treat CPP. What are each agent’s advantages and disadvantages in terms of duration of action, route of administration, and AEs? How can you as the pharmacist best individualize the recommendation of a GnRHa agent for your patients?

Consensus Statements

Although the introduction of GnRHa therapies, with their favorable safety and efficacy profiles, has transformed the treatment paradigm of CPP, providers need additional clinical guidance regarding best practices for use. The European Society for Paediatric Endocrinology and the Lawson...
Wilkins Pediatric Endocrine Society issued a 2009 consensus statement addressing these needs. In 2019, the International Consortium, comprising multiple pediatric societies globally, updated these clinical practice guidelines regarding the appropriate use of GnRHa in children.

Initially, prescribers used the 4-week GnRHa depot injections most frequently. Other longer-acting formulations (12-week, 24-week, and 12-month implants) and different GnRHa therapies became available in the past 10 years. Prospective head-to-head studies comparing the efficacy of various GnRHa agents are currently lacking. Prescribers should discuss the potential short-term and long-term AEs, frequency of administration, and therapy duration of all the available agents with the patients and families. The International Consortium recommends individualization of treatment to meet the needs of the patients. Patients with severe needle phobia or those with special needs may choose the implant over the injectable formulation. Other patients may choose the longer-acting injectable GnRHa due to the decreased number of injections required. The annual cost for most long-acting formulations is similar, so using longer-acting agents may improve therapy adherence.

Initiation of Therapy
Initiation of treatment with GnRHa suppresses puberty and, in most patients, increases adult height when treatment is started at 7 years in girls and 9 years in boys. However, prescribing GnRHa in patients with a minimally early onset of puberty, as in girls aged 7 to 9 years, may not result in the same clinical treatment benefit as younger patients with rapid progression of pubertal changes. A determination to initiate treatment is dependent on consideration of certain factors. Providers should consider treatment in boys younger than 9 years and in girls younger than 7 years whose initial clinical presentation demonstrates progressive central puberty or advanced pubertal development with a rapid linear growth in order to preserve adult height potential. To assess the pace of pubertal progression, the International Consortium recommends a 4- to 6-month observation period before offering GnRHa treatment for girls older than 7 years with Tanner stage II breast development. A review summarizing 29 studies demonstrated the increase in adult height from treatment varied from 2 cm to 10 cm, suggesting not all patients experience benefit from treatment started at this age. A meta-analysis of 6 studies of 332 girls between the ages of 7 and 10 years treated with GnRHa showed no increase in adult height. Most girls in this age range with CPP who were not treated with GnRHa reached a normal range of adult height, but some were shorter than their mid-parental height range.

The psychological morbidity of girls with CPP and early menses may not be as frequent as once believed, as noted previously. When puberty begins around 8 years, menses usually occurs 2.5 to 3 years later. Knowing this, a parent may decrease their child’s apprehension and psychological distress concerning early menses.

A conversation with parents and the child discussing the realistic expectations and goals of treatment facilitates observation, reassurance, and judicious use of GnRHa treatment, because the benefits are not clear-cut in girls beginning puberty at 7 to 9 years of age. Some key points of discussion with parents of early maturing girls with pubertal onset at age 7 to 9 years should include that puberty may not progress rapidly in all patients. A 4- to 6-month observation period is prudent to assess how rapidly puberty is advancing. Additionally, in children with above-average height and not significantly advanced bone age, GnRHa treatment may not significantly improve adult height, which will most likely be normal without treatment. Although psychosocial stress may sometimes occur from CPP, treatment with GnRHa may not diminish this stress. Some studies have shown a lack of benefit of treatment in terms of adult height in girls treated with GnRHa after 8 years of age, with some girls losing height as a result. Lastly, treatment may be expensive and associated with stress due to clinic visits, periodic injections, and implant insertion or removal. These same principles apply to boys with a marginally early pubertal onset. Unless the bone age is significantly advanced, GnRHa therapy may not increase adult height, especially if treatment interrupts a pubertal growth spurt.

Treatment Discontinuation
The optimal age to stop GnRHa treatment is controversial, so individualizing the decision to discontinue is prudent. Assessing the patient’s and parents’ desire to stop is essential because pubertal development will restart within months of stopping treatment. It may take from 6 months to more than 2 years after stopping GnRHa therapy in girls for menses to return. Discontinuing therapy at the age when the child’s peers experience pubertal progression is rational. Continuation of GnRHa therapy past a bone age of 12.5 years in girls and 14 years in boys may only result in minimal height increases or losses in adult height. Discontinuation of GnRHa
treatment depends on growth rates and height prediction rather than bone age alone, as well as patient willingness to resume puberty.

The Role of the Specialty Pharmacist

Overview of Specialty Pharmacy Programs

Specialty pharmacy concentrates on high-cost, complicated medications that are sometimes available through limited distribution, have Risk Evaluation and Mitigation Strategy programs, and require special storage, administration, or handling. Patients receiving specialty medications require substantial patient-centered medication management due to complexity of therapy. Some of these medications require special billing and prior authorization for insurance coverage. Services offered by specialty pharmacies, besides dispensing, may include patient education and counseling on AEs, patient monitoring for effectiveness and safety, patient outreach for prescription refill and renewal, adherence programs, prior authorization assistance, and enrollment in other financial and patient assistance programs. These high-touch services by skilled specialty pharmacists and staff help ensure the delivery of quality care and optimal patient outcomes.

Economic Burden of GnRHa Treatment for CPP

Those patients receiving GnRHa treatment for CPP may have disproportionately higher costs due to medical care than patients without CPP. GnRHa treatment is expensive, requiring periodic biochemical laboratory tests and radiographic screening of bone age to monitor pubertal suppression. Additionally, patients with CPP may have a greater incidence of comorbid medical conditions associated with a greater all-cause health care utilization than patients without CPP. A recent retrospective observational cohort study examined health care resource utilization and costs of patients treated for CPP with GnRHa treatment on both Medicaid and commercial insurance. The study included 1236 patients with CPP in the commercial insurance group and 673 patients with CPP in the Medicaid group, with 24,206 and 11,965 without CPP in the respective control groups. Study results demonstrated that patients with CPP in the first year post-index had a greater number of unique medications, unique diagnosis codes, comorbid conditions, and higher all-cause and disease-related health care utilization than controls. Patients with CPP with commercial insurance paid 12.25 times more and patients with CPP with Medicaid spent 6.42 times more on health care in the year following treatment initiation on GnRHa than controls after adjusting for baseline characteristics.

Improving Clinical and Economic Outcomes for Patients With CPP

Patient Assistance Programs

GnRHa treatment may be very costly for the underinsured and uninsured. Patients who cannot afford their medications may skip doses or forgo taking the drug altogether, but nonadherence may lead to health complications. Pharmacists can aid the uninsured as well as patients with limited insurance coverage to obtain their medicines at no cost or at a reduced cost through patient assistance programs. Requirements to qualify for assistance vary from program to program. Patient assistance programs may also provide other patient support services. The patient assistance programs currently available for GnRHa treatment include Lupron Support Plus/myAbbVie Assist, Fensolvi TotalSolutions Program, Trip-todur Care Program, and Supprelin LA Support Center/Supprelin LA Shares. TABLE 3 provides details about the individual programs.

Reconstitution, Administration, and Storage

Pharmacists serve as expert sources of drug information regarding proper reconstitution, administration, and storage of GnRHa therapy for patients, caregivers, and health care providers. These agents have complicated instructions for appropriate use and require administration by a health care professional.

Additionally, GnRHa drugs are subject to United States Pharmacopeia (USP) chapter <800> standards. The USP chapter <800> Hazardous Drugs (HD)-Handling in Healthcare Settings, is an enforceable standard containing best practice directives to decrease the risk of exposure for health care workers, patients, and the environment. The National Institute for Occupational Safety and Health (NIOSH) identifies an HD if it exhibits carcinogenicity, developmental toxicity (including teratogenicity), reproductive toxicity, genotoxicity, low-dose organ toxicity, or structure/toxicity profiles similar to other existing HDs. USP chapter <800> describes requirements for proper receipt, storage, dispensing, compounding, administration, and disposal of HDs for sterile and nonsterile compounding. Entities that handle HDs must incorporate USP chapter <800> standards into their occupational safety plan. Leuprolide, triptorelin, and...
leuprolide acetate 1-month and 3-month IM formulations are available as prefilled dual-chamber syringes. One chamber contains sterile lyophilized microspheres of leuprolide acetate and the second chamber contains 1 mL or 1.5 mL of diluent for the 1-month and 3-month depot injections, respectively. Prescribing information recommends storing leuprolide acetate 1-month and 3-month dual-chamber syringes at controlled room temperature (59-86 °F). After reconstituting the preservative-free lyophilized microspheres, the suspension should be injected immediately as a single IM injection or discarded after 2 hours if unused. Pharmacists can refer health care providers responsible for administration to manufacturer prescribing information, which provides specific details on how to reconstitute, mix, and administer the dual-chamber syringes properly. Once reconstituted, the health care provider injects the leuprolide acetate 1-month or 3-month formulation IM into the gluteal area, anterior thigh, or shoulder, being sure to alternate injection sites.

The recently approved 6-month leuprolide acetate SC formulation is available as a kit containing 2 trays, a prefilled Syringe A and Syringe B tray.24 Syringe A contains the diluent for reconstitution (ATRIGEL Delivery System) and Syringe B contains 45 mg of lyophilized leuprolide acetate powder. The polymeric delivery system consists of a biodegradable polyDL-lactide-co-glycolide polymer formulation dissolved in N-methyl-2-pyrrolidone. The manufacturer recommends storing the product under refrigeration at 35.6 °F to 46.4 °F. For easier administration, the product should be removed from refrigeration and reach room temperature before reconstitution. The prescribing information allows for storage in original packaging at room temperature (59-86 °F) for up to 8 weeks before reconstitution and administration. Once reconstituted, the 6-month leuprolide formulation should be administered within 30 minutes or discarded. Prescribing information includes step-by-step instructions to reconstitute and inject the medication aseptically. Recommended SC injection sites are the abdomen, upper buttocks, or areas with adequate SC tissue without excessive nodules, hair, pigment, or lesions; areas compressed by clothing should be avoided (eg, belt or waistband). Providers should also rotate injection sites.

The histrelin implant is a nonbiodegradable, diffusion-controlled hydrogel polymer reservoir designed to deliver histrelin acetate for 12 months continuously. The implant insertion and removal are surgical procedures done under aseptic conditions. The histrelin implant is stable when stored in its sealed vial, pouch, and carton under refrigeration (36-46 °F). The implant may be removed from refrigeration and remain at room temperature (77 °F) for up to 7 days before the procedure. If not surgically inserted within 7 days, the implant may be refrigerated again until the expiration date on the packaging. A separate implantation kit, which is stored at room temperature, contains the local anesthetic, sterile mosquito clamp, and insertion tool needed to insert or remove the implant. The prescribing information includes specific instructions for insertion and removal for health care providers. Using proper aseptic technique for insertion or removal of the implant is necessary to minimize infection risk.

Triptorelin 22.5-mg single-use kit consists of a single-dose vial containing sterile lyophilized triptorelin powder and a prefilled glass syringe containing 2 mL of sterile water diluent. The manufacturer recommends storage of triptorelin 6-month IM extended-release injectable suspension at controlled room temperature (68-77 °F). The prescribing information provides detailed instructions on how to reconstitute and aseptically administer triptorelin. Once the triptorelin 6-month formulation is reconstituted and mixed, it is crucial to inject without delay. The suspension separates into diluent and microgranules very quickly and may block the needle during injection if injection preparation is interrupted.

Pharmacists can work with health care providers to educate them about the proper storage, reconstitution, and administration of GnRHs treatment options to enhance patient outcomes. Incorrect medication use may have adverse consequences, negatively affecting the safety and efficacy of treatment.

**Monitoring GnRHs Therapy and Managing Adverse Effects**

Pharmacists have an important role in educating patients about potential AEs and the best course of action to take should they occur. Pharmacists can also communicate these adverse drug events to health care providers. Working together with the patient, caregiver, and the health care team, the pharmacist can help uncover and mitigate medication-related issues to assure adherence and best outcomes.
Pharmacists should also confirm that appropriate monitoring of safety and efficacy parameters occurs during GnRHa treatment to optimize patient outcomes. Drug therapy monitoring involves continual evaluation of a patient’s medical records to identify and resolve drug therapy issues, such as inadequate lab assessments, lack of follow-up, and adverse drug events. Pharmacists possess the necessary knowledge base and skill set required for this role.

Monitoring Clinical Outcomes to Assess Efficacy
Once treatment initiation occurs, evaluation for stabilization of physical development should occur every 3 to 6 months. Within months of starting GnRHa treatment, the growth velocity usually slows to prepubertal levels. After 6 months of GnRHa treatment, decreases in bone age advancement and increases in predicted adult height should occur with normal growth. Providers may measure stimulated or basal serum

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<td>Based on financial need determination of:</td>
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<td>• Billing and coding questions</td>
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<td></td>
<td>• Prescription transfer to a dedicated specialty pharmacy</td>
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<td>• Prior authorization information</td>
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<td></td>
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<td>Supprelin LA Shares</td>
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<td>• Co-pay amounts exceeding $2000 may be eligible for additional assistance</td>
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<td>Co-pay assistance is not available to patients receiving prescription reimbursement through any federal, state, or government-funded insurance plans</td>
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<td>• Prior authorization and appeals support</td>
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<td>• Dedicated care team for providers and parents</td>
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<td>• Co-pay savings program for patients with commercial insurance</td>
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LH and sex steroid levels to evaluate HPG axis suppression, although a decrease in the amount of breast tissue in girls and slowing of growth rate are good clinical indications of efficacy. Basal LH levels within the prepubertal range usually indicate HPG axis suppression, but levels above the prepubertal range do not always demonstrate failure of suppression. During treatment, as previously discussed under the individual agents, the FDA labeling recommends periodic monitoring of LH levels, sex steroids, and bone age. Accelerated bone age progression, failure of growth rate to decrease, and clinical signs of continued pubertal development may indicate treatment failure. The pharmacist can assess patient adherence and timing of GnRHα administration. Lack of suppression of stimulated LH levels (LH >4 IU/L), sex steroid levels above prepubertal range, or continuation of clinical symptoms may confirm treatment failure. Reconsideration of the cause of PP (CPP vs PPP) should occur in the case of treatment failure.

Monitoring for Safety

Pharmacists should be aware of the warnings, precautions, contraindications, and AEs of GnRHα therapy. GnRHα therapy is generally well tolerated and has a commendable safety profile. The most commonly reported AEs are local injection-site reactions that are usually mild and limited. Sterile abscess formation may occur after depot injection or implant insertion and may be due to a response to the inert polymer in the product formulation. As previously discussed, the most common AE occurring from the histrelin implant was implant-site reaction (including implant insertion or removal complications) in 51.1% of patients. Additionally, fracture of implant upon removal occurs in approximately 22% to 28% of cases, although it occurs more frequently with implants left in place longer than 2 years.

Very rarely, hypersensitivity to GnRHα therapy occurs and can include anaphylaxis. Patients and caregivers should know how to recognize symptoms of anaphylaxis and when to seek emergency medical attention. Contraindications include hypersensitivity reactions to GnRHα agents or excipients in formulation, as well as pregnancy. During the first few weeks of GnRHα therapy, there is an initial rise in gonadotropins and sex steroids before suppression occurs. As a result, there may be increased clinical symptoms of puberty. Withdrawal bleeding in girls with a significant endometrial lining and hot flushes due to decreasing estrogen levels may occur initially but usually resolve quickly. Parents must be aware of this possibility. Patients and caregivers should notify their health care provider if this persists beyond 2 months. Vaginal bleeding after 2 months may indicate inadequate gonadotropin suppression or a different cause needing investigation.

Post-marketing surveillance reported convulsions in patients with epilepsy, CNS lesions, tumors, cerebrovascular disorder, or concomitant medications lowering the seizure threshold, such as bupropion and selective serotonin reuptake inhibitors. There have also been periodic case reports of convulsions in patients without these conditions.

Psychiatric symptoms of increased emotional lability, such as crying, irritability, anger, aggression, and impatience, may be caused by GnRHα treatment. There have been post-marketing reports of depression, with rare reports of suicidal ideation and attempt. Some patients, but not all, had a history of psychiatric illness or other conditions contributing to an increased risk for depression. Pharmacists should monitor for the development or deterioration of psychiatric symptoms during GnRHα treatment. There have been reports of prolonged QT interval in adult men treated with GnRHα therapy for prostate cancer. The International Consortium recommends a screening electrocardiogram (ECG) only in children receiving QT interval-prolonging medications or a history of congenital heart disease, arrhythmia, or long QT syndrome. Additionally, in children with a family history of long QT syndrome or experiencing long QT syndrome symptoms, providers should initially screen with an ECG.

During or after stopping GnRHα therapy, slipped capital femoral epiphysis may rarely occur. Symptoms of slipped capital femoral epiphysis may include pain in the hip, groin, thigh, or knee pain with limping. Slipped capital femoral epiphysis requires prompt management and may be related to inadequate sex steroid exposure during bone formation. Some children may gain weight while on GnRHα treatment, but evidence suggests that GnRHα therapy does not impact the long-term development of obesity during adolescence or adulthood. GnRHα treatment may also decrease bone mineral density during therapy. However, the data suggest that bone mineral density appears to return to the normal range during late adolescence several years after stopping treatment.

STAR

When counseling a patient with CPP or their caregiver, what questions should pharmacists ask to evaluate the safety and efficacy of GnRHα treatment? How can pharmacists ensure appropriate monitoring of therapy?
**Education on CPP to Promote Appropriate Screening**

A recent survey to describe the timeline to diagnosis for children with CPP reported that the average time from onset of symptoms to treatment initiation is 2 years.22 Short adult height was only a concern for 18% of caregivers. Surveys indicated that some children diagnosed with CPP never received treatment. Delays in seeking medical attention for the symptoms of this rare disease may underscore the need for educational intervention. Pharmacists may play an integral role in educating patients and caregivers and encouraging them to seek CPP treatment.

**Education on GnRH to Promote Appropriate Prescribing**

Consensus guidelines suggest that treatment initiation before 6 years of age in girls results in the most significant adult height preservation.30 When clinically appropriate, pharmacists can help inform health care providers about the benefits of early initiation of GnRHa treatment regarding adult height. Pharmacists may inform providers that more prolonged treatment up to a bone age of 12.5 years in girls and 14 years in boys may result in increased height preservation.15 This information may help guide individualization of the timing of treatment discontinuation by the patient, caregiver, and provider through informed decision making.

**Conclusion**

Specialty pharmacists provide complex medication therapy to patients who require intensive patient management. They need expertise regarding disease states they treat and drug information about the medications they dispense. CPP is a rare disease associated with significant psychosocial and financial burden that sometimes goes untreated. Pharmacists can educate patients and caregivers about the importance of evaluation, diagnosis, and treatment of CPP. Additionally, they can help underinsured and uninsured patients receive the medication they need through connection with patient assistance programs. Specialty pharmacies frequently have greater accessibility than primary provider offices, sometimes with 24-hour access to pharmacists. Specialty pharmacists are often the first contact point for patients with questions about their medications and managing AEs. Earlier intervention and timely outreach to health care providers, when necessary, may result in mitigation of AEs and overall improvements in patient adherence and outcomes. Specialty pharmacists can also assist health care providers by dispensing information about proper storage, reconstitution, and GnRHa treatment administration as well as help ensure appropriate monitoring of GnRHa therapy. Collaboration among the patients, caregivers, health care providers, and specialty pharmacists may improve patient care and, ultimately, outcomes for patients with CPP.

**ADDITIONAL RESOURCES**

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<td>Pediatric Endocrine Society</td>
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<tr>
<td>National Organization for Rare Disorders Precocious Puberty Database</td>
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Go to www.pharmacytimes.org/go/puberty to access the online version of this activity.
Click “Proceed,” then complete the online pretest.
Once completed, click “Next” until reaching the online activity posttest.
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POSTTEST QUESTIONS

1. In which of the following does early activation of the hypothalamic-pituitary-gonadal axis (gonadotropin-releasing hormone [GnRH] dependent) occur before 8 years in girls and 9 years in boys?
   A. Central precocious puberty (CPP)
   B. Premature adrenarche (PA)
   C. Peripheral precocious puberty (PPP)
   D. Premature thelarche (PT)

2. Which biochemical parameter has the best diagnostic value for CPP?
   A. Follicle-stimulating hormone (FSH)
   B. Luteinizing hormone (LH)
   C. Testosterone or estradiol
   D. Bone age

3. What is the most common genetic mutation linked to CPP?
   A. KISS1 gain of function mutation
   B. KISS1R gain of function mutation
   C. DLK1 loss of function mutation
   D. MKRN3 loss of function mutation

4. Which GnRH agonist (GnRHa) treatment is administered by intramuscular injection every 24 weeks (6 months)?
   A. Histrelin acetate
   B. Leuprolide acetate depot suspension
   C. Leuprolide acetate suspension
   D. Triptorelin

5. GT is a 6-year-old girl recently diagnosed with CPP. She presents with Tanner stage III breast development and markedly advanced bone age. GT has severe needle phobia, and her caregiver would like to avoid injections altogether. What GnRHa agent may the pharmacist recommend to improve adherence to GnRHa treatment?
   A. Histrelin acetate
   B. Leuprolide acetate 1-month
   C. Leuprolide acetate 3-month
   D. Triptorelin

6. What is the only GnRHa administered by subcutaneous injection?
   A. Histrelin acetate
   B. Leuprolide acetate 3-month
   C. Leuprolide acetate 6-month
   D. Triptorelin

7. The 2019 International Consortium Update on the Use of GnRHa in Children recommends an observation period of _____ in girls diagnosed with CPP and older than 7 years with Tanner stage II breast development to assess the tempo of pubertal development before offering GnRHa treatment.
   A. 2 months
   B. 3 months
   C. 4 to 6 months
   D. 1 year

8. The prescribing information for which GnRHa recommends injection immediately after reconstitution to avoid separation of suspension into diluent and microgranules and potential blockage of needle during injection?
   A. Histrelin acetate
   B. Leuprolide acetate 1-month
   C. Leuprolide acetate 3-month
   D. Triptorelin

9. In a recent survey, what was the average time from onset of symptoms to treatment initiation for CPP?
   A. 6 months
   B. 1 year
   C. 2 years
   D. 3 years

10. Which of the following may indicate GnRHa treatment failure?
    A. Suppression of sex steroids to prepubertal levels
    B. Slowdown of growth
    C. Lack of suppression of stimulated LH levels (LH >4 IU/L)
    D. Decrease of bone age progression
Advancements in Cardiovascular Disease Beyond Statins: Clinical Data and Evidence for Omega-3 Fatty Acids

**EDUCATIONAL OBJECTIVES**

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

- Examine the burden of atherosclerotic cardiovascular disease (ASCVD) and associated cardiovascular event risk
- Explore the role of omega-3 fatty acids in reducing ASCVD event risk and improving patient outcomes
- Analyze evidence-based guidelines, recent clinical trial outcomes, and cost utilization for current treatments that lower ASCVD risk in patients with elevated triglycerides
- Illustrate the role of the pharmacist in proper identification of patients at high risk for ASCVD events and provide recommendations to reduce risk and improve quality of care

**TARGET AUDIENCE:** Retail pharmacists

**ACTIVITY TYPE:** Application

**RELEASE DATE:** February 26, 2021

**EXPIRATION DATE:** March 15, 2022

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

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

**Epidemiology and Pathophysiology of Atherosclerotic Cardiovascular Disease and Hypertriglyceridemia**

Globally and in the United States, cardiovascular disease (CVD) is the leading cause of death.1 Between 2013 and 2016, approximately 121.5 million people had some form of CVD, with the associated cost estimated to be $351.3 billion.1 One of the leading contributors of mortality and morbidity to this alarming statistic is atherosclerosis. Atherosclerosis is a systemic disease where deposits made up of fat, cholesterol, calcium, and other substances create plaques.2 Over time, these plaques can harden and narrow arteries, leading to ischemia due to impairment of blood and oxygen delivery to vital organs, or they can acutely rupture prior to hardening, leading to heart attack and stroke. The constellation of atherosclerotic diseases includes acute coronary syndrome, history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), and peripheral artery disease, including aortic aneurysm, and defines clinical atherosclerotic cardiovascular disease (ASCVD).3

The risk factors for ASCVD have been well documented and include those that are nonmodifiable, such as advancing age, sex, and family history of early ASCVD, as well as those that are modifiable, such as hypertension, diabetes, smoking, and dyslipidemia.3 Specifically, in terms of dyslipidemia, identification and treatment of individuals with elevated lipids is critical to mediation of ASCVD risk. As outlined, serum cholesterol and its lipoprotein carriers (low-density lipoprotein cholesterol [LDL-C], very low-density lipoprotein cholesterol [VLDL-C], and...
high-density lipoprotein cholesterol [HDL-C]) are known to have a relationship with ASCVD due to their key role in plaque development.2,3 The key role of LDL-C has been well defined in the pathogenesis and perpetuation of ASCVD, and elevations of LDL-C above 100 mg/dL are associated with heightened risk of ASCVD events. Aggressive lowering of these levels produces a marked reduction in these outcomes.7 Evidence and current guidelines recommend lifestyle changes and treatment with moderate- to high-intensity HMG-CoA reductase inhibitors (ie, statins) to reduce LDL-C concentrations in primary and all secondary prevention patients.3 Despite statin treatment, several patients still have elevated residual risk due to inability to meet LDL-C goals or elevations in non–HDL-C (non-HDL-C = Total Cholesterol – HDL-C) after achieving appropriate LDL-C reductions.3 Use of agents such as ezetimibe and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors further lowers LDL-C to assist in reaching LDL-C goals but does not assist in targeting non–LDL-C factors contributing to ASCVD risk.4 Furthermore, PCSK9 inhibitors can be cost-prohibitive for some patients.3

The triglyceride (TG)-rich VLDL-C and its remnants (intermediate-density lipoproteins, chylomicron remnants, and VLDL remnants) have been demonstrated to be atherogenic similar to LDL-C.5 It is thought that these lipoproteins contain apolipoprotein B (apoB), which may be the key driver in ASCVD development, and the TG are more likely the carriers.5 Thus, excess degrees of VLDL and its remnants can lead to elevated levels of plasma TG. Subsequently, this concept may link to the epidemiological and mendelian randomization studies that suggest hypertriglyceridemia (HTG) is potentially associated with increased risk of ASCVD.6,7

Fasting plasma TG levels can be categorized as normal (<150 mg/dL), borderline (150-199 mg/dL), high (200-499 mg/dL), and very high (≥500 mg/dL).8 More than 25% of all US adults (56.9 million) have TG levels at 150 mg/dL or greater.9 For patients with very high TG, the primary goal is to reduce levels to lower than 500 mg/dL to mitigate the risk of pancreatitis via lifestyle modifications and use of select pharmacologic agents where indicated.8,10 For patients who are categorized as borderline or high TG, clinicians should also address secondary causes of TG elevations, including medications (TABLE 1) and modifications of lifestyle factors, such as weight loss, physical activity, reduced alcohol consumption, and changes to dietary habits.3,8,10 Dietary change should include decreased consumption of refined carbohydrates and simple sugars, substitution of saturated and trans fats with unsaturated fats, and increased consumption of seafood, including fatty fish.8 Diets not consistent with these practices may lead to elevated TG, which can subsequently increase the amount of VLDL and its remnants.

The 2018 American Heart Association/American College of Cardiology (AHA/ACC)/Multisociety Guideline on the Management of Blood Cholesterol and the 2019 European Society of Cardiology (ESC) Management of Dyslipidemia Guidelines endorse the use of statin therapy in patients with borderline or high TG and who have elevated ASCVD risk (≥7.5% via Pooled Cohort Risk Equation) to reduce TG levels after lifestyle modifications and removal of secondary causes (IIa, B-R for AHA/ACC/Multisociety; I-B for ESC).3,11 Statins lower TG between 7% and 30% from baseline, with more potent statins at higher doses demonstrating a more robust reduction.3,12 Despite lifestyle changes, removal of secondary causes, and statin treatment, an estimated 12.3 million individuals will still have TG levels at 150 mg/dL or greater.13 Observational data suggest patients who are on statin therapy with goal LDL-C (<100 mg/dL) and who still have elevated TG are at increased risk of ASCVD events. One study revealed that more than one-third of projected ASCVD events (3.4 million) occurred in patients with TG levels 150 mg/dL or greater, including in 1.14 million patients on statin therapy.14 In addition, a claims-based database analysis of the Optum Research Database found patients with TG levels 150 mg/dL or greater who were on statins were significantly more likely to have an initial major CVD event than a corresponding propensity-matched cohort with TG levels lower than 150 mg/dL (hazard ratio [HR], 1.26; 95% CI, 1.19-1.34; P < .001).15

Two studies from the integrated health system Kaiser Permanente have corroborated the association between elevated TG and CVD events. The first study compared the outcomes in 2702 statin-treated adults with CVD and LDL-C between 40 mg/dL and 100 mg/dL who had high TG (200-499 mg/dL) and 14,481 individuals with normal TG (<150 mg/dL). The investigators noted patients with high TG had a significantly 20% higher risk of nonfatal MI, 18% higher risk of coronary revascularization, and 56% higher risk of peripheral revascularization compared with patients with

<table>
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<th>TABLE 1. MEDICATIONS THAT INCREASE TRIGLYCERIDES5,8</th>
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<td>Oral estrogens</td>
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<td>Tamoxifen</td>
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<td>Systemic glucocorticoids</td>
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<tr>
<td>Retinoic acid derivatives</td>
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<td>Nonselective β blockers</td>
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normal TG. The second study compared the outcomes in 5542 statin-based adults with diabetes, LDL-C between 40 mg/dL and 100 mg/dL, and a diagnosis of ASCVD or at least 1 other CVD risk factor with high TG to 22,411 patients with normal TG levels. Compared with patients who had normal TG, patients with diabetes and high TG had a significantly 30% higher risk of nonfatal MI, 23% increase in nonfatal stroke, and 21% in coronary revascularization. Thus, there may be a role for therapies that reduce TG, VLDL and its remnants, and, ultimately, apoB.

**Pharmacologic Therapies for HTG**

Lipid-lowering agents have varying degrees of impact on TG as noted in **TABLE 2.** As outlined, statin therapy can reduce TG levels by 7% to 30% as well as VLDL and other apoB-related particles associated with elevated TG. Also, given their strong ASCVD risk reduction benefits, statins are recommended in major guidelines after lifestyle changes for HTG. \(^{5,10,12}\) Fibrates have demonstrated anywhere from a 20% to 50% reduction in HTG and are often utilized when seeking to reduce risk of pancreatitis in patients with TG levels 500 mg/dL or greater. \(^{10,12}\) Despite the large reductions in TG, the impact of fibrate therapy on ASCVD outcomes has been variable, with most trials reporting no major adverse cardiovascular events (MACE) benefit in the primary outcome analyses. However, subgroup analyses have indicated possible benefit in patients with TG levels above 200 mg/dL and HDL-C below 40 mg/dL, especially when being treated with statin therapy. \(^{10,12}\) Further research is needed to determine if a true ASCVD benefit exists in this population. The potential increased risk of treatment-related muscle adverse effects (AEs) with the combination of fibrates and statin therapy must also be taken into consideration. \(^{10}\) Niacin has been shown to have a TG reduction of 10% to 50%. \(^{12}\) However, in both the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High TG: Impact on Global Health Outcomes (AIM-HIGH) and the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trials, niacin therapy failed to reduce the primary end point of MACE in patients at LDL-C goal and demonstrated a higher rate of AEs, such as glucose intolerance and gastrointestinal (GI) symptoms. \(^{18,19}\)

### **TABLE 2. TRIGLYCERIDE-LOWERING EFFECT BY MEDICATION CLASS**\(^{12}\)

<table>
<thead>
<tr>
<th>Lipid-Lowering Therapy</th>
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<tr>
<td>Fibrates</td>
<td>20-50</td>
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<tr>
<td>Niacin</td>
<td>10-50</td>
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<tr>
<td>Omega-3 fatty acids</td>
<td>20-50</td>
</tr>
<tr>
<td>Statins</td>
<td>7-30</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5-10</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>0 (may increase up to 10%)</td>
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<tr>
<td>PCSK9 inhibitors</td>
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**The Role of the Omega-3 Fatty Acids**

Omega-3 fatty acids cause a substantial reduction in TG levels. The omega-3 fatty acids include the plant-derived alpha-linoleic acid (ALA) and both the marine-derived long-chain docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). In the literature, the vast majority of discussion is dominated on the use of DHA, EPA, or the combination of the two as these agents have the desired TG-lowering effect and have demonstrated potential to decrease ASCVD risk when provided via supplementation. In addition, ALA does not lower TG values and should not be used for HTG; therefore, the rest of this review will focus on the marine-based omega-3 fatty acids DHA and EPA.

**Mechanism of Action for DHA and EPA**

Both DHA and EPA reduce serum TG levels by decreasing VLDL synthesis. More specifically, these agents work to increase fatty acid β-oxidation, decrease hepatic lipogenesis, and increase intracellular apoB degradation, which leads to the reduction in VLDL and, subsequently, TG. \(^{10,12}\) Furthermore, these agents augment lipoprotein lipase-mediated clearance of TG. This may explain some of the potential impact for ASCVD risk reduction, but experts also speculate that TG lowering alone may not fully explain the cardiovascular benefit of these agents and the true mechanisms are yet to be fully elucidated. Theorized explanations include anti-thrombotic effects, membrane stabilization, altered prostaglandin synthesis, and anti-inflammatory actions. \(^{22}\)

**STAR**

When assessing patient-specific ASCVD risk and secondary causes of HTG, what patient data should be collected and evaluated?

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

How often should safety be monitored in patients using omega-3 fatty acid supplements or prescription products? What are the similarities and differences in the monitoring parameters between omega-3 products?
Omega-3 Fatty Acid Products

There are a variety of products on the market that contain omega-3 fatty acids (EPA and DHA), and these products can be categorized into 2 fractions: omega-3 dietary supplements and prescription drugs. It is important for clinicians to have knowledge regarding these products in order to provide the best recommendations for patients.

Omega-3 fatty acid dietary supplements are widely accessible and popular among patients. A 2012 study reported that 7.8% adults (18.8 million) attested to using a fish oil dietary supplement in the prior 30 days. Furthermore, a survey of more than 700 patients with ASCVD found 86% were taking omega-3 fatty acid supplements without being recommended to by a healthcare provider. As with most dietary supplements, omega-3 fatty acid supplements are not subject to the strict regulation of prescription products. Therefore, these products could contain variable levels of EPA and/or DHA, which could be inconsistent with labeled quantities, could potentially be poor quality, or could have contaminants like polychlorinated biphenyls. Data suggest contamination may counteract any potential ASCVD benefits. A survey of omega-3 fatty acid supplements completed by the US Department of Agriculture concluded that the majority contained 180 mg of EPA and 120 mg of DHA per dose, which was, for the most part, reflective of the labeled amounts. However, this survey only encompassed a limited number of products. Due to these concerns, patients seeking use should be directed to omega-3 fatty acid supplements that have been voluntarily tested by the US Pharmacopeial Convention to confirm content; these products are indicated via a USP-verified mark on the label. Other challenges associated with the use of omega-3 fatty acid supplements include high pill burden to achieve higher EPA/DHA dose for TG reduction, ability for consistent dosing, fishy taste, and cost.

In contrast to dietary supplement formulations, prescription omega-3 fatty acids are highly purified and are required to meet the standards of Food and Drug Administration (FDA) approval. There are 3 FDA-approved prescription omega-3 fatty acid products containing both DHA and EPA (Lovaza and Omtryg, both of which are an ethyl esters form; and Epanova, which is in carboxylic acid form) and one 100% EPA-alone product (Vascepa, which is a highly purified and stable icosapent ethyl [IPE] form). The omega-3-carboxylic acid (Epanova) and omega-3-acid ethyl ester (Omtryg) are no longer marketed in the United States. Given the formulation differences, these products should not be substituted with use of dietary supplements or with each other.

### Table 3. Prescription Omega-3 Fatty Acid Products

<table>
<thead>
<tr>
<th>Generic (Brand)</th>
<th>Formulation</th>
<th>DHA</th>
<th>EPA</th>
<th>Approved Indication(s)</th>
<th>Dose</th>
<th>US Approval/Marketing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3-carboxylic acids (Epanova)</td>
<td>1-gram capsules</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjunct to diet to reduce TG levels in adult patients with severe HTG</td>
<td>2-4 grams daily</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Omega-3-acid ethyl esters (Lovaza)</td>
<td>1-gram capsules</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjunct to diet to reduce TG levels in adult patients with severe HTG</td>
<td>2 capsules twice daily or 4 capsules daily</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Omega-3-acid ethyl esters A (Omtryg)</td>
<td>1.2-gram capsules</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjunct to diet to reduce TG levels in adult patients with severe HTG</td>
<td>2 capsules twice daily or 4 capsules daily with meals</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>
| Icosapent ethyl (Vascepa)                    | 0.5- and 1-gram capsules | No   | Yes  | 1) Adjunct to diet to reduce TG levels in adult patients with severe HTG  
2) Adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (≥150 mg/dL) and established CVD or diabetes with ≥2 additional risk factors for CVD | 1) A total of 4 each of the 0.5-gram capsules twice daily with food or two 1-gram capsules twice daily with food  
2) A total of 4 grams given as two 1-gram capsules twice daily with food | Yes/Yes                |

CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MI, myocardial infarction; HTG, hypertriglyceridemia; TG, triglyceride.
The Use of DHA and EPA for TG Reduction

All 4 of the FDA-approved omega-3 fatty acid products have indications for reducing very high TG in conjunction with lifestyle modifications and statin therapy where indicated (Table 3). Each agent has been tested at 4 grams daily due to the large effect in reducing TG at this dose. A recent AHA science advisory states prescription omega-3 fatty acids at 4 grams daily produce TG reductions in the range of 20% to 30% in patients with TG levels between 200 mg/dL and 400 mg/dL and of at least 30% in patients with TG levels at 500 mg/dL or greater. No head-to-head trial of each omega-3 fatty acid product in this population exists. Furthermore, the DHA in the products with mixed DHA/EPA also raised LDL-C by about 7 mg/dL, whereas the IPE product, which contains EPA alone, did not. Elevations in LDL-C are dependent on the baseline TG level and represent an increase in the size of the LDL-C particles versus more LDL-C. Lastly, in some patients with very high TG, use of omega-3 fatty acids on top of lifestyle modifications and statin therapy may not allow patients to achieve the goal TG lower than 500 mg/dL and other TG-lowering agents, such as fibrates, may need to be considered. In patients with TG levels between 200 mg/dL and 500 mg/dL, placebo-controlled trials have demonstrated 4 grams daily of omega-3 fatty acids as monotherapy or in conjunction with statins effectively lowered TG between 20% and 30%. In a meta-analysis of the various trials, greater reductions of TG were seen in patients with baseline values of 177 mg/dL or greater compared with those with values less than 177 mg/dL (34% vs 25%).

The Use of DHA and EPA for ASCVD Reduction

Interest in the use of DHA and EPA for ASCVD risk reduction can be traced back to a 1985 observational study which found that people of The Netherlands, who consumed more than 1 meal of fatty fish per week, had 50% reduction in mortality. This spurred other investigators to examine and confirm that regular fish consumption (1-3 times per week) was associated with a lower risk of cardiovascular death. These observational and retrospective studies provided enough foundation to generate a hypothesis for the prospective, randomized Gruppo Italiano per lo Studio della Sopravivenza Prevenzione (GISSI-P) study in 1999. In this trial, 11,324 patients surviving a recent MI were given omega-3 fatty acid with a content of EPA plus DHA not lower than 85% and an average 1:2 ratio of EPA/DHA, vitamin E (300 mg daily), both, or placebo over a 3.5-year period. The results demonstrated a small but significant 10% relative risk reduction in the combined primary end point of death, nonfatal MI, and nonfatal stroke and a 17% reduction in cardiovascular death in the omega-3 fatty acid arm. While positive, the results occurred during a period when statins and percutaneous coronary intervention (PCI) were not used routinely as standard of care practice, which has brought the application of these results into question.

Given the results of the observational data and the GISSI-P trial, a 2002 scientific statement of the AHA recommended that patients with documented ASCVD could consume approximately 1 gram daily of combination DHA/EPA, preferably from oily fish. They stated use of supplementation, due to lack of prescription products at that time, could be considered in consultation with a clinician. The statement also indicated additional studies would need to be done to confirm the findings of the GISSI-P trial. A decade after the GISSI-P trial, the OMEGA trial was conducted in 104 centers that evaluated the use of 1 gram daily of omega-3 fatty acids versus placebo for 1 year on the rate of sudden cardiac death in 3851 acute MI survivors. The background therapy for these patients was more contemporary, with 93.8% of the patients having received PCI and all having received statin therapy. The rate of sudden cardiac death was 1.5% in each group. However, the study had a short duration and was underpowered, with investigators estimating more than 20,000 patients needed in order to determine the true results. In addition, both groups self-reported increased fish consumption during the course of the trial.

In addition to the OMEGA trial, the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial randomized 12,536 patients with diabetes who were at high risk of ASCVD events to 1 gram daily of omega-3 fatty acids (DHA/EPA) or olive oil placebo. After a 6.2-year follow-up period, the investigators found no statistical difference in the primary outcome of CVD death (relative risk [RR], 0.98; 95% CI, 0.87-1.10; P = .72). The investigators denoted a large number of arrhythmic deaths in the trial despite there being no differences between the groups. One concern of this study was that the use of the olive oil, which may be beneficial in ASCVD risk reduction, could have offset the benefit of the omega-3 fatty acid. In contrast to the ORIGIN trial, the GISSI-Heart Failure (GISSI-HF) trial explored the use of 1 gram daily of omega-3 fatty acids (DHA/EPA) supplementation versus olive oil placebo in 6875 patients with heart failure (both reduced and preserved ejection fraction). This trial found a minor but significant reduction in total mortality in the treatment arm (RR, 0.91; 95% CI, 0.83-0.99; P = .0041). Lastly, the Japan EPA Lipid Intervention Study (JELIS) was a randomized, open-label, blinded end point study exploring 1.8 grams daily of
pure EPA omega-3 fatty acids versus usual care in 18,645 Japanese patients who were mostly at risk of ASCVD and were on low-intensity statin therapy over a 4.6-year period. The investigators reported an impressive 19% relative risk reduction in the primary end point of combined sudden cardiac death, fatal and nonfatal MI, unstable angina, and coronary revascularization (RR, 0.81; 95% CI, 0.69-0.95; P = .011). Strengths of this trial included its large sample size and long follow-up, but the trial was limited by the weakness of its open-label design. This trial was unique in the fact it used pure EPA versus mixed DHA/EPA omega-3 fatty acids.40

The mixed results of these trials and many others led researchers to conduct a Cochrane meta-analysis addressing the question of omega-3 fatty acids for primary and secondary ASCVD risk reduction. This review included 79 high-quality clinical studies of omega-3 fatty acids. The authors noted that, based on the combination of the evidence, DHA/EPA did not appear beneficial or harmful toward mortality of ASCVD events.40 These results influenced a 2017 AHA science advisory to not recommend omega-3 fatty acid supplementation for the prevention of ASCVD events in patients with diabetes or prediabetes and deem there to be a lack of consensus on the matter for patients at high ASCVD risk. The authors noted that patients with ASCVD could consider the use of omega-3 fatty acids for modest secondary prevention.40

Interest continued in the use of omega-3 fatty acids for the reduction in CVD outcomes. Investigators devised and completed A Study of Cardiovascular Events in Diabetes (ASCEND) trial, which enrolled 15,480 patients with diabetes aged 40 years or older with no ASCVD to 1 gram daily of omega-3 fatty acids (DHA plus EPA) or olive oil placebo.41 After a period of 7.4 years, the investigators found no significant difference in the primary end point of first serious vascular event defined as nonfatal MI, stroke, TIA, or vascular death (RR, 0.97; 95% CI, 0.87-1.08; P = .55). Similarly, the randomized, placebo-controlled, Vitamin D and Omega-3 Trial (VITAL) examined if 1 gram daily of omega-3 fatty acids (DHA plus EPA) versus placebo could be effective in the primary prevention of ASCVD events in men aged 50 years or older or women aged 55 years or older in the United States. After 5.3 years of follow-up, there were no statistically significant differences in the primary composite outcome of MI, stroke, or death from cardiovascular causes (HR, 0.92; 95% CI, 0.80-1.13; P = .56); additionally, from a safety perspective, there was no reported difference in bleeding, GI symptoms, or other AEs.42

The aforementioned trials all explored 1 gram daily of omega-3 fatty acid in an effort to reduce ASCVD events. With the approval of high-dose prescription products, trials were designed to investigate if these agents would impact ASCVD events. Expanding on the positive results of the EPA-only JELIS trial, the randomized, double-blind, placebo-controlled Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention (REDUCE-IT) trial investigated the use of IPE or placebo (using mineral oil to maintain blinding) in 19,212 patients at high risk for ASCVD events. Patients included in the trial were 45 years or older with established ASCVD (secondary prevention) or 50 years or older with 1 additional CVD risk factor (primary prevention); all patients had to have moderately elevated TG (≥150 mg/dL but <500 mg/dL) despite optimized LDL-C (41-100 mg/dL) on stable statin therapy. The vast majority of the patients (70.7%) were considered secondary prevention patients. Approximately 93% of participants were receiving moderate- to high-intensity statin therapy, and just 6% were on ezetimibe. IPE was dosed 2 grams twice daily. After a median follow-up of 4.9 years, the primary end point, which was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke, occurred in 17.2% of the IPE-treated patients and in 22.0% in the placebo arm (HR, 0.75; 95% CI, 0.68-0.83; P < .001; number needed to treat, 21). At 1 year, there was a 19.7% greater reduction in TG in the IPE arm compared with placebo (P < .001), a 13.1% greater reduction in non–HDL-C in IPE compared with placebo, and a 6.6% increase in LDL-C in placebo compared with IPE. There was also a 39.9% reduction in high-sensitivity C-reactive protein (hs-CRP) in the IPE arm. In terms of safety, there was a nonsignificant trend toward more bleeding-related disorders in the IPE arm (2.7% vs 2.1%). The investigators also noted statistically significantly higher rates of atrial fibrillation (AF) (5.3% vs 3.9%; P = .003), specifically AF requiring hospitalization (3.1% vs 2.1%; P = .004) in the IPE arm. The results were consistent across numerous prespecified subgroups, including baseline TG or on-treatment categories. A larger relative risk reduction was observed in patients with high TG levels (≥200 mg/dL) and low HDL-C (≤35 mg/dL). The result of this trial garnered IPE an FDA label indication as an adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (150-499 mg/dL) and with established CVD or diabetes and 2 or more additional risk factors for CVD.43

The double-blind, randomized, multicenter, placebo-controlled Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova to High Cardiovascular Risk Patients with HTG (STRENGTH) trial explored the ability of the carboxylic acid form of omega-3 fatty acids, which consists
of both DHA and EPA, to reduce ASCVD events in 13,078 patients. Like REDUCE-IT, all patients had to be adults with one of the following: (1) presence of ASCVD, (2) diabetes and older than 40 years for men or older than 50 years for women with 1 additional CVD risk factor, or (3) high-risk primary men aged at least 50 years or women aged at least 60 years with at least 1 additional risk factor. Also, similar to REDUCE-IT, all patients had to be on a stable dose of statin, have an LDL-C below 100 mg/dL or be on maximally tolerated statin therapy, have TG between 180 mg/dL and 500 mg/dL, and have HDL-C lower than 42 mg/dL for men and lower than 47 mg/dL for women. Patients were randomized to 4 grams daily for omega-3 fatty acid in the carboxylic acid form or placebo (using corn oil to maintain blinding). The primary end point was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina. The trial was stopped early by the data monitoring committee when 1384 primary events (goal was 1600) had be recorded in 13,078 patients due to low probability of demonstrating a clinical benefit with treatment. The primary end point occurred in 785 (12.0%) patients in the treatment arm and in 796 (12.2%) patients in the placebo arm (HR, 0.99; 95% CI, 0.90-1.09; P = .84). Patients in the treatment arm had a greater reduction in TG compared with placebo (−19% vs −0.9%; P < .001) with modest changes in LDL-C (1.2% vs −1.1%; P < .001) and non–HDL-C (−6.1% vs −1.1%; P < .001). There was also a significant reduction in hs-CRP (−20.0% vs −6.3%; P < .001). In terms of safety, patients in the omega-3 fatty acid arm experienced more GI events compared with placebo (24.7% vs 14.7%). More AF events were observed in the omega-3 fatty acid treatment arm (2.2% vs 1.3%; P < .001), which was also consistent with REDUCE-IT.44

The last of the more contemporary omega-3 fatty acids trials is the Omega-3 Fatty Acids in Elderly with Myocardial Infarction (OMEMI) trial. In this multicenter, randomized controlled trial, 1027 older adult patients (aged 70-82 years) with a recent MI were given 1.8 grams daily of mixed DHA/EPA omega-3 fatty acid supplement or corn oil placebo. The primary end point was a composite of nonfatal MI, unscheduled revascularization, stroke, all-cause death, and heart failure hospitalization after 2 years of follow-up. The secondary outcome was AF. All patients received contemporary management for their MI. The primary end point occurred in 21.4% of patients in treatment and in 20.0% in placebo (HR, 1.08; 95% CI, 0.82-1.41; P = .06). The secondary end point of AF was numerically higher in the omega-3 fatty acid group (7.2% vs 4.0%; P = .06).45 TABLE 4 provides a summary of omega-3 fatty acid trial data.

Putting It All Together
The clear question derived from culmination of these data is why pure IPE demonstrated a positive effect in both JELIS and REDUCE-IT whereas other trials of mixed omega-3 fatty acids have not. It could reasonably be deduced that the difference in dosing (high at 4 grams daily vs 1 gram daily) could explain the result. However, both the STRENGTH and the OMEMI trials used higher doses and did not demonstrate an ASCVD reduction. Most obvious is the fact that

<table>
<thead>
<tr>
<th>Trial (Year)</th>
<th>Patient Population</th>
<th>Formulation and Dose</th>
<th>Placebo</th>
<th>Primary Outcome (Significant in Green)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JELIS (2007)</td>
<td>N = 18,645 Primary prevention on statins</td>
<td>EPA 1800 mg/day</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ORIGIN (2012)</td>
<td>N = 12,536 High-risk CV events</td>
<td>EPA + DHA 840 mg/day</td>
<td>Olive oil</td>
<td></td>
</tr>
<tr>
<td>ASCEND (2018)</td>
<td>N = 15,480 Patients with diabetes</td>
<td>EPA + DHA 840 mg/day</td>
<td>Olive oil</td>
<td></td>
</tr>
<tr>
<td>VITAL (2019)</td>
<td>N = 25,871 Primary prevention men or women aged &gt;50 years</td>
<td>EPA + DHA 840 mg/day</td>
<td>Olive oil</td>
<td></td>
</tr>
<tr>
<td>REDUCE-IT (2019)</td>
<td>N = 8179 CVD on statin therapy</td>
<td>EPA 4 grams/day</td>
<td>Mineral oil</td>
<td></td>
</tr>
<tr>
<td>STRENGTH (2020)</td>
<td>N = 13,086 CVD on statin therapy</td>
<td>EPA + DHA 4 grams/day</td>
<td>Corn oil</td>
<td></td>
</tr>
</tbody>
</table>

CV, cardiovascular; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.
mixed DHA/EPA may not be effective at reducing ASCVD events. Further investigation is needed to understand the reason, but hypotheses include potential tissue distribution that more effectively imparts the non-TG, pleiotropic effects of omega-3 fatty acids, as the results of REDUCE-IT cannot be explained by TG levels alone. In fact, in the randomized, double-blind, placebo-controlled Effect of Vascepa on Improving Coronary Atherosclerosis in People with High TG Taking Statin Therapy (EVAPORATE) trial, 80 patients were given IPE 4 grams daily, similar to REDUCE-IT, or mineral oil placebo on a background of dietary and statin changes in patients with known ASCVD. The trial aimed to determine whether IPE would result in a greater change of atherosclerotic plaque volume measured by serial multidetector computed tomography. The trial demonstrated a significant regression of 17% plaque compared with a 109% increase in placebo (P = .0061); this provides mechanistic support for ASCVD reductions.

Another debate regarding the outcomes of these trials is the choice of placebo used. Clearly, a placebo should be inert but resemble the active ingredient. Often in these omega-3 fatty acids trials, the placebo consisted of olive, corn, or mineral oils, which can contain saturated, mono-unsaturated, and omega-6 polyunsaturated fatty acids. These oils can impact various cardiovascular parameters. In the REDUCE-IT trial, mineral oil was used as the placebo due to its clear color, like IPE, and it has been approved by the FDA as a placebo in regulatory studies. Some critics of the REDUCE-IT trial demonstrated that the mineral oil placebo increased hs-CRP and potentially had adverse consequences on the placebo group, possibly through impairment of statin absorption. However, an FDA advisory committee concluded that the increased levels likely had little effect on the outcomes. Patients receiving IPE should be educated regarding the increased risk of AF, as this was consistent in all 3 trials with higher dose omega-3 fatty acids. Patients will need to be monitored periodically for AF and be educated about the signs and symptoms of AF, such as heart palpitations, chest pain, pressure or discomfort, shortness of breath, lightheadedness, and dizziness. Furthermore, in REDUCE-IT there was a numerically but not statistically significant increased risk of bleeding-related disorders. The antiplatelet effects of omega-3 fatty acids are well known. The FDA labels for these products recommend patients on these agents and antiplatelets/anticoagulation medications monitor for signs of bleeding and report to the prescribing clinician. Finally, there was no increase in GI intolerance with IPE versus placebo.

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**TABLE 5. Published Recommendations for Icosapent Ethyl for ASCVD Risk Reduction**

<table>
<thead>
<tr>
<th>Class of Recommendation</th>
<th>Level of Evidence</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019 National Lipid Association Scientific Statement</td>
<td>I, B-R</td>
<td>For patients aged 45 years or older with clinical ASCVD, or 50 years or older with diabetes requiring medication and ≥1 additional risk factor, with fasting TG 135-499 mg/dL on high-intensity or maximally tolerated statin, with or without ezetimibe, treatment with icosapent ethyl is recommended for ASCVD risk reduction.</td>
</tr>
<tr>
<td>2021 American Diabetes Association Standards of Care</td>
<td>A</td>
<td>In patients with ASCVD or other CV risk factors on statin with controlled LDL-C but elevated TG (135-499 mg/dL), the addition of icosapent ethyl can be considered to reduce CV risk.</td>
</tr>
</tbody>
</table>

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
The Pharmacist’s Role in Caring for Patients With HTG and ASCVD

Pharmacists can have a significant impact on the management of patients with HTG. There is broad support regarding the participation of pharmacists in patient education and multidisciplinary management of dyslipidemia. Several studies have demonstrated that pharmacists play a key role in improving cholesterol management, especially in community pharmacies and ambulatory care settings. Pharmacists can provide a wide range of functions, including assessing patients’ medical histories, monitoring laboratory values, selecting appropriate therapy, and providing education about the critical nature of adherence. These interventions can lead to improved lipid control and achievement of cholesterol goals, which should translate into ASCVD risk reduction. Evidence from a meta-analysis of 26 trials evaluating the pharmacist’s involvement in lipid intervention programs demonstrated that pharmacist intervention significantly reduced LDL-C and TG levels compared with standards of care.52 No single intervention alone was found to be significant in reducing lipid levels, and interventions included in the meta-analysis were varied, with the majority being in-person contact and some via telephone interview. Interventions encompassed patient education on medications and lifestyle changes, adherence counseling, medication therapy management, and lab review. The frequency of contact varied from a single contact to monthly and as frequently as on a weekly basis.

Specifically, in relation to omega-3 fatty acids and HTG, pharmacists should be able to identify patients with residual ASCVD risk, despite statin therapy, and contextualize the patient in relation to the IPE label and clinical trial. Furthermore, pharmacists should provide patient education regarding diet and lifestyle changes that can improve TG levels. This includes education regarding a diet, such as a plant-based, Mediterranean, or Dietary Approaches to Stop Hypertension (DASH), that has reduced fat content, especially saturated and trans fats, substituting complex carbohydrates for refined or simple sugars, along with an appropriate balance of proteins, carbohydrates, and fat.5 Patients should also be advised to limit alcohol intake (men no more than 2 drinks per day and women 1 drink per day) and be approached about smoking cessation by the 5 A’s (Ask, Advise, Assess, Assist, and Arrange) approach. Furthermore, pharmacists can do an extensive medication profile review to determine if the patient is using therapies that could elevate TG (TABLE 15). If the patient still has elevated TG or is concerned about ASCVD risk reduction, the pharmacist can discuss various treatment options with the patient or their clinician.

When the patient or other provider is interested in the use of omega-3 fatty acids, the pharmacist can provide education regarding the benefits and risks of using dietary supplements versus FDA-approved prescription products.24 In doing so, pharmacists should also caution patients and providers regarding the inability to interchange the various products due to different content and dosing.24 Pharmacists have important roles in assisting in education and monitoring for various product-specific AEs, such as bleeding, GI intolerance, and AF. As mentioned, from a GI perspective, over-the-counter (OTC) agents can include fishy taste and eructation (burping), and all omega-3 fatty acid products can cause diarrhea and nausea.8 In the cases where this occurs with OTC fish oil, pharmacists can recommend freezing the fish oil, switching to a different formulation, consuming with meals, or changing intake to a different time of day. Education about all available prescription products,
especially ethyl ester formulations that require administration with food and not to be opened or crushed to enhance absorption, should be addressed as well. Pharmacists should be knowledgeable that prescription-based omega-3 fatty acid products have shown little risk of cytochrome P450-mediated drug interactions. Finally, pharmacists could alleviate concerns regarding fish/seafood allergies with prescription products, given they are highly purified and do not appear to be allergenic, despite the FDA label denoting caution.

Ensuring medication adherence is a vital aspect of care, especially with drug therapy that is taken on a chronic basis. When recommending therapy for HTG, such as IPE, it is particularly important to communicate the need for twice-daily administration with food (TABLE 3). Pharmacists can apply established adherence methods and techniques, such as examination of prescription refills, open-ended questions, motivational interviewing, and patient questionnaires, and recommend use of tools including pillboxes, medication alarms, and smartphone applications. Lastly, pharmacists can help patients through access issues by helping to navigate the prior authorization process or assisting with manufacturer-based patient assistance programs.

Conclusion
Patients with elevated TG should be managed accordingly with lifestyle interventions and pharmacotherapy. Omega-3 fatty acids can be one class of agents to assist in achieving goals in reducing TG levels. If a patient is seeking additional ASCVD risk reduction in conjunction with TG lowering, it is prudent to recommend IPE based on the results of the REDUCE-IT trial. More research is needed to better understand the role of omega-3 fatty acids in ASCVD management. Pharmacists can play a key role in proper identification of patients at risk of adverse sequelae due to elevated HTG, offer treatment recommendations, and promote adherence and monitoring for safety.

REFERENCES
10. Simha V. Management of hypertriglyceridemia. BMJ. 2020;371:m3109. doi: 10.1136/bmj.m3109


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Begin the activity by reading the content in its entirety.
Go to www.pharmacytimes.org/go/CVD-Omega-3 to access the online version of this activity.
Click “Proceed,” then complete the online pretest.
Once completed, click “Next” until reaching the online activity posttest.
Complete the online posttest and activity evaluation form.
After successfully completing the posttest and evaluation form, this information will be uploaded to CPE Monitor.
You must complete these steps before the activity expires in order to receive your credit.
You may view your credit within 48 hours at www.mycpemonitor.net.

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POSTTEST QUESTIONS

Please use the following case to answer questions 1 and 2.

FO is a 55-year-old White man with a history of diabetes, hypertension, hypertriglyceridemia (HTG), and a history of acute pancreatitis. He drinks 6 to 10 beers/day. He currently is on lisinopril 20 mg daily, chlorthalidone 50 mg daily, amlodipine 10 mg daily, and metformin 1000 mg twice daily. He reports 5 pounds of weight loss but still is obese. His HbA1c is 6.9%. Fasting lipid panel returns with the following:

- Total cholesterol, 157 mg/dL
- LDL-C, 78 mg/dL
- HDL-C, 38 mg/dL
- Triglycerides (TG), 588 mg/dL

FO has normal renal and hepatic function, and his blood pressure is 118/76 mm Hg.

1. Which factors may be contributing to this patient’s HTG?
   A. Alcohol consumption, poorly controlled diabetes, lisinopril
   B. Alcohol consumption, amlodipine, weight loss
   C. Obesity, alcohol consumption, chlorthalidone
   D. Obesity, poorly controlled diabetes, metformin

2. In addition to lifestyle modifications, which medication is the best option to lower FO’s TG?
   A. Ezetimibe 10 mg daily
   B. Fenofibrate 145 mg daily
   C. Omega-3 fatty acids 1 gram daily
   D. Rosuvastatin 20 mg daily

3. Which of the following products would be the most optimal to recommend in order to reduce atherosclerotic cardiovascular events in patients with elevated TG (150-499 mg/dL)?
   A. Icosapent ethyl (IPE)
   B. Omega-3-acid-carboxylic acids
   C. Omega-3-acid-ethyl ester
   D. Over-the-counter fish oil supplement

4. Which adverse effect should patients monitor for when starting an IPE omega-3 fatty acid regimen?
   A. Atrial fibrillation
   B. Headache
   C. Muscle cramps
   D. Pulmonary embolism

5. Which class of agents can further raise elevated TG levels?
   A. Bile acid sequestrants
   B. Fibrates
   C. Statins
   D. Niacin

6. Which patient is the most ideal candidate for the use of IPE for atherosclerotic cardiovascular disease (ASCVD) risk reduction?
   A. A 24-year-old man with a history of type 1 diabetes who is not currently on statin therapy.
   B. A 40-year-old woman with rheumatoid arthritis who has a 4.4% risk of ASCVD events in the next 10 years and is on rosuvastatin 5 mg daily.
   C. A 45-year-old man with no past medical history but whose father died of coronary artery disease at 49 years old.
   D. A 55-year-old woman with a history of myocardial infarction 1 year ago taking atorvastatin 80 mg with TG levels of 180 mg/dL.

7. Which of the following is a modifiable ASCVD risk factor?
   A. Age
   B. Diabetes
   C. Epilepsy
   D. Height

8. Which education point is most appropriate for a patient regarding omega-3 fatty acid dietary supplements versus prescription products for ASCVD risk reduction?
   A. Omega-3 fatty acid dietary supplements are tightly regulated by the Food and Drug Administration.
   B. Omega-3 fatty acid dietary supplements are pure, free of contamination, and always reflect labeled dose.
   C. Omega-3 fatty acid dietary supplements could require similar or more capsules to achieve ASCVD reduction dosing.
   D. Omega-3 fatty acid dietary supplements are reasonable to substitute for prescription omega-3 fatty acids products.
POSTTEST QUESTIONS (continued)

9. Which response would be the most appropriate to a clinician when explaining the potential differences between the REDUCE-IT and STRENGTH trials?
   A. The REDUCE-IT trial used corn oil as the placebo, and the STRENGTH trial used mineral oil.
   B. The REDUCE-IT trial used 1 gram daily of IPE, whereas the STRENGTH trial used 4 grams daily of omega-3-acid-carboxylic acid.
   C. The REDUCE-IT trial and the STRENGTH trial demonstrated an increased risk of atrial fibrillation.
   D. The REDUCE-IT trial’s primary outcome was ASCVD risk reduction, whereas the STRENGTH trial’s primary outcome was just TG reduction.

10. EP is being prescribed IPE for ASCVD risk reduction. Which counseling point is the most appropriate for this patient?
    A. If you have a fish/seafood allergy, you are absolutely contraindicated to this product.
    B. Administration with food will improve absorption.
    C. The dose is a 1-gram capsule daily.
    D. You should avoid grapefruit due to inhibition of cytochrome P450 enzymatic metabolism of the product.
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