An official publication of the American Pharmacists Association

Pharmacy Today

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Improving medication use. Advancing patient care.
APhA

FEBRUARY 2015

20th anniversary
1995–2015

CPE
American Pharmacists Association
Continuing Pharmacy Education

Hepatitis C therapy: Looking toward interferon-sparing regimens

CHEST research: Asthma, COPD

FDA approves slew of drugs

HPV vaccine: Protecting teens

OTC survey

INTERVENTIONS span continuum of care in New Mexico

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Patients Choose It

- Nearly 90% said they would choose it again for their next vaccination

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Important Safety Information

AFLURIA®, influenza vaccine, is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. Administration of AFLURIA with a needle and syringe is approved for use in persons 5 years of age and older. Administration of AFLURIA with the PharmaJet® Stratis® Needle-Free Injection System is approved for use in persons 18 through 64 years of age only.

AFLURIA is contraindicated in individuals with known severe allergic reactions (eg, anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine.

Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with postmarketing reports of increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years; these increased rates were confirmed by postmarketing studies. Febrile events were also observed in children 5 to less than 9 years of age.

If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA should be based on careful consideration of the potential benefits and risks.

If AFLURIA is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

AFLURIA should be given to a pregnant woman only if clearly needed.

AFLURIA has not been evaluated in nursing mothers. It is not known whether AFLURIA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AFLURIA is administered to a nursing woman.

Antibody responses in persons 65 years of age and older were lower after administration of AFLURIA as compared to younger adult subjects.

In children 5 through 17 years of age, most common injection-site adverse reactions observed in clinical studies of AFLURIA when administered by needle and syringe were pain, redness, and swelling. The most common systemic adverse events were headache, myalgia, irritability, malaise, and fever.

In adults 18 through 64 years of age, the most common injection-site adverse reactions observed in clinical studies of AFLURIA when administered by needle and syringe were tenderness, pain, swelling, and redness, itching. The most common systemic adverse reactions observed were muscle aches, headache and malaise.

In adults 18 through 64 years of age, the most common injection-site adverse reactions observed in clinical studies with AFLURIA when administered by the PharmaJet Stratis Needle-Free Injection System up to 7 days post-vaccination were tenderness, swelling, pain, redness, itching and bruising. The most common systemic adverse events within this period were myalgia, malaise, and headache.

In adults 65 years of age and older, the most common injection-site adverse reactions observed in clinical studies of AFLURIA when administered by needle and syringe were tenderness and pain.

Vaccination with AFLURIA may not protect all individuals.

Please see brief summary of full prescribing information on next page.

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

PharmaJet: 1-888-900-4321 or visit www.pharmajet.com
For a list of authorized Afluria distributors, call 1-888-4FLU-OFF (1-888-435-8633).

bioCSL

AFLURIA, Influenza Vaccine
Suspension for Intramuscular Injection
2014-2015 Formula
Initial U.S. Approval: 2007

BRIEF SUMMARY OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AFLURIA safely and effectively. See full prescribing information for AFLURIA.

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2) 08/2014

----------INDICATIONS AND USAGE----------
- AFLURIA is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. (1)
- AFLURIA is approved for use in persons 5 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
For intramuscular (IM) injection only, by needle and syringe (5 years of age and older) or by PharmaJet® Stratis® Needle-Free Injection System (18 through 64 years of age). A single dose is 0.5 mL. (2)

Age	Schedule
5 years through 8 years	One dose or two doses at least 1 month apart[a]
9 years and older	One dose

[a]1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
AFLURIA is a suspension for injection supplied in two presentations:
- 0.5 mL pre-filled syringe (single dose) (3, 11)
- 5 mL multi-dose vial (ten 0.5 mL doses) (3, 11)
-

----------CONTRAINDICATIONS----------
- Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine. (4, 11)

----------WARNINGS AND PRECAUTIONS----------
- Administration of CSL's 2010 Southern Hemisphere influenza vaccine was associated with increased rates of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years. Febrile events were also observed in children 5 through 8 years of age. (5.1)
- If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give AFLURIA should be based on careful consideration of the potential benefits and risks. (5.2)
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.3)
- Immunocompromised persons may have a diminished immune response to AFLURIA. (5.4)

----------ADVERSE REACTIONS----------
- In children 5 through 17 years of age, the most common injection-site adverse reactions when administered by needle and syringe were pain (≥60%), redness (≥20%) and swelling (≥10%). The most common systemic adverse events were headache, myalgia (≥20%), irritability, malaise and fever (≥10%). (6.1)
- In adults 18 through 64 years of age, the most common injection-site adverse reactions when administered by needle and syringe were tenderness (≥60%), pain (≥40%), swelling (≥20%), and redness, itching (≥10%). The most common systemic adverse events were muscle aches (≥30%) and headache, malaise (≥20%). (6.1)
- In adults 18 through 64 years of age, the most common injection-site adverse reactions when administered by the PharmaJet Stratis NeedleFree Injection System up to 7 days post-vaccination were tenderness (≥80%), swelling, pain, redness (≥60%), itching (≥20%) and bruising (≥10%). The most common systemic adverse events within this period were myalgia, malaise (≥30%), and headache (≥20%). (6.1)
- In adults 65 years of age and older, when administered by needle and syringe the most common injection-site adverse reactions were tenderness (≥30%) and pain (≥10%). No systemic adverse events occurred in ≥10% of subjects in this age group (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact bioCSL Inc. at 1-844-275-2461 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------USE IN SPECIFIC POPULATIONS----------
- Safety and effectiveness of AFLURIA have not been established in pregnant women or nursing mothers. (8.1, 8.3)
- Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)
- AFLURIA is not approved for use in children less than 5 years of age because of increased rates of fever and febrile seizures. One comparator-controlled trial demonstrated higher rates of fever in recipients of AFLURIA as compared to a trivalent inactivated influenza vaccine control. (8.4)

Based on August 2014 Version

NEWS *you can use*

Medicare will cover second dose of pneumococcal vaccine

Beginning February 2, 2015, CMS will cover a second dose of pneumococcal vaccine to align with updated recommendations from CDC's Advisory Committee on Immunization Practices (ACIP).

In September 2014, ACIP issued a recommendation to use the existing vaccine (PPSV23) and a recently FDA-approved vaccine (PCV13) in adults 65 years and older for the prevention of pneumococcal disease. Until now, Medicare never paid providers—with the exception of an appropriate booster dose of the same vaccine (PPSV23)—who followed the recommendation to administer a second dose.

"The coverage change will ensure that providers doing the right thing and protecting all adults 65 years and older according to the new ACIP recommendations are not penalized with inadequate payment," said Litjen Tan, MS, PhD, Chief Strategy Officer at the Immunization Action Coalition.

In alignment with ACIP, CMS recommends that the second pneumococcal vaccine be administered 1 year after the first vaccine is administered.

However, Tan said that the CMS guidance is still not completely in sync with the ACIP recommendations. If a provider gives PCV13 first, then PPSV23 can be given after 6 to 12 months. However, in this case, providers would be advised to wait a year to ensure payment from CMS.

Tan said he is confident CMS is looking into this issue.

In addition, CMS does not require that a physician under Medicare Part B order the pneumococcal vaccine or its administration. Patients can receive the vaccine upon request without their physician's order or supervision.

"The announced policy change removes a barrier for patient access to an ACIP-recommended vaccination administered by pharmacists and supports completion of the pneumococcal vaccination series," said Mitchel Rothholz, BSPharm, MBA, APhA's Chief Strategy Officer. "We thank CMS for the policy change to protect the public from vaccine-preventable diseases."

APhA, along with other immunization stakeholders, advocated for a change to CMS's Medicare Part B coverage policy related to pneumococcal vaccinations.

Pharmacy Today: 20 years ago today ...

Following are top headlines from February 1995:

- "Technician certification program established": The Pharmacy Technician Certification Board was formed by four organizations—APhA, American Society of Health-System Pharmacists, Illinois Council of Hospital Pharmacists, and Michigan Pharmacists Association—to develop and conduct the pharmacy technician certification program.
- "Pharmacists should alert patients about potential toxicity from taking nonprescription analgesics": Acetaminophen could cause liver damage if extra doses are combined with fasting, and pharmacists should be on the lookout for patients who are chronic users of these medications.
- "Boldly go where no pharmacist has gone before": NASA (National Aeronautics and Space Administration) exhibited a full-scale, walk-through replica of its International Space Station at APhA1995 in Orlando, FL; the exhibit, held in conjunction with a CPE course, was to address the health benefits of space exploration and research.

CPPA launches specialty pharmacy accreditation program

The Center for Pharmacy Practice Accreditation (CPPA) announced on January 20 the launch of a new accreditation program for specialty pharmacy practices.

The specialty pharmacy accreditation program, which CPPA announced it was developing in October 2013, is the second new accreditation program from CPPA. Last year, CPPA launched a program to accredit outpatient pharmacy practices in community, hospital, health systems, and clinics. CPPA's consensus-based standards for community pharmacy practice were approved in 2013.

CPPA said the size and scope of specialty pharmacy is growing rapidly. In addition, specialty medications require ongoing clinical monitoring, special handling, and patient education.

"Specialty pharmacy practice involves a great deal of complex and high-cost patient care," said Lynnae Mahaney, BSPharm, MBA, FASHP, CPPA Executive Director. "A pharmacy practice that is undergoing the CPPA specialty accreditation process has shown a commitment to the highest level of pharmacy care and cost-effective outcomes for patients receiving specialty medications, which distinguishes that practice within the health care system."

CPPA defines a specialty pharmacy

practice as one that both manages the medication access and handling requirements of specialty pharmaceuticals, including dispensing and distribution, as well as provides clinical management services for patients with chronic, serious, life-threatening, and rare diseases who receive specialty medications.

CPPA was formed in 2011 as a pharmacy practice accreditation body to ensure pharmacists are involved in shaping the direction of standards for pharmacy practice and accreditation programs.

CPPA is accepting applications for the voluntary Specialty Pharmacy Practice Accreditation Program. The application is available at http://pharmacypracticeaccredit.org.

IOM: Including patients, caregivers on health care teams

A new Institute of Medicine (IOM) discussion paper provides important insights for health care providers, including pharmacists, on what it takes to create effective health care teams that include patients and their families as partners on the team.

"For pharmacists involved in direct patient care, this IOM discussion paper can provide important perspectives on what patients think is important and what it means from the patient's perspective to be engaged with their health care team," said Edwin Webb, PharmD, MPH, Associate Executive Director of the American College of Clinical Pharmacy. Webb was one of two pharmacists who helped author the report as a participant from the Best Practices Innovation Collaborative of the IOM Roundtable on Value & Science-Driven Health Care.

The paper, based on interviews with patients and various stakeholders, opens up the dialogue to more clearly define the role of patients on the health care team. The authors conclude that there is a need for shared decision making and better communication between patients and other health care team partners.

"It's the beginning of this dialogue and the formation of these types of teams," said Sandra Leal, PharmD, FAPhA, CDE, then the Medical Director of Clinical Pharmacists/Broadway Clinic at El Rio Community Health Center in Tucson, AZ, and now Vice President for Innovation at SinfoniaRx. "Getting the pharmacist involved early on and plugging in as much as they can is important right now."

Leal said pharmacists should not only make sure they are included on these teams, but also convey the message to their patients that they are their advocate and a member of their health care team—even if they are not onsite with the provider.

"Pharmacists can look at this paper and say, 'How do I fit into this team? How do I make sure I'm a part of the team, and then how do I engage other members and communicate with them?'" said Leal.

According to the IOM paper, the sampling serves to highlight the importance of the issue and underscores the need for more research and investigation.

"All health professionals should take the opportunity in reading this paper to adopt a fuller commitment to making patient-centered care more than just a buzzword," said Webb. "It must be the foundation upon which the practice of each health professional is built if care is to be truly meaningful to patients."

Capitol Hill publication profiles Rep. Buddy Carter, BSPharm

After only 2 weeks of being sworn into the 114th Congress, Rep. Buddy Carter (R-GA), BSPharm, was profiled in a widely read Capitol Hill publication about his legislative priorities. At the top of that list: provider status recognition.

Carter, the only pharmacist currently elected to Congress, told *CQ Roll Call* that he plans to push for APhA's top priority—legislation that would allow patient access to, and coverage for, Medicare Part B services by state-licensed pharmacists in medically underserved communities. H.R. 4190 gained 123 bipartisan cosponsors in the last Congress, and a new bill is expected to be introduced into the new Congress soon.

Carter also told *CQ Roll Call* that he plans on joining both the House Community Pharmacy Caucus and the GOP Doctors Caucus. These are in addition to the Education and the Workforce and Oversight and Government Reform panels, to which he is already assigned.

He is believed to be the first pharmacist to serve in Congress who owned his own pharmacy.

Carter also voiced his support to *CQ Roll Call* for legislative action to allow pharmacies in medically underserved areas to participate in Medicare drug plan networks. Currently, some pharmacies are excluded from a plan's "preferred" network, either forcing seniors to cut ties with the pharmacy they've had a long-term relationship with, or in some cases, making them drive long distances to a pharmacy that takes their insurance.

"If you're willing to accept the reimbursement then, you know, you should be allowed to participate," Carter told *CQ Roll Call*.

Legislation, Ensuring Seniors Access to Local Pharmacies Act (H.R. 4577), was introduced last year and garnered bipartisan support in both the House and Senate.

Head of CMS to step down

Marilyn Tavenner, BSN, MHA, CMS Administrator, announced to staff through a memo on January 16 that she would be stepping down from her position in February. She gave no reason for her departure.

Tavenner, who officially took over as head of CMS in 2013, oversaw the tumultuous rollout of the Affordable Care Act's health insurance exchanges. Even through the technical glitches on HealthCare.gov, Republicans continued to support her.

According to CMS officials, Andy Slavitt, MBA, who is Principal Deputy Administrator at CMS, will take over as Acting Administrator until the White House and Congress can agree on a permanent successor to lead the agency.

Slavitt, who is also a former executive at UnitedHealth, worked through a parent company to lead the cleanup effort for HealthCare.gov. He was then hired as CMS's second-in-command in 2014 by new U.S. Department of Health & Human Services Secretary Sylvia Mathews Burwell.

Clarification

On page 36 of the December 2014 issue of ***Pharmacy Today***, a quote attributed to Allen Nichol, PharmD, "Some states are sitting on a gold mine and not doing anything," followed a sentence about California's SB 493 not addressing reimbursement. The juxtaposition may have led readers to infer that Nichol was referring to California. He was not.

The California Pharmacists Association seeks to clarify the issue with a response (following).

Payment for pharmacist care is critical

We appreciate the December 2014 ***Pharmacy Today*** article regarding supply and demand for pharmacist jobs. We see efforts such as advancing provider status as one way to encourage new practice innovations and job opportunities for pharmacists.

We agree that payment for pharmacist care is critical. Aligning incentives among payers, practitioners, and patients is important for delivering quality, cost-effective care. However, mandating payment for services in cash-strapped California would have immediately resulted in the bill's demise in the legislature or been met with a veto by the governor. Payment for health care involves a contract between payers and those delivering care. Legislating payment is not a policy we envision many states having an appetite to embrace. Budget-conscious states will reject this in their Medicaid programs, and opposition from commercial health plans will be strong and vocal.

California has been working to advance payment for services since the provider status legislation was enacted. The California Pharmacists Association (CPhA), schools/colleges of pharmacy, independent and chain pharmacists, payers, and consumer stakeholders convened under a CPhA Payment Taskforce that has engaged in extensive research regarding barriers and opportunities for payers and pharmacists to align financial incentives. The taskforce is moving into an implementation phase where we will actively engage pharmacies and payers in delivering compensated care.

Federal provider status will be a significant step forward in advancing the important conversation about payment for services, which is why CPhA is a strong advocate of H.R. 4190. However, to suggest that individual states are sitting idle waiting for the federal government to solve this problem is inaccurate.

Kathy Besinque, PharmD, President, and **Jon R. Roth, CAE,** CEO, California Pharmacists Association, Sacramento, CA (jroth@cpha.com)

The Letters column of ***Pharmacy Today*** provides a forum for APhA members and other readers to discuss current events in pharmacy and health care and comment on articles and columns published in the magazine. Letters should be limited to 250 words in length and are edited and published at the editor's discretion. Send letters to mposey@aphanet.org.

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Remembering the basics

Even as the profession speeds ahead with the provider status initiative, this issue of *Pharmacy Today* serves as a reminder to keep tending to the basics.

This effort is evident in the Special OTC Section that starts on page 54. Here we present the results of the most recent survey of practicing pharmacists about the nonprescription products they most frequently recommend in 89 product categories. We all have mental algorithms for these common questions (Is your throat scratchy? Your head hurting? Fever? Cough?), and the answers take us to a logical recommendation with the right ingredients. Patients who come from the OTC aisles with several products in hand and a confused look on their faces are very appreciative of our years of education and experience.

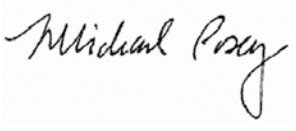
In the two articles that accompany the survey, we are reminded how important it is to help patients with OTCs. Smoking rates are at an all-time low, but the decline in tobacco use has plateaued. Marketers of the burgeoning nicotine-delivery devices are minimizing the dangers of this addicting agent in their efforts to hook young people (page 62). On page 64, the story of Rachel Katz–Gallat reminds us of our obligation to help patients with difficult questions about OTC use during pregnancy and lactation—and details her unique solution.

L. Michael Posey, BSPharm, MA, Editor, *Pharmacy Today*

In new drug articles in this issue, we cover agents approved during FDA's December frenzy. No matter how much our cognitive services expand and develop, serving as the steward of optimal medication use for the health care system is the foundation of pharmacy. The new agents detailed on pages 20, 32, 34, 35, 36, and 38 will change our approaches to several diseases, from otitis externa to hepatitis C virus infection and advanced ovarian cancer. The CPE article that starts on page 75 adds further perspective on hepatitis C. We should all make sure we're up to speed on these new medications and what our colleagues and patients need to know about them.

Combined with articles on innovative practices and the provider status initiative throughout these pages, pharmacists will have the latest information to be at the cutting edge of practice. Let us know what you think at PTDaily@aphanet.org.

Enjoy your Special OTC Section and your February ***Today***!



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ISSUE FOCUS: ALLERGY AND IMMUNOLOGY

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HSE6

Health-System Edition

Begins after page 48

These articles appear only in the Health-System Edition. Readers of the National Edition who wish to access this material may do so at www.pharmacytoday.org.

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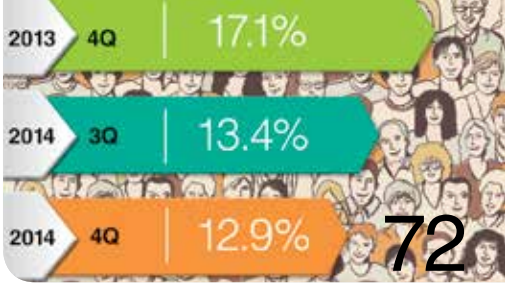

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The word is out!

Thomas E. Menighan, BSPharm, MBA, ScD (Hon), FAPhA, Executive Vice President and CEO

For quite a while now, I've asked you to become our profession's storytellers and communicate the impact we make on the lives of patients across the country. I'm so pleased to tell you that our efforts are paying off and your stories are being heard.

Recently the National Governors Association (NGA) released a report that draws attention to the important role of pharmacists as members of integrated health care teams. NGA's paper highlights numerous states that have expanded pharmacists' scope of practice, integrated pharmacists into chronic care delivery teams, and developed other team-based models of care that include pharmacists. I am proud to say that many of the examples cited were based on articles published in APhA's ***Pharmacy Today,*** in ***JAPhA,*** or on pharmacist.com. These stories truly matter, and I applaud you for pursuing innovative care models and continuing to stand up and earn the respect of influencers and policy makers all over the country. (For more information, see page 68.)

The theme of APhA2015 is "Advancing as One." Each report, study, or discussion with a decision maker helps advance our efforts. Federal legislation now before Congress would enable patient access to, and coverage for, Medicare Part B services authorized by the state scope of practice for licensed pharmacists in medically underserved communities. Efforts at the federal and state level continue to advance progress toward achieving our ultimate vision.

Advancing as One requires the engagement of many! Are you in the game with us? What value do your patients get from services you provide? Do your U.S. senators and representative know your story?

One of my favorite quotes is, "A fast talker is someone who says things they haven't thought of yet." Don't be a fast talker! I encourage each one of you to work out a 30-second elevator speech and practice it. When the opportunity comes for you to tell your patient care story, whether in a formal or informal setting, you need the bullet points and flow already figured out.

A great way to get energized and engage in our efforts to Advance as One is to connect with others about patient care stories and advocacy efforts by attending APhA's Annual Meeting & Exposition in San Diego, March 27–30, 2015. Here you can experience comprehensive programming, captivating speakers, and professional networking opportunities, and see firsthand the unity we've created among members of the profession.

Registration for APhA's Annual Meeting is now open. Visit www.aphameeting.org for more information.

Media vibe

During the months of November and December, APhA External Communications and Media Advisors responded to nearly 15 media inquiries, including:

- *Chain Drug Review:* 2015 health care outlook
- Huffington Post: Ways to use your pharmacist that you may not have thought of
- Grandparents.com: Five drugs you should never take while driving
- *Drug Store News:* Pharmacist's role in the future switch of some meds from Rx to OTC
- *Pink Sheet:* FDA's proposed rule to require electronic distribution of prescribing information

> "APhA is thrilled that the National Governors Association cites the use of pharmacists and their patient care services as an opportunity for states to provide more effective and efficient health care."
>
> —Stacie Maass, BSPharm, JD, APhA Senior Vice President of Pharmacy Practice and Government Affairs, regarding a report for state governments that explains how pharmacists and their patient care services are an integral part of the patient's health care team

THIS SMELLS.[1] THIS DOESN'T.

Which would your patients prefer?

NASACORT®. RIGHT ON SHELF. RIGHT NOW.

Reference: 1. Flonase Allergy Relief question and answer book. 14-0033AWL. Clifton, NJ: GlaxoSmithKline; 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205434Orig1s000lbl.pdf. Accessed September 18, 2014.

Members are talking about ...

Join the conversation ... at pharmacist.com

The Diabetes Management Special Interest Group (SIG) provides a forum for APhA members to discuss issues, ask questions, and share information about nuclear pharmacy. Below are excerpts from a recent Diabetes Management SIG discussion about the new sodium–glucose cotransporter 2 (SGLT2) medications on the market.

Just curious how many of you have experience with the new SGLT-2 medications on the market?

I think there are three of them on the market now—Invokana, Farxiga, and Jardiance.

What type of patients are you recommending these for, and do you have any efficacy/adverse effect stories to share?

I have seen an uptick in patients receiving Invokana, one on Farxiga, and one on Jardiance recently. My main counseling point is methods of prevention of fungal infections.

I have seen Invokana prescribed but not the other ones as much.

Our patients are absolutely loving this class! I was hesitant to use this class initially; however, the patients who are taking them refuse to come off due to lowered blood glucose values, improved weight, and improved blood pressures.

APhA's SIGs are now located on Engage, APhA's new members-only online community. Visit pharmacist.com, click on "Get Involved," and select "Engage Communities." For subsequent visits after the initial contact, visit engage.pharmacist.com.

Visit pharmacist.com to access APhA's members-only APhA–APPM SIGs.

A minute with ...

John W. (Jack) West, BSPharm

Retired pharmacist, Holland Hospital, Holland, MI

APhA member since 1962

West is an Emeritus Member of APhA. He achieved Emeritus status by being a member of APhA for more than 50 years.

I first became interested in being a pharmacist ... as a high school student working at Warner's Drug Store in Lansing. I admired the pharmacists with whom I worked.

I joined APhA because ... I believe it is a professional obligation. It was also part of the affiliation action taken by the much-heralded APhA Executive Director, Bill Apple, who with Bob Johnson, Michigan Pharmacists Association (MPA) Executive Director, was leading the drive in Michigan. I was also a member of the American Society of Health-System Pharmacists (ASHP) and a Hospital Fellow of American College of Apothecaries (ACA). I was proud to be part of the leadership during a very exciting affiliation movement launched first in Michigan.

If I weren't a pharmacist, I would have been ... a dentist. I was offered a partnership with a dentist in Lansing if I would change from pharmacy school to dental school. I stayed in pharmacy school.

If I could have dinner with anyone living or dead, it would be ... Jennie Banning. She was a pharmacist and a member of APhA, MPA, and ASHP. She was also a charter member of ASHP. I worked for her for several years at Holland Hospital before she retired. She believed that pharmacist concerns were very important.

APhA2015: Developing a plan for success

APhA2015 is the premier event in the pharmacy profession nationwide. The upcoming APhA Annual Meeting & Exposition, to be held March 27–30, 2015, in San Diego, will bring the entire pharmacy community together for networking, education, and advocacy opportunities.

Crafting a path to success

APhA2015 sessions empower you to advance both your practice and career by offering the opportunity for you to earn up to 20 hours of continuing pharmacy education (CPE) credits.

- Knowledge-based activities are designed to enhance or add to a practitioner's knowledge of a specific topic.
- Application-based activities provide pharmacists and technicians the opportunity to apply their knowledge, usually through case studies.
- Practice-based activities are more comprehensive, with at least 15 hours that incorporate skill, knowledge, and performance. These activities are also known as certificate training programs.

Personalized learning experience

Each pharmacist is unique, which is why APhA2015 offers customizable education pathways to meet the needs of each practitioner. At APhA2015, pharmacists can also learn about CPR certification and annual OSHA requirements for immunizers. To help pharmacists gain the competitive edge to advance within the field, sessions will be held on professionalism; interprofessional education and leadership for educators; and the latest in clinical and legal topics.

Premium registration

Maximize the benefits of APhA2015 with the Premium Registration Package. This package includes CPE courses; APhA2015 highlights Video on Demand; and a 1-year membership for nonmembers. The Video on Demand offers 11 recorded education sessions that can be accessed from the comfort of your home or office for a total of 22 CPE credits. The Premium Registration Package gives pharmacists the opportunity to continue reaping the benefits of APhA2015 long after the meeting has ended.

Registration is open

Visit www.aphameeting.org to view the education schedule, to purchase the Premium Registration Package, and to register.

Natosha McNeal, contributing writer

'Engage' in APhA policy discussions

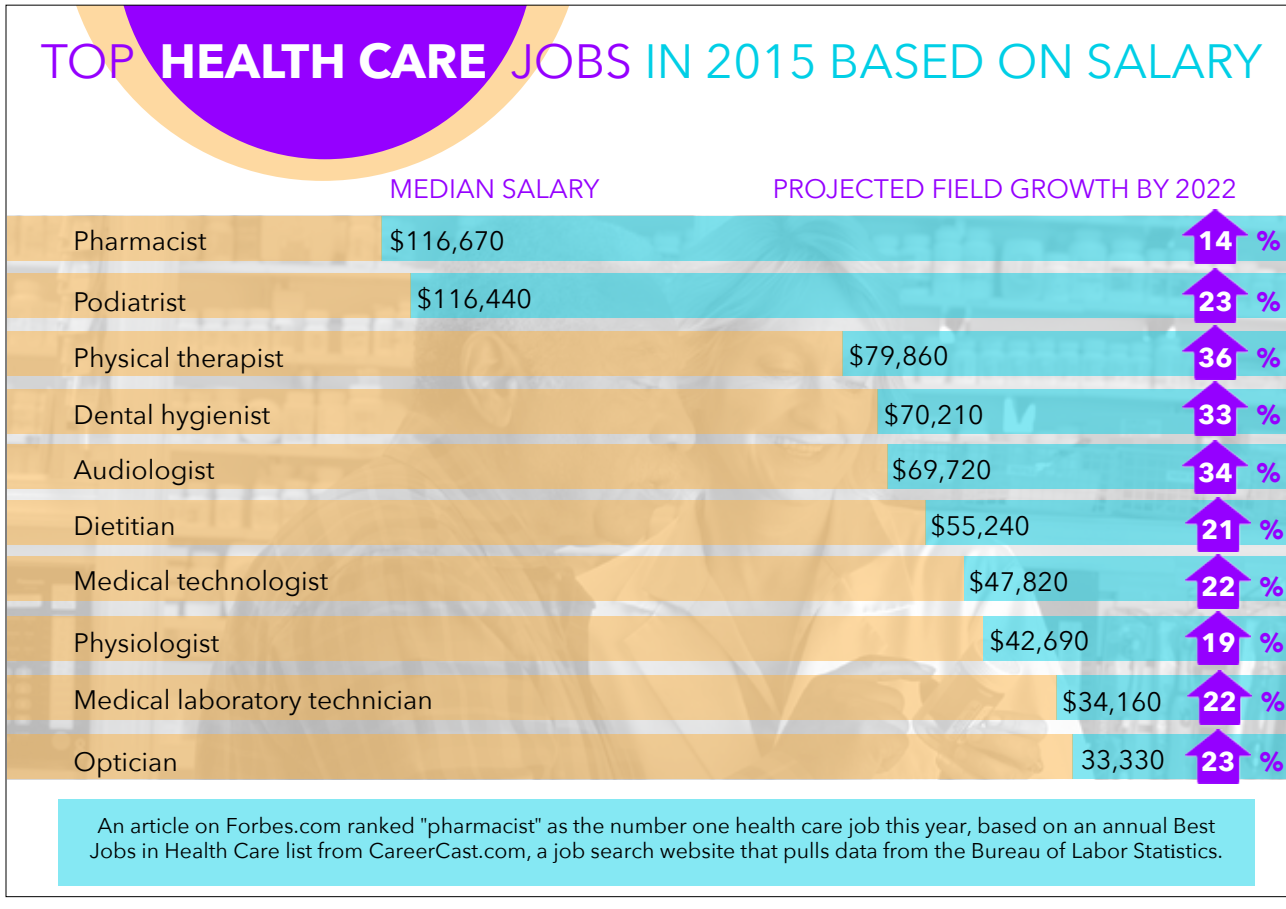
What's your opinion on pharmacists' role in the care of patients using cannabis? Should there be an integrated nationwide prescription drug monitoring program? What challenges do you face with electronically communicating patient information to other health care providers?

Share your thoughts and opinions with your colleagues through APhA's online members-only community, Engage.

These three issues will be considered during the APhA House of Delegates sessions at the 2015 APhA Annual Meeting & Exposition on March 27–30. Statements adopted by the House become official policy of the Association. As a result, your input is extremely important to the policy development process.

With APhA Engage, joining the conversation is easy! Simply visit engage.pharmacist.com, log in with your APhA username and password, and join one of the three House of Delegates discussion communities.

Once you have joined the communities, you can review the proposed policy statements for each of the three topics, network with colleagues, ask questions, and share your opinion.



Show us your teeth!

February is National Children's Dental Health Month. The APhA Foundation has partnered with America's ToothFairy: National Children's Oral Health Foundation to highlight the issue of untreated oral disease in children.

"It is astonishing that one in five children goes without dental care. As one of the most accessible health care providers, pharmacists have the opportunity to help raise awareness about this health concern," said Mindy Smith, BSPharm, Executive Director of the APhA Foundation.

During the month of February, the America's ToothFairy is holding its second annual Smile Drive, a national campaign to collect toothbrushes, toothpaste, floss, and rinse for at-risk children. In 2014, more than 430,000 oral care products were collected and delivered to children in need.

Pharmacists are invited to participate in America's ToothFairy activities for 2015, which include toothbrush drives, "Meet the ToothFairy" events, and dissemination of oral health educational materials.

For more information about America's ToothFairy or to download a Smile Drive toolkit, visit www.ncohf.org. A "Defeat Monster Mouth" poster is available to download at the American Dental Association's website at www.ada.org.

APhA DrugInfoLine™

Here is this month's top trending DrugInfoLine article

Alternative Medicines Corner
Nicole M. Maisch, Section Advisor

The latest drug news

Check out **APhA DrugInfoLine**, an online pharmacotherapy news resource for APhA members. Each week, **DrugInfoLine** editors work with a panel of pharmacy experts in 20 disease states to highlight the most relevant studies and guidelines published in peer-reviewed journals that affect drug therapy choices.

Recent top trending DrugInfoLine articles

- **Updated guidelines released for primary prevention of stroke**
- **Metformin: Still best initial therapy for type 2 diabetes**
- **What do drug labels say about pharmacogenomic tests?**

VISIT www.aphadruginfoline.com

Probiotic supplement linked to death of premature infant

Key point

Use of a probiotic supplement (i.e., ABC Dophilus Powder—Solgar) was linked to a fatal case of gastrointestinal (GI) mucormycosis, a rare fungal infection, in a premature infant after testing of unopened bottles revealed that the product contained the mold *Rhizopus oryzae.*

Finer points

A Cochrane review published earlier this year concluded that use of probiotics containing strains of either lactobacillus alone or in combination with bifidobacterium was effective in preventing necrotizing enterocolitis (NEC) and all-cause mortality in preterm infants. On the basis of these data, probiotics are used in preterm infants to aid in the prevention of NEC.

In October, a preterm infant born at 29 weeks gestation at a Connecticut hospital received 4 days of probiotic therapy with ABC Dophilus Powder started on the first day of life. After its use, the infant developed signs of NEC, and surgical exploration of the infant's abdomen revealed complete GI ischemia from the esophagus to the rectum. After surgery, the infant developed multiple areas of vascular occlusion, which is not a sign of NEC, and subsequently died. Examination of the infant's necrotic bowel showed an angioinvasive fungal infection, and CDC subsequently identified the fungus as *R. oryzae,* which causes mucormycosis.

An investigation into the infant's death resulted in testing of unopened bottles in the specific lot (i.e., number 074024–01R1), which were positive for mold contamination. On November 14, the manufacturer issued a voluntary recall of lots 074024–01R1, 074024–01, and 074024–02 with a July 31, 2015, expiration date.

What you need to know

NEC is the most common serious acquired disease of the GI tract in preterm infants, occurring in approximately 10% of infants of very low birth weight. Because the infant's death was linked to use of this probiotic supplement, FDA, CDC, and the Connecticut Department of Public Health have launched an investigation. On November 25, CDC issued a health advisory recommending against the use of Solgar's ABC Dophilus Powder. The advisory recommended that clinicians evaluating infants for NEC or those who have signs of GI mucormycosis (e.g., abdominal distension, nausea, vomiting) should determine whether this probiotic was used. If the patient consumed the product within the previous 30 days, clinicians should consider a consultation with an infectious disease specialist to determine if there is a source of infection and if empiric treatment with antifungals that are active against mucormycete infections is needed.

What your patients need to know

Educate patients that ABC Dophilus Powder should not be used because of the risk of mold contamination. Remind patients that dietary supplements are not regulated by FDA, and encourage those who have this dietary supplement to return the product immediately.

Sources

CDC. Fatal gastrointestinal mucormycosis in an infant following ingestion of contaminated dietary supplement–Connecticut, 2014. Accessed December 2, 2014.

AlFaleh K et al. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD005496.

NEW APPROVALS

■ FDA has approved **secukinumab (Cosentyx—Novartis)** to treat adults with moderate to severe plaque psoriasis who are candidates for systemic therapy, phototherapy, or both.

Secukinumab is an antibody that binds to a protein (interleukin [IL]-17A) and inhibits its ability to trigger the inflammatory response that plays a role in the development of plaque psoriasis. It is administered as an injection under the skin.

The Medication Guide informs patients that, because secukinumab affects the immune system, they may have a greater risk of getting an infection. Serious allergic reactions have been reported with its use. Caution is advised when considering use in patients with a chronic infection or history of recurrent infection and in patients with active Crohn disease.

The most common adverse effects include diarrhea and upper respiratory infections.

■ The anticlotting drug **edoxaban (Savaysa—Daiichi Sankyo)** has been FDA approved to reduce the risk of stroke and dangerous blood clots in patients with atrial fibrillation that is not caused by a heart valve problem.

Edoxaban also has been approved to treat deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who have already been treated with an anticlotting drug administered by injection or infusion for 5 to 10 days.

The most common adverse effects observed in trial participants were bleeding and anemia. As with other FDA-approved anticlotting drugs, bleeding, including life-threatening bleeding, is the most serious risk with edoxaban. There is no treatment that has been proven to reverse edoxaban's anticoagulant effect.

Edoxaban has a boxed warning that states edoxaban is less effective in atrial fibrillation patients with a creatinine clearance greater than 95 mL per minute.

■ FDA has approved **liraglutide injection, rDNA origin (Saxenda—Novo Nordisk A/S)** under the trade name Saxenda as a treatment option for chronic weight management in addition to a reduced-calorie diet and physical activity.

The drug is approved for use in adults with a body mass index (BMI) of 30 or greater (obesity) or adults with a BMI of 27 or greater (overweight) who have at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia.

Liraglutide is a glucagonlike peptide-1 (GLP-1) receptor agonist and should not be used in combination with any other drug belonging to this class, including Victoza, a treatment for type 2 diabetes. Saxenda and Victoza contain the same active ingredient, liraglutide, at different doses: 3 mg and 1.8 mg, respectively. However, Saxenda is not indicated for the treatment of type 2 diabetes, as the safety and efficacy of Saxenda for this use has not been established.

Patients using Saxenda should be evaluated after 16 weeks to determine if the treatment is working. If a patient has not lost at least 4% of baseline body weight, Saxenda should be discontinued, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Saxenda has a boxed warning stating that tumors of the thyroid gland have been observed in rodent studies with Saxenda but that it is unknown whether Saxenda causes thyroid C-cell tumors. Saxenda should not be used in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2.

Serious adverse effects reported include pancreatitis, gallbladder disease, renal impairment, and suicidal thoughts. Saxenda can also raise heart rate and should be discontinued in patients who experience a sustained increase in resting heart rate.

In clinical trials, the most common adverse effects observed in patients treated with Saxenda were nausea, diarrhea, constipation, vomiting, low blood glucose, and decreased appetite.

HOT APPS

eGFR Calculator. Estimate kidney function using five separate estimated glomerular filtration rate (eGFR) calculators. Includes reference list and other information to help identify risk factors, evaluate for chronic kidney disease (CKD), and manage progression using evidence-based strategies. Android, iPhone, and iPad. Free. www.kidney.org/apps/professionals/egfr-calculator

Relative Risk, Monitoring, and Referral in Patients with CKD. Summarizes new science that explains how eGFR and urinary albumin-to-creatinine ratio (ACR) are independent risk factors for the following adverse outcomes: all-cause mortality, cardiovascular mortality kidney failure, acute kidney injury, and progressive CKD. Free. iPhone. www.kidney.org/apps/professionals/relative-risk-monitoring-and-referral-patients-ckd

NEW INDICATIONS

■ The **dermal filler Bellafill (Suneva Medical)** has received FDA approval for the treatment of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients older than 21 years of age.

■ FDA approved a new indication for **ivacaftor (Kalydeco—Vertex Pharmaceuticals)** in people with cystic fibrosis aged 6 years and older who have the R117H mutation in the cystic fibrosis transmembrane conductance regulator gene. The drug was previously approved for the mutations G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D.

NEW FORMULATION

■ FDA approved a lower dose formulation (40 µg) of **beclomethasone dipropionate (QNASL—Teva),** a nonaqueous intranasal corticosteroid for treatment of allergic rhinitis in children aged 4 years to 11 years. QNASL Nasal in 80 mcg was previously approved for adults and adolescents aged 12 years and older.

Allergic and pseudoallergic reactions

CAROL J. ROLLINS

Allergic reactions, or hypersensitivity reactions, can be associated with any class of drug and with any type of pharmaceutical product, including OTCs. They can develop at any age and can be outgrown. Many allergic reactions are mild and easily treated with OTC antihistamines; others result in significant morbidity, and a few result in mortality. Anaphylactic shock and asphyxiation from throat swelling are the two most common causes of death from anaphylactic reactions, which result in about 500 deaths per year in the United States.[1]

The classic anaphylactic reaction is mediated by immunoglobulin E (IgE) and classified as a type I reaction, or immediate hypersensitivity. Mast cells and basophils release preformed histamine, proteases, and chemotactic factors in response to an antigen. Other mediators, including prostaglandins and leukotrienes, are synthesized in response to the antigen. Drugs that affect the lipoxygenase and cyclooxygenase pathways, including nonsteroidal anti-inflammatory drugs and omega-3 fatty acids (fish oil), may thus affect the overall response.

Type I reactions are relatively rare, occurring at a rate of less than 2%,[2] and require prior exposure to the antigen. Once antibodies have formed, the reaction develops rapidly and becomes stronger on repeat exposure. The immune system's T and B cells are both important in antibody development.

Non–IgE-mediated hypersensitivity reactions can mimic classic type I reactions, with symptoms ranging from mild flushing or erythema to life-threatening angioedema, bronchospasm, or hypotension.[2] In these reactions, mast cells and basophils degranulate, releasing their preformed histamine, proteases, and chemotactic factors in response to the anaphylatoxins C3a and C5a rather than an antigen trigger.[2,3] Previously known as anaphylactoid reactions, these complement-mediated pseudoallergies are now known as C activation–related pseudoallergy (CARPA). Reactions can occur on first exposure since antibodies are not involved, and symptoms may improve or resolve with repeated exposure.

CARPA reaction rates can approach 50% and occur within minutes of using some liposomal and lipid-based injectable medications.[4] Excipients and solubilizing agents, such as polysorbates or tweens, can cause release of anaphylatoxins C3a and C5a, resulting in CARPA with such injectable products.[5]

[Pseudoallergic] reactions can occur on **first exposure since antibodies** are not involved, and symptoms may improve or resolve with **repeated exposure.**

Less is known about CARPA with oral medications; however, polysorbates are used in a variety of foods, mouthwashes, and similar products. This type of CARPA may help explain seemingly unrelated reactions and multiple allergies in some patients.

Using the traditional Gell and Coombs classification, the other types of hypersensitivity reactions are classified as types II, III, and IV.[1] Hypersensitivity reactions can involve more than a single type of reaction. Type II reactions involve complement fixation and Ig-G and Ig-M antibodies; they are known as cytotoxic hypersensitivity reactions. Damage typically occurs to cells and tissue as a result of the reaction.

Type III reactions involve inflammation as a result of immune complex deposition within the body. When the complexes are large enough to activate complement, systemic reactions occur. Serum sickness is an acute type III reaction, in contrast to the more chronic type III reaction associated with diseases such as systemic lupus erythematosus and certain types of vasculitis and glomerulonephritis. Type IV reactions are T cell–mediated, delayed hypersensitivity reactions. Poison ivy is an example of a type IV hypersensitivity reaction for which OTC products may provide some relief when used early after exposure.

When talking with your patients about OTC antihistamines, inquire about possible allergic reaction history and determine the best course of action, whether pharmaceutical or referral.

HIGHLIGHTS

- Allergic reactions can develop at any age and can be outgrown.
- CARPA reaction rates can approach 50% and occur within minutes of using some liposomal and lipid-based injectable medications.

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2. Toxicology. 2005;216(2–3):106–21
3. Cancer Immunol Immunother. 2012;61(9):1575–84
4. Adv Drug Deliv Rev. 2011;63(12):1020–30
5. Eur J Pharm Sci. 2012;45(4):492–8

Carol J. Rollins, PharmD, BCNSP, Clinical Professor, University of Arizona College of Pharmacy, Tucson

Daniel L. Krinsky, BSPharm, MS, column coordinator (dkrinsky@neomed.edu), and Editor-in-Chief, APhA's *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care, 18th ed.* (online at PharmacyLibrary.com)

FDA approves Gardasil 9 to protect against five more HPV types

LOREN BONNER

Since 2006, when FDA approved the first vaccine for the prevention of certain strains of human papillomavirus (HPV), CDC's Advisory Committee on Immunization Practices (ACIP) has recommended Gardasil (Merck) in three doses for routine vaccination of adolescent girls and boys aged 11–12 years. FDA-approved Cervarix (GlaxoSmithKline) is a similar vaccine recommended for girls this age as well.

Now a third vaccine has been approved by FDA. Gardasil 9 (Merck) protects against five more HPV types—31, 33, 45, 52, and 58—than Gardasil. According to FDA, it has the potential to prevent approximately 90% of cervical, vaginal, and anal cancers and is approved for use in females aged 9–26 years and males aged 9–15 years.

"It really shores up our cancer protection **side and bumps up cervical cancer** coverage from 70% to 90%."

"It really shores up our cancer protection side and bumps up cervical cancer coverage from 70[%] to 90%, which is good," Jeff Goad, PharmD, MPH, FAPhA, FCPhA, FCSHP, Professor and Chair in the Department of Pharmacy Practice at Chapman University, told ***Pharmacy Today***.

Gardasil 9 will be available in February, and ACIP is expected to release recommendations after its meeting at the end of February.

Increasing HPV vaccination rates

Besides a modest increase in 2013, HPV vaccination coverage rates in boys and girls—particularly completion rates—have remained low, according to results from CDC's 2013 National Immunization Survey on teens (NIS-Teen).

"It will be interesting to see if there's an increase in vaccination rates with the new Gardasil," Dennis Stanley, BSPharm, Pharmacy Wellness Manager at Martin's Food Market Pharmacy in Richmond, VA, told ***Today***.

Virginia is 1 of 46 states that allow pharmacists to administer the HPV vaccine, although reimbursement challenges in all states prevent some pharmacies from stocking and offering the vaccine.

Stanley said he will typically administer the vaccine to young women aged 20–25 years who no longer see their pediatrician. In other cases, he occasionally administers follow-up of the second and third doses after the patient's pediatrician administers the first dose.

"I think pediatricians have been good at recommending the vaccine. The issue is with the completion rates," said Stanley.

He said having a working relationship with pediatricians is important. In Stanley's case, local pediatricians oftentimes recommend that their patients go to their pharmacy if they can't follow up on doses at the pediatrician's office.

HIGHLIGHTS

- HPV vaccination coverage rates in boys and girls have remained low.
- Pharmacists can identify teens who haven't been immunized.
- Pharmacists can strongly recommend that teens get this vaccine.

Strong recommendation for HPV vaccine needed

The NIS-Teen found that the percentage of parents who reported receiving a recommendation for HPV vaccine increased in 2013; on the other hand, approximately one-third of parents of girls and more than one-half of parents of boys said their child's clinician did not recommend the HPV vaccination.

"Experts in HPV vaccination coverage believe that it is the lack of a strong recommendation from a health care provider that is a major contributor to the low HPV immunization rates among adolescents," Mary Hayney, PharmD, MPH, BCPS, Professor in the School of Pharmacy at the University of Wisconsin–Madison, told ***Pharmacy Today***.

The HPV vaccine has been notoriously hard for parents and teens to get on board with, in large part because HPV is transmitted sexually.

"When the public or legislatures hear 'sexually transmitted,' the walls go up, and they are not hearing the protective side of the vaccine," said Goad.

He said studies have shown that when a provider gives what is called a strong recommendation—"I recommend strongly that you get this vaccine"—it can carry a lot of weight.

"Even if they can't give the vaccine in their state, pharmacists should give the strong recommendation," said Goad.

He urges pharmacists to continue talking to patients and their parents about the vaccine.

"Pharmacists everywhere can participate in advocacy and identifying adolescents that are behind and haven't been immunized," said Goad.

Loren Bonner, MA, Reporter

A new approach to type 2 diabetes therapy starts here

Trulicity™ is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use: Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. Has not been studied in patients with a history of pancreatitis; consider another antidiabetic therapy. Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Not a substitute for insulin. Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. Not for patients with pre-existing severe gastrointestinal disease. Has not been studied in combination with basal insulin.

Select Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies.

Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Counsel regarding the risk factors and symptoms of thyroid tumors.

Please see Important Safety Information including Boxed Warning about possible thyroid tumors including thyroid cancer and Brief Summary of Prescribing Information on following pages.

trulicity™

dulaglutide injection once weekly

0.75 mg/0.5 mL, 1.5 mg/0.5 mL

A new once-weekly GLP-1 RA therapy is now approved[1]

Trulicity™ offers your patients once-weekly dosing, and proven glycemic control, in the Trulicity pen.[1]

Trulicity is a new option for adult patients with type 2 diabetes who need more control than oral medications are providing.[1]

To learn more about Trulicity and the savings card for patients, talk to your Lilly sales representative.

Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

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Trulicity is contraindicated in patients with a prior serious hypersensitivity reaction to dulaglutide or any of the product components.

Risk of Thyroid C-cell Tumors: Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (eg, a mass in the neck, dysphasia, dyspnea, persistent hoarseness). Patients with elevated serum calcitonin (if measured) and patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation.

Pancreatitis: Has been reported in clinical trials. Observe patients for signs and symptoms including persistent severe abdominal pain. If pancreatitis is suspected discontinue Trulicity promptly. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapy.

Please see Important Safety Information continued on following page.

DG92005 10/2014 PRINTED IN USA

Important Safety Information, continued

Hypoglycemia: The risk of hypoglycemia is increased when Trulicity is used in combination with insulin secretagogues (eg, sulfonylureas) or insulin. Patients may require a lower dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia.

Hypersensitivity Reactions: Systemic reactions were observed in clinical trials in patients receiving Trulicity. Instruct patients who experience symptoms to discontinue Trulicity and promptly seek medical advice.

Renal Impairment: In patients treated with GLP-1 RAs there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. In patients with renal impairment, use caution when initiating or escalating doses of Trulicity and monitor renal function in patients experiencing severe adverse gastrointestinal reactions.

Severe Gastrointestinal Disease: Use of Trulicity may be associated with gastrointestinal adverse reactions, sometimes severe. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Trulicity or any other antidiabetic drug.

The most common adverse reactions reported in ≥5% of Trulicity-treated patients in placebo-controlled trials (placebo, Trulicity 0.75 mg and 1.5 mg) were nausea (5.3%, 12.4%, 21.1%), diarrhea (6.7%, 8.9%, 12.6%), vomiting (2.3%, 6.0%, 12.7%), abdominal pain (4.9%, 6.5%, 9.4%), decreased appetite (1.6%, 4.9%, 8.6%), dyspepsia (2.3%, 4.1%, 5.8%), and fatigue (2.6%, 4.2%, 5.6%).

Gastric emptying is slowed by Trulicity, which may impact absorption of concomitantly administered oral medications. Use caution when oral medications are used with Trulicity. Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered with Trulicity. In clinical pharmacology studies, Trulicity did not affect the absorption of the tested, orally administered medications to a clinically relevant degree.

Pregnancy: There are no adequate and well-controlled studies of Trulicity in pregnant women. Use only if potential benefit outweighs potential risk to fetus.

Nursing Mothers: It is not known whether Trulicity is excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue Trulicity taking into account the importance of the drug to the mother.

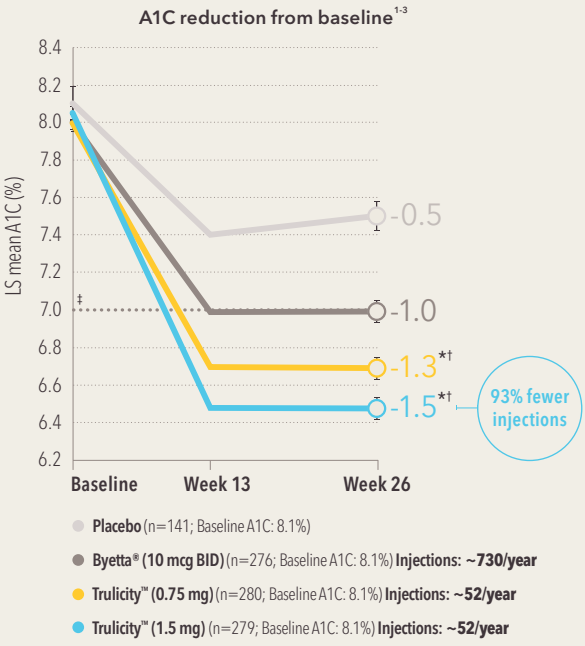
Pediatric Use: Safety and effectiveness of Trulicity have not been established and use is not recommended in patients less than 18 years of age.

Please see Brief Summary of Full Prescribing Information including Boxed Warning about possible thyroid tumors including thyroid cancer on following pages. Please see Instructions for Use included with the pen.

DG HCP ISI 18SEP2014

Once-weekly Trulicity 1.5 mg showed significant A1C reduction[1]

Recommended starting dose is 0.75 mg. Dose can be increased to 1.5 mg for additional glycemic control.



Data represent least-squares mean ± standard error.
* Multiplicity-adjusted 1-sided *P* value <.025 for superiority of Trulicity vs Byetta for A1C.
† Multiplicity-adjusted 1-sided *P* value <.001 for superiority of Trulicity vs placebo for A1C.
Mixed model repeated measures analysis.
After 26 weeks, placebo-treated patients were switched in a blinded fashion to Trulicity 1.5 mg or Trulicity 0.75 mg.
‡ American Diabetes Association recommended target goal. Treatment should be individualized.[4]

- 52-week, randomized, placebo-controlled phase 3 study (open-label assignment to Byetta or blinded assignment to Trulicity or placebo) of adult patients with type 2 diabetes treated with maximally tolerated metformin (≥1500 mg/day) and Actos® (up to 45 mg/day)
- Primary objective was to demonstrate superiority of Trulicity 1.5 mg vs placebo on change in A1C from baseline at 26 weeks (-1.5% vs -0.5%, respectively; difference of -1.1%; 95% CI [-1.2, -0.9]; multiplicity-adjusted 1-sided *P* value <.001; analysis of covariance using last observation carried forward); primary objective met

References

1. Trulicity [Prescribing Information]. Indianapolis, IN: Lilly USA, LLC; 2014.
2. Data on file, Lilly USA, LLC. TRU20140910A.
3. Data on file, Lilly USA, LLC. TRU20140919C.
4. American Diabetes Association. Standards of medical care in diabetes–2014. *Diabetes Care*. 2014;37(Suppl 1):S14-S80.

trulicity™
dulaglutide injection once weekly
0.75 mg/0.5 mL, 1.5 mg/0.5 mL

Trulicity™

(dulaglutide)

Brief Summary: Consult the package insert for complete prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS

- **In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies.**
- **Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Counsel regarding the risk factors and symptoms of thyroid tumors.**

INDICATIONS AND USAGE

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

Limitations of Use:

Not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise. Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. It is not a substitute for insulin. Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. Not recommended in patients with pre-existing severe gastrointestinal disease. The concurrent use of Trulicity and basal insulin has not been studied.

CONTRAINDICATIONS

Do not use in patients with a personal or family history of MTC or in patients with MEN 2. Do not use in patients with a prior serious hypersensitivity reaction to dulaglutide or to any of the product components.

WARNINGS AND PRECAUTIONS

Risk of Thyroid C-cell Tumors: In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. Glucagon-like peptide (GLP-1) receptor agonists have induced thyroid C-cell adenomas and carcinomas in mice and rats at clinically relevant exposures. It is unknown whether Trulicity will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of this signal could not be determined from the clinical or nonclinical studies. One case of MTC was reported in a patient treated with Trulicity. This patient had pretreatment calcitonin levels approximately 8 times the upper limit of normal (ULN). Trulicity is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the risk for MTC with the use of Trulicity and inform them of symptoms of thyroid tumors (eg, a mass in the neck, dysphagia, dyspnea, persistent hoarseness). The role of serum calcitonin monitoring or thyroid ultrasound monitoring for the purpose of early detection of MTC in patients treated with Trulicity is unknown. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin as a screening test for MTC and a high background incidence of thyroid disease. Very elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. Patients with thyroid nodules noted on physical examination or neck imaging should also be referred to an endocrinologist for further evaluation.

Pancreatitis: In Phase 2 and Phase 3 clinical studies, 12 (3.4 cases per 1000 patient years) pancreatitis-related adverse reactions were reported in patients exposed to Trulicity versus 3 in non-incretin comparators (2.7 cases per 1000 patient years). An analysis of adjudicated events revealed 5 cases of confirmed pancreatitis in patients exposed to Trulicity (1.4 cases per 1000 patient years) versus 1 case in non-incretin comparators (0.88 cases per 1000 patient years). After initiation of Trulicity, observe patients carefully for signs and symptoms of pancreatitis, including persistent severe abdominal pain. If pancreatitis is suspected, promptly discontinue Trulicity. If pancreatitis is confirmed, Trulicity should not be restarted. Trulicity has not been evaluated in patients with a prior history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: The risk of hypoglycemia is increased when Trulicity is used in combination with insulin secretagogues (eg, sulfonylureas) or insulin. Patients may require a lower dose of sulfonylurea or insulin to reduce the risk of hypoglycemia.

Hypersensitivity Reactions: Systemic hypersensitivity reactions were observed in patients receiving Trulicity in clinical trials. If a hypersensitivity reaction occurs, the patient should discontinue Trulicity and promptly seek medical advice.

Renal Impairment: In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Because these reactions may worsen renal failure, use caution when initiating or escalating doses of Trulicity in patients with renal impairment. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.

Severe Gastrointestinal Disease: Use of Trulicity may be associated with gastrointestinal adverse reactions, sometimes severe. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Trulicity or any other antidiabetic drug.

ADVERSE REACTIONS

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

Pool of Placebo-controlled Trials:

These data reflect exposure of 1670 patients to Trulicity and a mean duration of exposure to Trulicity of 23.8 weeks. Across the treatment arms, the mean age of patients was 56 years, 1% were 75 years or older and 53% were male. The population in these studies was 69% White, 7% Black or African American, 13% Asian; 30% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.0 years and had a mean HbA1c of 8.0%. At baseline, 2.5% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60mL/min/1.73 m^2) in 96.0% of the pooled study populations.

Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of Trulicity-Treated Patients: Placebo (N=568), Trulicity 0.75mg (N=836), Trulicity 1.5 mg (N=834) (listed as placebo, 0.75 mg, 1.5 mg) nausea (5.3%, 12.4%, 21.1%), diarrhea[a] (6.7%, 8.9%, 12.6%), vomiting[b] (2.3%, 6.0%, 12.7%), abdominal pain[c] (4.9%, 6.5%, 9.4%), decreased appetite (1.6%, 4.9%, 8.6%), dyspepsia (2.3%, 4.1%, 5.8%), fatigue[d] (2.6%, 4.2%, 5.6%). ([a] Includes diarrhea, fecal volume increased, frequent bowel movements. [b] Includes retching, vomiting, vomiting projectile. [c] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, gastrointestinal pain. [d] Includes fatigue, asthenia, malaise.) Note: Percentages reflect the number of patients that reported at least 1 treatment-emergent occurrence of the adverse reaction. Gastrointestinal Adverse Reactions: In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving Trulicity than placebo (placebo 21.3%, 0.75 mg 31.6%,1.5 mg 41.0%). More patients receiving Trulicity 0.75 mg (1.3%) and Trulicity 1.5 mg (3.5%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.2%). Investigators graded the severity of gastrointestinal adverse reactions occurring on 0.75 mg and 1.5 mg of Trulicity as "mild" in 58% and 48% of cases, respectively, "moderate" in 35% and 43% of cases, respectively, or "severe" in 7% and 11% of cases, respectively. In addition to the adverse reactions ≥5% listed above, the following adverse reactions were reported more frequently in Trulicity-treated patients than placebo (frequencies listed, respectively, as: placebo; 0.75 mg; 1.5 mg): constipation (0.7%; 3.9%; 3.7%), flatulence (1.4%; 1.4%; 3.4%), abdominal distension (0.7%; 2.9%; 2.3%), gastroesophageal reflux disease (0.5%; 1.7%; 2.0%), and eructation (0.2%; 0.6%; 1.6%).

Pool of Placebo- and Active-Controlled Trials:

The occurrence of adverse reactions was also evaluated in a larger pool of patients with type 2 diabetes participating in 6 placebo- and active-controlled trials evaluating the use of Trulicity as monotherapy and add-on therapy to oral medications or insulin. In this pool, a total of 3342 patients with type 2 diabetes were treated with Trulicity for a mean duration 52 weeks. The mean age of patients was 56 years, 2% were 75 years or older and 51% were male. The population in these studies was 71% White, 7% Black or African American, 11% Asian; 32% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.2 years and had a mean HbA1c of 7.6-8.5%. At baseline, 5.2% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60 ml/min/1.73 m^2) in 95.7% of the Trulicity population. In the pool of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed as ≥5% above.

Other Adverse Reactions:

Hypoglycemia: **Incidence (%) of Documented Symptomatic (≤70 mg/dL Glucose Threshold) and Severe Hypoglycemia in Placebo-Controlled Trials:** Add-on to Metformin at 26 weeks, Placebo (N=177), Trulicity 0.75 mg (N=302), Trulicity 1.5 mg (N=304), Documented symptomatic: Placebo: 1.1%, 0.75 mg: 2.6%, 1.5 mg: 5.6%; Severe: all 0. Add-on to Metformin + Pioglitazone at 26 weeks, Placebo (N=141), TRULICITY 0.75 mg (N=280), Trulicity 1.5 mg (N=279), Documented symptomatic: Placebo: 1.4%, 0.75 mg: 4.6%, 1.5 mg: 5.0%; Severe: all 0. Hypoglycemia was more frequent when Trulicity was used in combination with a sulfonylurea or insulin. Documented symptomatic hypoglycemia occurred in 39% and 40% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with a sulfonylurea. Severe hypoglycemia occurred in 0% and 0.7% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with a sulfonylurea. Documented symptomatic hypoglycemia occurred in 85% and 80% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with prandial insulin. Severe hypoglycemia occurred in 2.4% and 3.4% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with prandial insulin. Heart Rate Increase and Tachycardia Related Adverse Reactions: Trulicity 0.75 mg and 1.5 mg resulted in a mean increase in heart rate (HR) of 2-4 beats per minute (bpm). The long-term clinical effects of the increase in HR have not been established. Adverse reactions of sinus tachycardia were reported more frequently in patients exposed to Trulicity. Sinus tachycardia was reported in 3.0%, 2.8%, and 5.6% of patient treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Persistence of sinus tachycardia (reported at more than 2 visits) was reported in 0.2%, 0.4% and 1.6% of patients treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Episodes of sinus tachycardia, associated with a concomitant increase from baseline in heart rate of ≥15 beats per minute, were reported in 0.7%, 1.3% and 2.2% of patient treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Immunogenicity: Across four Phase 2 and five Phase 3 clinical studies, 64 (1.6%) TRULICITY-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in Trulicity (ie, dulaglutide). Of the 64 dulaglutide-treated patients that developed dulaglutide ADAs, 34 patients (0.9% of the overall population) had dulaglutide-neutralizing antibodies, and 36 patients (0.9% of the overall population) developed antibodies against native GLP-1. 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 dulaglutide cannot be directly compared with the incidence of antibodies of other products. Hypersensitivity: Systemic hypersensitivity adverse reactions sometimes severe (eg, severe urticaria, systemic rash, facial edema, lip swelling) occurred in 0.5% of patients on Trulicity in the four Phase 2 and Phase 3 studies. Injection-site Reactions: In the placebo-controlled studies, injection-site reactions (eg, injection-site rash, erythema) were reported in 0.5% of Trulicity-treated patients and in 0.0% of placebo-treated patients. PR Interval Prolongation and Adverse Reactions of First Degree Atrioventricular (AV) Block: A mean increase from baseline in PR interval of 2-3 milliseconds was observed in Trulicity-treated patients in contrast to a mean decrease of 0.9 millisecond in placebo-treated patients. The adverse reaction of first degree AV block occurred more frequently in patients treated with Trulicity than placebo (0.9%, 1.7% and 2.3% for placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively). On electrocardiograms, a PR interval increase to at least 220 milliseconds was observed in 0.7%, 2.5% and 3.2% of patients treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Amylase and Lipase Increase: Patients exposed to Trulicity had mean increases from baseline in lipase and/or pancreatic amylase of 14% to 20%, while placebo-treated patients had mean increases of up to 3%.

DRUG INTERACTIONS

Trulicity slows gastric emptying and thus has the potential to reduce the rate of absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with Trulicity. Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered with Trulicity. In clinical pharmacology studies, Trulicity did not affect the absorption of the tested, orally administered medications to any clinically relevant degree.

USE IN SPECIFIC POPULATIONS

Pregnancy - Pregnancy Category C: There are no adequate and well-controlled studies of Trulicity in pregnant women. The risk of birth defects, loss, or other adverse outcomes is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes to maintain good metabolic control before conception and throughout pregnancy. Trulicity should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In rats and rabbits, dulaglutide administered during the major period of organogenesis produced fetal growth reductions and/or skeletal anomalies and ossification deficits in association with decreased maternal weight and food consumption attributed to the pharmacology of dulaglutide.

Nursing Mothers: It is not known whether Trulicity is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for clinical adverse reactions from Trulicity in nursing infants, a decision should be made whether to discontinue nursing or to discontinue Trulicity, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of Trulicity have not been established in pediatric patients. Trulicity is not recommended for use in pediatric patients younger than 18 years.

Geriatric Use: In the pool of placebo- and active-controlled trials, 620 (18.6%) Trulicity-treated patients were 65 years of age and over and 65 Trulicity-treated patients (1.9%) 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.

Hepatic Impairment: There is limited clinical experience in patients with mild, moderate, or severe hepatic impairment. Therefore, Trulicity should be used with caution in these patient populations. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no clinically relevant change in dulaglutide pharmacokinetics (PK) was observed.

Renal Impairment: In the four Phase 2 and five Phase 3 randomized clinical studies, at baseline, 50 (1.2%) Trulicity-treated patients had mild renal impairment (eGFR ≥60 but <90 mL/min/1.73 m^2), 171 (4.3%) Trulicity-treated patients had moderate renal impairment (eGFR ≥30 but <60 mL/min/1.73 m^2) and no Trulicity-treated patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). No overall differences in safety or effectiveness were observed relative to patients with normal renal function, though conclusions are limited due to small numbers. In a clinical pharmacology study in subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in dulaglutide PK was observed. There is limited clinical experience in patients with severe renal impairment or ESRD. Trulicity should be used with caution, and if these patients experience adverse gastrointestinal side effects, renal function should be closely monitored.

Gastroparesis: Dulaglutide slows gastric emptying. Trulicity has not been studied in patients with pre-existing gastroparesis.

OVERDOSAGE

Overdoses have been reported in clinical studies. Effects associated with these overdoses were primarily mild or moderate gastrointestinal events (eg, nausea, vomiting) and non-severe hypoglycemia. In the event of overdose, appropriate supportive care (including frequent plasma glucose monitoring) should be initiated according to the patient's clinical signs and symptoms.

PATIENT COUNSELING INFORMATION See FDA-approved Medication Guide

- Inform patients that Trulicity causes benign and malignant thyroid C-cell tumors in rats and that the human relevance of this finding is unknown. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, persistent hoarseness, dysphagia, or dyspnea) to their physician.
- Inform patients that persistent severe abdominal pain, that may radiate to the back and which may (or may not) be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue Trulicity promptly, and to contact their physician, if persistent severe abdominal pain occurs.
- The risk of hypoglycemia may be increased when Trulicity is used in combination with a medicine that can cause hypoglycemia, such as a sulfonylurea or insulin. Review and reinforce instructions for hypoglycemia management when initiating Trulicity therapy, particularly when concomitantly administered with a sulfonylurea or insulin.
- Patients treated with Trulicity should be advised of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients treated with Trulicity of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs.
- Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of GLP-1 receptor agonists. If symptoms of hypersensitivity reactions occur, patients must stop taking Trulicity and seek medical advice promptly.
- Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant.
- Prior to initiation of Trulicity, train patients on proper injection technique to ensure a full dose is delivered. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.
- Inform patients of the potential risks and benefits of Trulicity and of alternative modes of therapy. Inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and advise patients to seek medical advice promptly.
- Each weekly dose of Trulicity can be administered at any time of day, with or without food. The day of once weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days before. If a dose is missed and there are at least 3 days (72 hours) until the next scheduled dose, it should be administered as soon as possible. Thereafter, patients can resume their usual once weekly dosing schedule. If a dose is missed and the next regularly scheduled dose is due in 1 or 2 days, the patient should not administer the missed dose and instead resume Trulicity with the next regularly scheduled dose.
- Advise patients treated with Trulicity of the potential risk of gastrointestinal side effects.
- Instruct patients to read the Medication Guide and the Instructions for Use before starting Trulicity therapy and review them each time the prescription is refilled.
- Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.
- Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels towards the normal range. HbA1c is especially useful for evaluating long-term glycemic control.

Eli Lilly and Company, Indianapolis, IN 46285, USA

US License Number 1891

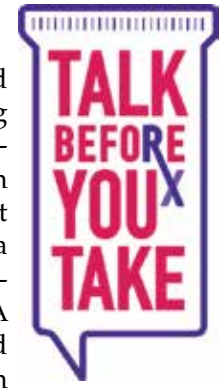
Additional information can be found at www.trulicity.com

DG HCP BS 18SEP2014

Trulicity™ (dulaglutide) HCP BS 18SEP2014

Communicating about medication risk and safety information

CARA ALDRIDGE YOUNG



A communication gap exists between patients and their health care providers when it comes to talking about medications—even when discussing the potential benefits and risks of prescription medications. In an effort to bridge this gap, the National Council on Patient Information and Education (NCPIE) has launched a "Talk Before You Take" campaign targeted to pharmacists and prescribers. The campaign is part of an FDA grant awarded to NCPIE to develop, implement, and assess a national educational program on medication risk reduction to promote safe and appropriate medication use.

Risk and safety survey

NCPIE began the campaign with an online survey to determine patients' and health professionals' knowledge, attitudes, and behaviors about medication risk and safety information. Following are some key findings:

- Approximately 62% of patients were not aware of any safety warnings about their medications.
- Ten percent of patients unaware of the possibility of a severe reaction or adverse effect to any of the medications they were taking actually experienced a serious drug reaction.
- 75% who reported being aware of a safety warning didn't recall which medication it was for or what the warning was about.
- Most patient respondents indicated they prefer both written and verbal communication about drug safety when visiting the prescriber (50%) or while filling prescriptions at a pharmacy (48%).
- More than one-half (58%) prefer prescribers to verbally describe the potential risks associated with medications. Older patients, who often have a higher number of comorbidities, expressed more satisfaction with the level and quality of communication than did younger patients.
- Of the sources used most frequently for medication risks and safety information, 59% of patients cited the Internet, 75% indicated prescribers, and 55% chose pharmacists.
- A majority of prescribers said they believe that pharmacists and the Internet are the most frequently used sources of information for patients. Only 31% of prescribers believe they are the primary source.

Pharmacists' role

The survey results revealed that pharmacists can play a prominent role in helping patients consider the potential benefits and risks of medications so they can make the best choices. Through regular, high-quality communication, pharmacists can counsel patients on how to lessen the possibility of a harmful interaction between a medication and a food, beverage, dietary supplement, or other medication; recognize and avoid adverse effects; and monitor their medications' effects.

Making sure patients fully understand the potential benefits and risks of their medications is particularly important for new prescriptions and with patients taking multiple medications. One way to do this is through medication synchronization: provide regularly scheduled appointment-based counseling (the appointment-based model, or ABM) that includes a medication regimen risk assessment. See the APhA Foundation's "Align My Refills" campaign (www.aphafoundation.org/align-my-refills) for ways you can engage with patients and caregivers through medication synchronization programs. NCPIE is a lead partner in the campaign.

Counseling tips

These tips from NCPIE can help guide your conversations with patients:

- Ask patients if they are aware of both the potential benefits and risks of their prescription medications.
- Be sure to ask about all of the medications your patients are taking—including OTCs, vitamins, and dietary supplements. Survey results indicated that patients across all age groups communicate information about their new OTCs significantly less often than about new prescription medications.
- Especially with new prescriptions, ask about any allergies or sensitivities patients may have.
- Encourage patients and caregivers to carefully read and follow the medication label directions and written information accompanying the medicine.
- Remind patients that if they have questions, ask.

For more information on "Talk Before You Take," see NCPIE's website at www.talkaboutrx.org.

Cara Aldridge Young, Senior Assistant Editor

Column coordinators: Wm. Ray Bullman, Executive Vice President; and **Deborah E. Davidson,** Membership Director, NCPIE, Rockville, MD

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Chronic kidney disease and use of dietary supplements

ANNE L. HUME

The prevalence of chronic kidney disease (CKD) among American adults has been estimated to be about 14%, based on data from the National Health and Nutrition Examination Survey (NHANES).[1] Among adults aged 60 years and older, the prevalence is higher, with an estimated 23% to 25% having stage 3 higher CKD.[1] The risk factors for CKD are well known and include diabetes, hypertension, obesity, and advanced age, among others. Although patients with CKD are commonly advised to avoid medications such as NSAIDs, which are known to potentially worsen renal function, many providers may not counsel individuals about use of dietary supplements.

National Kidney Foundation

The National Kidney Foundation (NKF) has a patient Web page devoted to herbal supplements and kidney disease.[2] The NKF site focuses on dietary supplements that may contain potassium and phosphorus, as well as products to specifically avoid because of their direct effects on the kidneys or on CKD risk factors. Herbals that may contain potassium include American ginseng, alfalfa, feverfew, dandelion, garlic leaf, lemongrass, noni, stinging nettle leaf, and turmeric rhizome among others.

The site also identified the 21 phosphorus-containing supplements that CKD patients should avoid because hyperphosphatemia is a common electrolyte abnormality in this population. The supplements included American ginseng, borage leaf, evening primrose, feverfew, flaxseed seed, milk thistle, pokeweed shoot, and stinging nettle leaf among others.

The site identifies 17 other supplements patients should avoid if they have CKD, are on dialysis, or have a transplant. Some of the supplements include astragalus, barberry, cat's claw, creatine, horsetail, goldenrod, huperzine A, licorice root, stinging nettle, pennyroyal, and yohimbe. Although evidence may be limited or contradictory, these products could have a range of adverse effects.

As an example, astragalus, an immune stimulant, might be associated with worsening lupus or potentially decrease the efficacy of drugs used following a kidney transplant. Licorice root containing glycyrrhizin might increase blood pressure and related complications because of its aldosteronelike effects.

A recent NHANES study used data from more than 20,000 participants over a 10-year period to estimate the use of supplements that are potentially harmful to patients with CKD.[3] Of the 5,280 unique supplements reportedly used by participants, 14% were potentially harmful, according to the NKF. Among these, ginseng was most frequently used, followed by ginger, alfalfa, capsicum, licorice, and dandelion, among others. Usage was lower (6.2%) in individuals with CKD than in those without (8.5%).

However, among individuals with risk factors for CKD, use of potentially harmful supplements was similar to those without risk factors for CKD. As shown in many studies, usage was greater among non-Hispanic whites and individuals with a higher income and educational level.

Emphasize that supplements, no matter **how seemingly harmless, should be** approved by the patient's nephrologist prior to **actual use.**

HIGHLIGHTS

- CKD patients should avoid phosphorus-containing supplements because hyperphosphatemia is a common electrolyte abnormality in this population.
- Other supplements could have a range of adverse effects.

Counseling

In counseling the patient with known CKD or who has multiple risk factors, the pharmacist should emphasize that supplements, no matter how seemingly harmless, should be approved by the patient's nephrologist before actual use. They should never be bought over the Internet unless from a reputable site.

When patients ask about specific supplements, pharmacists should consider the following: Is there any evidence suggesting the supplement is potentially nephrotoxic or could contain nephrotoxic adulterants? Can the supplement worsen risk factors for CKD, such as diabetes, hypertension, lupus, and so on? Can the supplement worsen the complications of advanced CKD, such as hyperkalemia and hyperphosphatemia?

Finally, can the supplement cause drug interactions with the multiple medications commonly taken by patients? Effective counseling should minimize the adverse risks from supplement use.

References

1. United States Renal Data System 2014 Annual Data Report
2. www.kidney.org/atoz/content/herbalsupp
3. Am J Kidney Dis. 2013;61(5):739–47

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Meeting summaries: Pain control, stress ulcer prophylaxis, metastatic colorectal cancer

MARIA G. TANZI

Society of Critical Care Medicine Congress

Phoenix, January 17–21, 2015 (www.sccm.org)

- In an evaluation of the impact of different sedating agents on ventilator-associated events, benzodiazepines, propofol, and opioids were associated with prolonged mechanical ventilation and longer hospital lengths of stay, whereas dexmedetomidine (Precedex—Hospira) and antipsychotics were associated with fewer ventilator days and lower mortality risk.
- In a small study evaluating the use of ketorolac for pain control in pediatric patients after cardiac surgery, those given ketorolac in the immediate postop period had equal pain control as their non–ketorolac-using counterparts and dramatically lower opioid use, as well as shorter intubation duration and length of stay, and no additional nephrotoxicity.
- An assessment of the impact of implementation of a stress ulcer prophylaxis (SUP) guideline and education in the ICU revealed that SUP indications were appropriate in 45% and 78% ($P < 0.001$) of the patients in the pre- to postimplementation period, respectively, and that appropriate use of pantoprazole increased significantly (23% vs. 65%; $P < 0.0001$) during the pre- to postimplementation period, respectively.
- A clinical evaluation describing the effectiveness and safety of enoxaparin (Lovenox—Sanofi) dosed at 0.5 mg/kg daily for venous thromboembolism prophylaxis in an obese hospitalized patient population (mean body mass index 43 kg/m^2) showed that this dosage regimen appears to be clinically effective with an acceptable complication rate.
- Results from a single-center study comparing clevidipine (Cleveprex—Medicines Company) with nicardipine for intensive blood pressure control in patients with hemorrhagic stroke, with concurrent hypertension requiring continuous infusions of an antihypertensive, found that mean time to goal systolic blood pressure was 71.5 minutes with nicardipine and 59 minutes with clevidipine ($P = 0.7$), with no difference in treatment failure, percent time in goal, incidence of rebleeding, or in-hospital mortality. Use of nicardipine, however, was associated with a shorter length of stay (5.4 vs. 11.8 d; $P = 0.02$).
- In a retrospective cohort study evaluating 205 patients who received either ranolazine (Ranexa—Gilead) 1,000 mg preoperatively, followed by 1,000 mg twice daily for 7 days, or no ranolazine, in combination with standard perioperative care surrounding coronary artery bypass graft, valve, or combination surgeries, use of ranolazine was independently associated with a significant decrease in postoperative atrial fibrillation development after these surgeries.
- Data from a case–control study including 168 patients suggested that combination therapy with two or more antibiotics with in vitro activity against carbapenem-resistant gram-negative (CR-GN) infections is associated with improved survival in critically ill patients with CR-GN bacteremia; however, there was no difference in survival with multiple-agent use when in vitro activity was not considered.

American Society of Clinical Oncology: 2015 Gastrointestinal Cancers Symposium

San Francisco, January 15–17, 2015 (www.asco.org)

- For patients with advanced colorectal cancer whose disease progressed on or after initial therapy, combination therapy with ramucirumab (Cyramza—Eli Lilly) and FOLFIRI (folinic acid, fluorouracil, and irinotecan) chemotherapy resulted in a statistically significant improvement in both progression-free (5.7 mo vs. 4.5 mo) and overall survival (13.3 mo vs. 11.7 mo) compared with standard treatment with FOLFIRI alone.
- Results from the Phase III TRIBE study indicated that for patients with metastatic colorectal cancer, treatment with FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) plus bevacizumab (Avastin—Genentech) compared with FOLFIRI plus bevacizumab significantly improved median overall survival (29.8 mo vs. 25.8 mo) and the 5-year overall survival rate (24.9% vs. 12.4%).
- For patients with newly diagnosed metastatic colorectal cancer, research showed that patients with the highest levels of vitamin D lived significantly longer compared with those with the lowest levels (32.6 mo vs. 24.5 mo), and higher vitamin D levels were also associated with a longer time to disease progression (12.2 mo vs. 10.1 mo, respectively).
- A retrospective review of clinical data collected at Memorial Sloan-Kettering Cancer Center between 2006 and 2014 on 145 patients with stage I–III rectal cancer who received radiation and chemotherapy (neoadjuvant therapy) and who experienced complete tumor regression indicated that survival rates after a median follow-up period of 3.3 years were similar for those who were either followed by watchful waiting (nonsurgical management) or taken for rectal surgery.

Maria G. Tanzi, PharmD, contributing writer

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Key research at CHEST 2014: Management of asthma, COPD

MARIA G. TANZI

Efficacy and safety of various treatment regimens for asthma and chronic obstructive pulmonary disease (COPD) were hot topics at the American College of Chest Physicians (CHEST) Annual Meeting. Numerous abstracts were presented that compared select long-term controller medications for the management of these pulmonary conditions. For COPD, data on withdrawing inhaled corticosteroids (ICS) in patients with severe disease gained a lot of attention, as did robust data with the use of tiotropium (Spiriva Respimat—Boehringer Ingelheim) for the management of asthma in pediatric and adult patients.

Following are a few key research studies in the areas of asthma and COPD presented at CHEST 2014, held October 25–30 in Austin, TX. For more information on presentations covering a variety of pulmonary topics, visit CHEST's website (http://2014.chestmeeting.chestnet.org).

Asthma research

Promising data for tiotropium. Data from two abstracts presented at CHEST indicate that use of tiotropium respimat as an add-on therapy to ICS in adolescent patients with poorly controlled asthma improves lung function without increasing adverse events, and use of this product in adult patients with asthma is safe and well tolerated.

Tiotropium respimat was approved in September 2014 for the management of COPD; however, tiotropium inhalation powder (Spiriva HandiHaler—Boehringer Ingelheim) has been available in the United States for more than 10 years for COPD. The new formulation, which provides a premeasured amount of medicine in a slow-moving mist, was developed to actively deliver medication in a way that does not depend on how fast air is breathed in from the inhaler. The manufacturer has sponsored a comprehensive Phase III clinical trial program investigating the use of tiotropium respimat in asthma patients.

A 48-week, Phase III, double-blind trial was conducted in 397 adolescent patients (mean age 14.3 y) with asthma who had a predicted forced expiratory volume in 1 second (FEV_1) between 60% and 90%. Patients were randomized to once-daily tiotropium respimat 5 µg (n = 134), tiotropium respimat 2.5 µg (n = 125), or placebo (n = 138) as add-on treatment to ICS. The primary endpoint was peak FEV_1 within 3 hours of dosing (FEV_1 [0–3 h] response) evaluated at week 24. Additional endpoints included other breathing measurement tests, evaluations of symptom control, and assessments of adverse events.

Results from a small prospective study **suggest that use of montelukast i**s not associated **with depression** symptoms.

Tiotropium respimat 5 µg demonstrated statistically significant improvement across lung function measurements, compared with placebo, at 24 weeks and 48 weeks. The adjusted mean difference for the FEV_1 (0–3 h) response with the 5 µg dose at week 24 was 174 mL. The percentage of patients who reported one or more adverse events was similar among the three groups, with adverse events being 59.4% in the placebo group, 63.2% in the 2.5 µg group, and 62.7% in the 5 µg group. The investigators concluded that tiotropium respimat as an add-on to ICS significantly improved lung function and was well tolerated in adolescent patients with asthma.

Safety data from five Phase III trials evaluating tiotropium respimat 2.5 µg and 5 µg as add-on therapy in 3,476 adult patients with symptomatic asthma also were presented. The five trials consisted of two trials evaluating tiotropium respimat added onto high-dose ICS plus a long-acting beta agonist (LABA), two trials of tiotropium respimat added onto medium-dose ICS, and one trial of this agent added onto low-dose ICS. A similar number of adverse events was observed across treatment groups within each trial, with the majority of events being mild or moderate in severity. Asthma, decreased peak expiratory flow, nasopharyngitis, upper respiratory tract infection, headache, and bronchitis were reported by 5% or more of patients across all treatment groups within each trial.

On the basis of these positive data and other available data, Boehringer Ingelheim announced on November 3 that FDA accepted its New Drug Application for tiotropium respimat for the long-term, once-daily, add-on maintenance treatment of asthma in patients aged 12 years and older who remain symptomatic on at least ICS therapy.

Montelukast and depression. Contrary to postmarketing reports linking montelukast and depression, results from a small prospective study suggest that use of this medication is not associated with symptoms of depression.

On the basis of an FDA review, the labels of all leukotriene inhibitors were updated to include information about neuropsychiatric events reported in patients using these products. Reported events included cases of agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness,

HIGHLIGHTS

- At CHEST 2014, data on withdrawing inhaled corticosteroids in patients with severe COPD gained a lot of attention.
- Robust data with the use of tiotropium for the management of asthma in pediatric and adult patients also gained attention.

suicidal thinking and behavior (including suicide), and tremor. This label update received a lot of press, with many patients and caregivers concerned about using this class of medications.

To assess the association between montelukast and depression, a small prospective study was conducted in 40 adult patients with asthma and allergic rhinitis, with or without a history of depression. On study day 1, a Hamilton Depression Rating Scale (HAM-D) score was obtained and patients were initiated on montelukast 10 mg daily. A subsequent HAM-D score was obtained in those patients who received at least 1 month of montelukast therapy.

Of the 24 patients who completed the study (mean age 54 y), 2 patients had a history of depression, and the baseline mean HAM-D score was 4.3 ± 3.8. No significant difference was observed between the baseline and follow-up HAM-D scores (mean 3.8 ± 3.8, $P = 0.57$). The results of this analysis demonstrated that montelukast was not associated with symptoms of depression; however, limitations of the data include a small size, short duration, and inclusion of adult patients only.

COPD research

Withdrawing ICS. In patients with severe and very severe COPD receiving a long-acting muscarinic antagonist (LAMA) plus a LABA, withdrawal of ICS therapy does not significantly increase the risk of COPD exacerbation compared with those who continue triple therapy, according to results of the WISDOM (Withdrawal of Inhaled Steroids During Optimized Bronchodilator Management) trial presented at CHEST and simultaneously published in the *New England Journal of Medicine*.

The current GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines recommend the addition of long-term ICS therapy for patients with severe and very severe disease and frequent exacerbations not adequately controlled by long-acting bronchodilators. However, the benefit of ICS in addition to two long-acting bronchodilators has not been fully determined. The WISDOM trial was designed to assess the stepwise withdrawal of ICS therapy in 2,485 patients with GOLD grade 3–4 COPD with a history of exacerbations who were treated with a LAMA plus LABA.

During the 12-month, double-blind trial, all patients received triple therapy with tiotropium 18 µg daily, salmeterol (Serevent—GlaxoSmithKline) 50 µg twice daily, and fluticasone 500 µg twice daily for the first 6 weeks, and then randomized 1:1 to continue triple therapy (n = 1,243) or a stepwise withdrawal of the ICS over 12 weeks (n = 1,242). For the primary endpoint, the data showed that the risk of experiencing an on-treatment COPD exacerbation with ICS withdrawal was noninferior to continued ICS therapy (hazard ratio 1.06 [95% CI 0.94–1.19]). In addition, similar results were observed for all predefined subgroup analyses. At week 18, when ICS withdrawal was complete, a greater reduction in trough FEV1 was observed in the withdrawal group compared with the continuation group (38 mL lower; $P < 0.001$), with a similar between-group difference observed at week 52 (43 mL lower; $P = 0.001$). No change in dyspnea and minor changes in health status occurred in the ICS withdrawal group.

The results of this trial suggest that ICS can be safely withdrawn in patients with severe COPD who are receiving combination long-acting bronchodilator therapy with a LAMA plus LABA, but it should be done cautiously, as patients in the ICS withdrawal group had a greater decrease in lung function compared with those who continued triple therapy.

LAMA/LABA versus ICS/LABA. When comparing controller regimens in patients with moderate to severe COPD with infrequent exacerbations, use of umeclidinium/vilanterol (Anoro Ellipta—GlaxoSmithKline) compared with fluticasone/salmeterol (Advair Diskus—GlaxoSmithKline) resulted in statistically significant and clinically meaningful improvements in lung function.

In December 2013, FDA approved the first combination LAMA/LABA treatment for chronic COPD, and clinicians have been working on determining where this therapy fits into the armamentarium for managing COPD. In an effort to compare this combination to ICS/LABA combination therapy, two 12-week studies were conducted comparing umeclidinium 62.5 µg/vilanterol 25 µg once daily with fluticasone 250 µg/salmeterol 50 µg twice daily in patients with moderate to severe COPD with infrequent exacerbations.

In both studies, which included 706 and 697 patients, respectively, patients in the LAMA/LABA groups had significantly greater improvements on all lung function measures compared with those in the ICS/LABA groups. In the first study, the improvement from baseline to day 84 (the primary study endpoint) in 0- to 24-hour weighted mean FEV_1 was 165 mL for the LAMA/LABA group compared with 91 mL in the ICS/LABA group. In the second study, the improvement in the two groups was 213 mL and 112 mL, respectively. The LAMA/LABA combination also improved trough FEV_1 on day 85 by 82 mL and 98 mL more than did the ICS/LABA combination in the two studies, respectively. Adverse events occurred at a similar rate across the two studies in both groups, ranging from 26% to 31%. The rate of serious adverse events was low (2%–4%).

These data suggest that two bronchodilators are an effective treatment option for patients with chronic COPD who have infrequent exacerbations, as the regimen resulted in greater lung function compared with an ICS/LABA combination. Of course, when selecting appropriate treatment regimens, clinicians should consider patient-specific factors such as treatments previously used and outcomes with these therapies.

Maria G. Tanzi, PharmD, contributing writer

Finafloxacin: New fluoroquinolone for acute otitis externa

MARIA G. TANZI

Finafloxacin (Xtoro—Alcon Laboratories) 0.3% otic suspension has been FDA approved for the treatment of acute otitis externa caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus.* Commonly referred to as swimmer's ear, acute otitis externa is an infection of the outer ear canal typically caused by bacteria in the ear canal. The most common pathogens causing this infection are *P. aeruginosa* (20%–60%) and *S. aureus* (10%–70%), often occurring as a polymicrobial infection.

The approval of finafloxacin adds to the number of antimicrobial drugs indicated for this condition. "The availability of multiple treatment options allows physicians and patients to find the treatment to meet their needs," said Edward Cox, MD, MPH, Director of the Office of Antimicrobial Products in FDA's Center for Drug Evaluation and Research, in an FDA news release.

Practice guidelines

In February 2014, the American Academy of Otolaryngology–Head and Neck Surgery Foundation published practice guidelines for the management of acute otitis externa.[1] The primary purpose of this guideline was to promote appropriate use of oral and topical antimicrobials and highlight the need for adequate pain relief in patients 2 years of age and older. The guidelines include eight key action statements that emphasize proper diagnosis, treatment, patient education, and follow-up.

Analgesic treatments are recommended for pain control and should be tailored to the severity of pain reported by patients. Topical antimicrobials are recommended as the drugs of choice for initial therapy of diffuse, uncomplicated acute otitis externa (e.g., acetic acid, acetic acid/hydrocortisone, ciprofloxacin/hydrocortisone, ciprofloxacin/dexamethasone, neomycin/polymyxin B/hydrocortisone, ofloxacin), and systemic antimicrobials should not be used as initial therapy unless there is extension outside the ear canal or the presence of specific host factors that would indicate systemic therapy is needed. The guidelines also include a detailed table on instructions that should be given to patients on how to properly administer prescribed ear drops. Reassessment of patients who fail to respond to initial therapy is also advised within 48 to 72 hours.

Clinical data

Data from two randomized, multicenter trials involving 1,234 patients aged 6 months to 85 years with acute otitis externa, including 560 patients who were pathogen positive for *P. aeruginosa* and/or *S. aureus,* showed that use of finafloxacin was superior to placebo for both clinical and microbiological outcomes, as well as time to cessation of ear pain.

Patient counseling

Counsel patients on proper dosage and administration and potential adverse events. Advise patients to shake the bottle well before use and warm the suspension by holding the bottle in their hand for 1 to 2 minutes before dosing to avoid dizziness, which may occur from administration of a cold suspension. Instruct patients to lie with the affected ear upward, instill the drops, and maintain the position for 60 seconds to aid in the penetration of the drops into the ear canal. Inform patients that itching of the ear and nausea were the most common adverse effects reported with use of the suspension and that rash may occur in those allergic to the drug or this class of drugs (i.e., quinolones).

Finafloxacin (Xtoro)

Manufacturer: Alcon Laboratories
Drug class: Fluoroquinolone antimicrobial
Indication: Treatment of acute otitis externa caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus* in patients 1 year and older
Dosage: Four drops into the affected ear(s) twice daily for 7 days
- For patients who require an otowick, the initial dose can be doubled to eight drops, followed by four drops into the affected ear(s) twice daily for 7 days. Instruct patients on proper administration as noted in the patient counseling section.

Of note: Prolonged use may result in overgrowth of nonsusceptible organisms, including yeast and fungi. Use should be stopped if this occurs, and an alternative therapy should be initiated.
- Allergic reactions to finafloxacin may occur in patients with a history of hypersensitivity to this agent or other quinolones; discontinue treatment and use an alternative therapy.

In the pathogen-positive group, clinical cure on day 11 was 71% in the finafloxacin group compared with 37% in the placebo group, and the median time to cessation of ear pain in this group was 3.5 days for active treatment versus 6.8 days for placebo. Microbiological success, defined as eradication of all baseline organisms, on day 11 was achieved by 67% of patients in the finafloxacin group compared with 13% of those in the placebo group.

Similar results for clinical outcomes and cessation of ear pain were seen in the intention to treat population (n = 1,234) for finafloxacin compared with placebo (71% vs. 50% clinical cures; 3.5 d vs. 5.3 d for cessation of ear pain, respectively). Of the 618 patients who were treated with active drug in these two studies, the most commonly reported adverse events, occurring in 1% of patients, were ear pruritus and nausea.

Reference

1. Otolaryngol Head Neck Surg. 2014;150(1 Suppl):S1–S24

Maria G. Tanzi, PharmD, contributing writer

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Olaparib: A new option for patients with advanced ovarian cancer

MOHAMED JALLOH

Olaparib (Lynparza—AstraZeneca), a new medication to treat women with advanced ovarian cancer associated with mutated BRCA (BReast CAncer) genes, has received accelerated FDA approval. Targeted to patients who have had repeated treatment failures with chemotherapy, olaparib was approved in conjunction with the BRAC Analysis Cdx, a genetic test used to detect mutated BRCA genes.

Olaparib (Lynparza)
Manufacturer: AstraZeneca
Drug class: PARP inhibitor
Indication: Monotherapy for patients with confirmed or suspected mutated BRCA advanced ovarian cancer who have received chemotherapy three or more times
Dosage: 400 mg (eight 50-mg capsules) twice daily (800-mg total daily dose)
- If patients experience adverse reactions, the total daily dose may be reduced to 400 mg (four 50-mg capsules twice daily) or to 200 mg (two 50-mg capsules twice daily)
- A dose recommendation cannot be made for pediatric patients, nursing mothers, and patients with hepatic impairments because of lack of safety and efficacy data.
- The capsule should not be chewed, dissolved, or opened.

Pathophysiology and mechanism of action

Epithelial cells form the outer layer of ovary tissue. Patients with ovarian cancer have ovarian epithelial cells replicating uncontrollably, with low DNA damage repair.

BRCA1 and BRCA2 are tumor-suppressor genes that produce DNA enzymes that repair DNA damage during replication. Patients with BRCA gene mutations have decreased DNA repair and thus an increased risk of developing ovarian cancer. During mutations, BRCA1 and BRCA2 have backup enzymes, such as poly-ADP polymerase (PARP), to function. Prior observations have found that in vitro BRCA gene mutations have resulted in increased sensitivity of cancer cells to PARP inhibitors.

PARP is an enzyme involved with normal cellular homeostasis, DNA transcription, and DNA damage repair. Olaparib directly inhibits PARP, allowing rapidly replicating cancer cells to remain damaged. When such cells remain damaged, they are purported to be more susceptible to apoptosis—automatic cell death.

Olaparib directly inhibits PARP, **allowing rapidly replicating cancer cells to** remain damaged.

Safety and efficacy

Olaparib's efficacy was evaluated in a study of 137 patients with advanced ovarian cancer associated with mutated BRCA genes. All patients had undergone at least three chemotherapy treatments.

Researchers evaluated objective response rate (ORR)—the percentage of patients who experienced complete disappearance or partial shrinkage of the tumor—and duration of response (DOR). The study showed that 34% of patients experienced ORR for a median duration of 7.9 months.

Adverse reactions

The most common adverse effects reported (>20% of patients) included nausea, vomiting, diarrhea, distorted taste, decreased appetite, indigestion, abdominal pain, headache, common coldlike symptoms, cough, joint paint, musculoskeletal pain, muscle pain, back pain, and dermatitis.

Serious adverse effects included developing myelodysplastic syndrome, a condition in which the bone marrow does not produce enough functioning blood cells; acute myeloid leukemia; and lung inflammation.

The most common laboratory abnormalities reported in patients receiving olaparib included an increase in serum creatinine and the mean corpuscular volume and a decrease in hemoglobin, absolute neutrophil count, platelets, and lymphocytes.

Contraindications, warnings, precautions

Olaparib has no contraindications. However, safety and efficacy of olaparib in pediatric patients, nursing mothers, and patients with hepatic impairment have not been studied; thus pharmacists should caution about use in these patient populations.

Mohamed Jalloh, PharmD, contributing writer

Patient counseling

Give patients the Medication Guide and review it with them carefully. If a patient misses a dose, instruct the patient to wait to take their next normal dose at the designated time. Tell patients to avoid taking olaparib with grapefruit or Seville oranges. Advise patients to contact their health care provider if they experience symptoms such as weakness, fatigue, fever, weight loss, etc., because these may be signs of myelodysplatic syndrome or acute myeloid leukemia. Advise patients to contact their health care provider if they experience symptoms such as new or worsening respiratory symptoms because they may be signs of pneumonitis. In addition, advise patients that nausea and vomiting are common and to contact their health care provider for antiemetic treatments.

Another hepatitis C regimen enters the market

MARIA G. TANZI

AbbVie has announced FDA approval of Viekira Pak, a therapy containing ombitasvir, paritaprevir, and ritonavir combination tablets copackaged with dasabuvir tablets, for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection, including those with compensated cirrhosis.

Unique mechanisms of action

The three new drugs in this combination pack all have unique mechanisms of action. Ombitasvir is an HCV NS5A inhibitor, paritaprevir is an HCV NS5A NS3/4A protease inhibitor, and dasabuvir is an HCV NS5A virus nonnucleoside NS5B palm polymerase inhibitor. The previously approved ritonavir acts as a cytochrome (CYP)3A inhibitor to boost levels of paritaprevir.

Efficacy was evaluated in six randomized, multicenter, Phase III trials involving more than 2,300 patients with genotype 1 chronic HCV infection.

Where does this agent fit in?

In December 2014, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) released recommendations for testing, managing, and treating HCV. Use of this new agent is addressed in these guidelines.

Following is a brief summary of HCV genotype 1 recommendations; review the full guidelines at www.hcvguidelines.org.

Treatment-naive

- Daily fixed-dose combination of ombitasvir/paritaprevir/ritonavir plus twice-daily dasabuvir and weight-based ribavirin (1,000 mg [<75 kg] to 1,200 mg [>75 kg]) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection. (Rating: Class I, Level A)
- Daily fixed-dose combination of ombitasvir/paritaprevir/ritonavir plus twice-daily dasabuvir for 12 weeks is recommended for treatment-naive patients with HCV genotype 1b infection. The addition of weight-based ribavirin is recommended in patients with cirrhosis. (Rating: Class I, Level A)

Treatment-experienced

- Daily fixed-dose combination of ombitasvir/paritaprevir/ritonavir plus twice-daily dasabuvir and weight-based ribavirin for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis and in whom prior pegylated interferon and ribavirin treatment has failed. (Rating: Class I, Level A)
- Daily fixed-dose combination of ombitasvir/paritaprevir/ritonavir plus twice-daily dasabuvir for 12 weeks is recommended for patients with HCV genotype 1b infection who do not have cirrhosis and in whom prior pegylated interferon and ribavirin treatment has failed. (Rating: Class I, Level A)
- Daily fixed-dose combination of ombitasvir/paritaprevir/ritonavir plus twice-daily dasabuvir and weight-based ribavirin for 24 weeks is recommended for patients with HCV genotype 1a infection and for 12 weeks for patients with HCV genotype 1b infection who have compensated cirrhosis and in whom prior pegylated interferon and ribavirin treatment has failed. (Rating: Class I, Level A)

Patient counseling

Advise patients to read the Medication Guide and educate them on proper dosing and administration, potential adverse effects (e.g., increases in liver enzymes), and the multitude of potential drug interactions. Women should also be educated on avoidance of pregnancy during treatment with this combination agent plus ribavirin.

Ombitasvir/paritaprevir/ritonavir with dasabuvir (Viekira Pak)

Manufacturer: AbbVie

Drug class: Ombitasvir is a hepatitis C virus NS5A inhibitor, paritaprevir is a hepatitis C virus NS3/4A protease inhibitor, and dasabuvir is a hepatitis C virus nonnucleoside NS5B palm polymerase inhibitor.

Indication: Treatment of adults with chronic hepatitis C genotype 1 infection, including those with compensated cirrhosis

Dosage: Two ombitasvir/paritaprevir/ritonavir 12.5-mg/75-mg/50-mg tablets once daily (in the morning) and one dasabuvir 250-mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content.

- Use of weight-based ribavirin is recommended for patients with genotype 1a infection without cirrhosis and genotype 1a and 1b infections with cirrhosis.
- A 12-week treatment duration is recommended for most patients, but 24 weeks is listed for those with genotype 1a infection with cirrhosis.

Of note: Contraindications include severe hepatic impairment; use with drugs that are highly dependent on CYP3A for clearance for which elevated levels may result in serious events; use with drugs that are strong inducers of CYP3A and CYP2C8 or those that are strong inhibitors of CYP2C8; and in patients with known hypersensitivity to ritonavir.

- Alanine transaminase elevations have been reported; hepatic laboratory monitoring is recommended for all patients during the first 4 weeks of treatment. See prescribing information for recommendations if elevated levels occur.
- Any contraindications and/or warnings and precautions listed in the ribavirin label also apply for regimens using this agent.

Maria G. Tanzi, PharmD, contributing writer

Ceftolozane/tazobactam: Novel antipseudomonal cephalosporin

MARIA G. TANZI

Another much-needed antibiotic enters the marketplace with FDA's approval of ceftolozane/tazobactam (Zerbaxa—Cubist) for the treatment of adult patients with complicated intra-abdominal infections (cIAI) in combination with metronidazole and for complicated urinary tract infections (cUTI), including pyelonephritis.

This new agent has demonstrated activity against gram-negative and gram-positive microorganisms, including *Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus,* and *Streptococcus salivarius*. It is the fourth antibiotic approved in the past year, following tedizolid (Sivextro—Cubist), dalbavancin (Dalvance—Durata), and oritavancin (Orbactiv—The Medicines Company).

"Of the four antibiotics approved this year, Zerbaxa is the only agent that has activity against gram-negative pathogens, including *Pseudomonas aeruginosa,*" Allana Sucher, PharmD, Associate Professor of Pharmacy Practice at Regis University, told ***Pharmacy Today.*** "As drug-resistant strains of gram-negative organisms are increasing, Zerbaxa provides clinicians with an additional antimicrobial treatment option," she said.

More approvals needed

Approval of new antibiotics is desperately needed to treat patients with life-threatening infections. In 2010, the Infectious Diseases Society of America called for the development of 10 new systemic antibacterial drugs by 2020. The organization noted that approval of ceftolozane/tazobactam marks the halfway point in reaching the goal laid out almost 5 years ago.

Another initiative aimed at increasing approvals is the passage of the Generating Antibiotic Incentives Now (GAIN) Act in 2012, which provides fast-track status, priority review, and 5 years of additional exclusivity for new antibiotics that treat serious or life-threatening infections. Cubist noted that ceftolozane/tazobactam is designated by FDA as a Qualified Infectious Disease Product for its indications under the GAIN Act.

Clinical efficacy, safety

Efficacy and safety for cIAI were assessed in a comparative study with meropenem that included 979 adult hospitalized patients. Ceftolozane/tazobactam plus metronidazole was noninferior to meropenem with regard to clinical cure rates at the test-of-cure (TOC) visit, which occurred 24 to 32 days after the first dose of study drug in the microbiological intent-to-treat population (n = 806). This group included all patients who had at least one baseline intraabdominal pathogen regardless of susceptibility to study drug.

Efficacy and safety for cUTI, including pyelonephritis, were assessed in a comparative study with levofloxacin that included 1,068 hospitalized adult patients. The primary efficacy endpoint was defined as complete resolution or marked improvement of clinical symptoms and microbiological eradication (all uropathogens found at baseline at $\geq 10^5$ were reduced to $<10^4$ CFU/mL) at the TOC visit 7 (± 2) days after the last dose of study drug. Ceftolozane/tazobactam demonstrated efficacy with regard to the composite endpoint of microbiological and clinical cure at the TOC visit.

In the two trials, the most common adverse events reported in 5% or greater of patients receiving ceftolozane/tazobactam for either indication were nausea, diarrhea, headache, and pyrexia. Adverse events resulting in treatment discontinuation occurred at a similar rate in patients receiving this new drug (2%) compared with comparator drugs (1.9%).

Patient counseling

Ask patients about any previous hypersensitivity reactions to other beta-lactams (including cephalosporins) and advise them that serious allergic reactions can occur. In addition, advise them of the potential for severe watery or bloody diarrhea and to report these symptoms to their provider immediately. Also inform patients of the most common adverse effects that have been reported with therapy, such as nausea, diarrhea, headache, and fever.

Ceftolozane/tazobactam (Zerbaxa)

Manufacturer: Cubist

Drug class: Cephalosporin and beta-lactamase inhibitor

Indication: Treatment of complicated intra-abdominal infections with metronidazole, and complicated urinary tract infections (cUTI), including pyelonephritis

Dosage: 1.5 g every 8 hours administered via I.V. infusion over 1 hour for adult patients with a creatinine clearance (CrCL) greater than 50 mL/min

- Duration of treatment varies and should be guided by the severity and site of infection and the patient's clinical and bacteriological progress.
- Dosage modifications are required for patients with renal impairment, as follows: CrCL 30–50 mL/min, 750 mg via I.V. every 8 hours; CrCL 15–29 mL/min, 375 mg via I.V. every 8 hours. For patients with end-stage renal disease who are on hemodialysis, 750 mg followed by a 150-mg maintenance dose via I.V. every 8 hours for the remainder of the treatment period; on hemodialysis days, dose should be administered at the earliest possible time following completion of dialysis.

Of note: Use is contraindicated in patients with known serious hypersensitivity to ceftolozane/tazobactam, piperacillin/tazobactam, or other members of the beta-lactam class.

- Warnings and precautions include decreased efficacy in patients with a CrCL of 30 to ≤50 mL/min, potential for hypersensitivity reactions, *Clostridium difficile*–associated diarrhea, and development of drug-resistant bacteria.

Maria G. Tanzi, PharmD, contributing writer

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First I.V. neuraminidase inhibitor approved to treat influenza

MARIA G. TANZI

In December, FDA approved the first intravenously administered influenza virus neuraminidase inhibitor, peramivir (Rapivab—BioCryst Pharmaceuticals), for the treatment of acute uncomplicated influenza in adult patients who have not been symptomatic for more than 2 days.

Peramivir is the third neuraminidase inhibitor approved, with oral oseltamivir (Tamiflu—Roche) and inhaled zanamivir (Relenza—GlaxoSmithKline) currently on the market. Neuraminidase is responsible for releasing viral particles from the plasma membrane of infected cells; therefore, inhibition prevents the virus from being released and passing through respiratory secretions to initiate new cycles of replication.

In 2009–10, peramivir was used to treat critically ill patients during the H1N1 pandemic under an FDA emergency use authorization. Efficacy and safety data for this agent also paved the way for its approval in other countries, such as Japan and South Korea in 2010.

CDC recommendations

According to its website, CDC is in the process of updating influenza antiviral information to reflect the approval of peramivir. CDC recommends the use of oral oseltamivir and inhaled zanamivir for treatment of influenza during the 2014–15 season. The agency noted that oseltamivir and zanamivir are chemically related antiviral medications that have activity against both influenza A and B viruses.

CDC also noted that amantadine and rimantadine, which have activity against influenza A viruses, are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza A viruses because high rates of resistance are seen with these agents.

Clinical efficacy, safety

Efficacy of peramivir was established in a randomized, multicenter, blinded trial conducted in Japan in which 297 patients with confirmed influenza received a single I.V. dose of peramivir 300 mg, 600 mg, or placebo. The 98 patients in the peramivir 600 mg group reported alleviation of their combined influenza symptoms a median of 21 hours sooner compared with patients in the placebo group. Median time to recovery to a normal temperature occurred 12 hours sooner in the peramivir group compared with placebo.

Safety data from 664 patients who received a 600-mg dose of peramivir showed that diarrhea was the most common adverse reaction, occurring in 8% of patients, compared with 7% given placebo. Other adverse events reported in the labeling include select laboratory abnormalities such as neutrophils, serum glucose, creatine phosphokinase, and alanine aminotransferase.

Clinical considerations

Efficacy of peramivir was not established in patients with serious influenza requiring hospitalization. Results from a double-blind, multicenter trial in which 398 patients who were hospitalized with serious influenza were randomized to peramivir 600 mg daily for 5 days plus standard of care, or placebo plus standard of care, showed that patients in the active treatment group had no improvement in the median time to clinical resolution compared with those given placebo.

In addition, peramivir's efficacy was established primarily in influenza infections caused mainly by influenza type A virus, with few patients being infected with type B virus. The prescribing information states that prescribers should consider available information from CDC on influenza drug susceptibility patterns and treatment effects when deciding whether to use peramivir. The use of peramivir is also not a substitute for the annual influenza vaccination, which should be administered to all patients 6 months of age and older.

Patient counseling

Tell patients that serious skin reactions and neuropsychiatric events have been reported with peramivir use. Instruct them to immediately report any of these symptoms to their provider.

Peramivir (Rapivab)

Manufacturer: BioCryst Pharmaceuticals

Drug class: Neuraminidase inhibitor

Indication: Treatment of adult patients 18 years and older with acute uncomplicated influenza who have been symptomatic for no more than 2 days

Dosage: 600 mg, given as an I.V. infusion for 15 to 30 minutes

- Dosage adjustments are needed for patients with impaired renal function, as follows: for creatinine clearance (CrCL) 30–49 mL/min, give 200 mg; for CrCL 10–29 mL/min, give 100 mg. Peramivir should be administered after dialysis at a dose adjustment based on renal function.

Of note: Rare cases of serious skin reactions, including erythema multiforme and Stevens–Johnson syndrome, have been reported with peramivir; if these reactions occur, appropriate treatment should be initiated immediately.

- Neuropsychiatric events (e.g., delirium, abnormal behavior) have been reported to occur in patients with influenza who were receiving neuraminidase inhibitors; patients should be monitored for any signs of abnormal behavior.
- Bacterial infections may occur in patients with influenza, and peramivir has no efficacy for any other illness other than influenza. Clinicians need to be alert for the potential for secondary bacterial infections and treat accordingly.
- Because of the potential interference between peramivir and the efficacy of live attenuated influenza vaccine (LAIV), the use of LAIV should be avoided for 2 weeks before or 48 hours after administration of peramivir unless medically indicated.

Maria G. Tanzi, PharmD, contributing writer

Starting from scratch: New Mexico pharmacists build care transitions program from ground up

AMY K. ERICKSON

Left to right: Angela Aldrich, PharmD, PhC, and Allison Burnett, PharmD, PhC, CACP

PHOTO CREDIT: WWW.TOMBRAHLPHOTO.COM

As innovators in patient care, pharmacists at the University of New Mexico Hospital (UNMH) saw a need to develop a transitions of care program for patients that spanned the inpatient and outpatient health care spectrum. The catch, however, was that there was no funding and no time in the staff's schedules to do the work.

Medication reconciliation

Allison Burnett, PharmD, PhC, clinical team lead for internal medicine, and Gretchen Ray, PharmD, PhC, BCACP, Associate Professor of Pharmacy Practice at the University of New Mexico College of Pharmacy, collaborated with other hospital leaders to launch a pilot quality improvement program that commandeered pharmacy residents to perform admission and postdischarge medication reconciliation activities. "At the time, we didn't have a position dedicated to care transitions, and we didn't have enough staff pharmacist time available, so the idea came about to have pharmacy residents dedicate 4 hours a week to care transitions and covering the service," said Ray.

HIGHLIGHTS

- UNMH pharmacists created a care transitions program that includes the inpatient and outpatient health care spectrum.
- Pharmacy residents perform admission and postdischarge medication reconciliation activities.

The first step in creating UNMH's Care Transitions Service (CTS) was getting a handle on what the hospital's care transitions needs were. "I met with providers and learned about the issues they were seeing and what was needed," said Burnett. She found that one of the leading physicians in the family practice department was very interested in working with the pharmacy department to reduce medication errors. "He expressed a real motivation and interest in collaborating with us because he was seeing that even after medication reconciliation was done by providers, patients were going on to experience adverse events and were being readmitted for medication errors," Burnett added.

Harnessing resident power

After much collaboration and discussion, "we basically volunteered the pharmacy residents to come up with a schedule, develop the tools needed for standardized patient interviews, a process for patient selection and identification, and a collaborative practice agreement between pharmacy and the family medicine unit that delineated which actions could be performed autonomously per pharmacy-driven protocol and which actions required involvement of the provider to get the medication discrepancies resolved," said Burnett, who served as project coordinator and provided oversight to the residents.

The team then worked with the University of New Mexico College of

Pharmacy to include student pharmacists and develop a longitudinal clinical rotation, thereby providing not just a clinical service, but also a learning experience for future pharmacists. "Prior to this, most of the rotations were month-long rotations," Burnett explained. "We recruited 4 students in the first year and 13 students in the second year of the program."

Top: Alex Rankin, MD; Aldrich; Vicente Jaramillo, PharmD candidate; and Brandi Bowman, PharmD candidate (left to right). **Left:** Pharmacy residents Cheyenne Newsome, PharmD, and Keenan Ryan, PharmD, triage patient lists. **Below:** Pharmacy resident Nwamaka Nwagbologu, PharmD, phones patients postdischarge.

Pilot phases

To promote buy-in and minimize resistance to change, Burnett and the group implemented the care transitions program in phases. They began by conducting admission medication interviews that augmented provider medication reconciliation. As this process became more streamlined, they began performing discharge medication reviews to ensure accuracy of discharge prescriptions and clarity of the patient's medication list. This process also included calling the patient's community pharmacy to deactivate any prescriptions no longer needed to avoid duplication of therapy through automated refill.

"The fact that we found these problems **after the admitting provider** had already performed medication reconciliation **showcases how pharmacists can have a big impact** on patient care."

To evaluate the success of the care transitions program, Burnett, Ray, and the group launched a 5-month pilot study focused on patients admitted to UNMH's family medicine service, which comprises two teams and has an average daily census of about 30 patients. Pharmacy residents and student pharmacists performed medication reconciliation and targeted medication-related interventions on a group of 191 patients from November 2012 to March 2013. The results were impressive.

According to Burnett, a total of 1,140 medication-related problems were identified, with an average of 6 per patient. About 70% of these problems were resolved using pharmacy-driven protocols and did not require input from a provider. "The fact that we found these problems after the admitting provider had already performed medication reconciliation showcases how pharmacists can have a big impact on patient care," said Burnett.

In addition to testing the program in the hospital, the postgraduate year (PGY)2 ambulatory care resident working in Ray's clinic conducted a 2-month pilot test of outpatient care transitions services. The PGY2 resident identified patients discharged from the hospital and conducted a medication review and reconciliation immediately before the patient saw his or her provider at the first postdischarge appointment. All medication-related problems were documented by the resident and reconciled in the patient chart as well as presented to the patient's postdischarge provider before the provider saw the patient. In 16 outpatients, 28 medication-related problems were identified, and in more than 80% of the cases, the number of problems declined from admission to postdischarge medication reconciliation.

Ray noted that the outpatient piece is very important. "Even after medication reconciliation took place at admission, we found additional medication-related problems after the patient was discharged," she said. "This means that in just a few days after discharge, medication issues arose before the patient was even seen for their first hospital discharge appointment."

Successful outcomes

Based on the overwhelming success of the CTS from admission to postdischarge, hospital leadership approved

Top: Pharmacy resident Cole Larsen, PharmD, interviews a patient. **Right:** Ryan and Larsen review student pharmacist documentation of patient interactions.

funding for a full-time care transitions coordinator. After a lengthy and extensive nationwide search, Angela Aldrich, PharmD, PhC, was selected for the position. "The first thing I wanted to do was use the platform built by Gretchen and Allison to create a care transitions system to expand the program," said Aldrich. "I use the student transitional care project as a platform to try to identify areas for improvement and places where tools need to be refined."

In addition to expanding the program, Aldrich reviews medications for patients seen by three medical teams and one hospital unit. "I go through all the patient profiles and look at their medication history, review the current medications that are active and look for any discrepancies, and for potential reasons for discrepancies," said Aldrich.

Catching medication problems

Aldrich believes that by using pharmacy-based care transitions services, pharmacists can play a critical role in making sure patients are taking the appropriate medications and the appropriate dose. For example, recently one of Aldrich's patients was on a psychotropic medication for which the dose was adjusted due to adverse events. When the patient was admitted, however, the dose recorded on admission was the original dose, not the adjusted dose. "The admitting team was not aware that the dose was adjusted during the patient's last outpatient interaction," explained Aldrich. By conducting interviews with the patients and confirming information with the outpatient provider, Aldrich made sure the correct dose was entered into the patient's electronic medical record.

Another example of the value of the pharmacist role in care transitions, noted Aldrich, was when a patient was instructed to use two fentanyl patches by an outpatient provider. "What the patient didn't realize was that the patches were intended to be two different strengths, so [the patient] was accidentally overdosing himself by about 25% by placing two of his original strength patches," said Aldrich. "We identified that problem through our pharmacy-led services."

Putting the pieces together

One of the reasons Aldrich was drawn to the transitional care coordinator position at UNMH was the opportunity to work across the entire health care system and with different medical disciplines. "There were no boundaries that were drawn for transitions of care," said Aldrich. "For the CTS program to work, we needed to coordinate with the college of pharmacy, the school of medicine, and work with every level of provider throughout the system."

Aldrich noted that everyone who helps take care of a patient has some hand in ensuring safe transitions. At UNMH, a network of community pharmacists and ambulatory care pharmacy team members come together to make a cohesive system. "All of those aspects are very exciting because all the pieces are there to make an excellent system," said Aldrich. "We just have to bring them all together."

Pharmacist roles

Burnett believes that pharmacists are a natural fit for creating and driving a care transitions program. "We are trained to be drug experts, that's the way we think," she said. "Whereas a hospitalist has limited time, pharmacists are taught to efficiently obtain the best possible medication history using at least two sources of information."

Members of the CTS team use information from the patient or caregiver and the community pharmacy, and cross-reference that information with data in the electronic health record. "We know how to use multiple resources of information and how to elicit the best kind of information from the patient using open-ended questions," Burnett explained.

Care during the continuum

One of the things that makes the UNMH's care transitions program stand apart is the fact that medication-related problems are identified throughout the continuum of care.

"We developed the program to look at different time points in the care transitions process, both at admission and postdischarge in the clinic," said Ray. "When pharmacists are incorporated into the care transitions flow, we can make an impact at so many points."

She noted that it is important to continue care into the outpatient setting. "Even though we have pharmacist interventions while the patient is hospitalized, medication-related problems do arise after a patient has been discharged," said Ray "It is important for pharmacists to have contact with the patient and their medical home teams after they've been discharged as well."

Another unique aspect is enlisting the help of student pharmacists and pharmacy residents. "We wove students and pharmacists together, so all of the care transitions activities are done in a less segregated manner. It's less isolated and more like an integrated set of activities that go along with other clinical daily duties," explained Burnett.

According to Aldrich, the next step in the CTS is to gather data to show that when medication-related problems are resolved, it potentially reduces readmissions and improves quality of life for patients. "Ultimately that's our goal—to improve patient care by keeping them out of the hospital and providing safe medication use," Aldrich said.

Amy K. Erickson, MA, Senior Editor

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Identifying and resolving medication nonadherence

RANDY P. MCDONOUGH

Now that our practice has fully implemented continuous medication monitoring services for all of our patients during the dispensing process, we are always looking for new ways to improve our patients' drug therapy adherence and outcomes. Our efforts are reflected in our pharmacy performance measures through the Electronic Quality Improvement Platform for Plans and Pharmacies (EQuIPP). We want our practice to be recognized as a high-performing pharmacy so that we're not only participating in performance-based networks but also receiving new revenues from payers who are willing to reimburse us on the basis of how well we improve patient outcomes and help to control health care spend.

While it might seem challenging to provide continuous medication monitoring services during dispensing functions, it is possible with the right workflow, technology, staffing, and documentation. To make continuous monitoring services work in a busy community pharmacy, pharmacists need to develop patient care processes that are both efficient and effective. Recently, I came across an article that discussed the Pennsylvania Project, a study that evaluated community pharmacists' efforts to improve their patients' medication adherence using screening tools and brief interventions.[1]

Pharmacist-led intervention

In the project, community pharmacies from the same chain were assigned to an intervention or control group. The intervention took place during a 12-month period, with the previous year serving as the comparator year. It consisted of screening tools to determine patients' risk of medication nonadherence and, for those patients whose risk scores reached a certain threshold, a brief pharmacist-led intervention.

In a 2- to 5-minute conversation with patients, pharmacists used motivational interviewing techniques to improve patient adherence to drug therapy. Results were as follows:

- Mean adherence rates were improved for all five medication classes studied—calcium channel blockers, oral diabetes medications, beta-blockers, statins, and renin–angiotensin system antagonists—in the intervention group compared with the control group.
- Health care costs were lower in the intervention group compared with the control group for patients who were using oral diabetes medications and statins.

Untapped resource

The study researchers indicated that community pharmacists are an untapped resource to help improve medication adherence at the population level. Their opinion was based not only on the study outcomes but also on the accessibility of community pharmacists and the trusting relationships pharmacists have developed with their patients. But, with the health care reform and the importance placed on quality performance of health care providers, community pharmacists must ensure that their clinical skills and knowledge are current and relevant, and that their interpersonal communication skills are highly effective.

Although medication therapy management is an important clinical service that pharmacists provide to patients, continuous medication monitoring provided at the time of dispensing is equally important to improving patient outcomes. It is during this time that pharmacists can provide succinct interventions that improve patient medication use and therapeutic outcomes. Continuous medication monitoring does not have to detract from the normal dispensing process but can be integrated into it, with technicians driving the dispensing and pharmacists providing patient counseling, medication monitoring, and targeted interventions.

[At the time of dispensing,] pharmacists **can provide succinct interventions** that improve patient medication use and therapeutic **outcomes.**

At a crossroad

Community pharmacy is at a crossroad. The business model for community pharmacy has changed. It is no longer about dispensing many prescriptions with minimal staff but about providing clinical services that have an impact on patient care, improve patient outcomes, and reduce health care spend. This new model may require an investment of money, time, and resources to re-engineer a community pharmacy practice to provide this level of service.

The Pennsylvania Project was able to involve a large number of pharmacists—283—in a community pharmacy setting to assess patient risk of nonadherence and provide brief interventions to improve patients' medication use. It required training, reinforcement, and feedback, but pharmacists stepped up to the challenge and improved care for more than 29,000 patients—not an easy undertaking, but one with impressive and very worthwhile results.

Community pharmacists are an untapped and underappreciated resource in our health care setting. It is time to recognize their value to patient care!

Reference

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Creating healthier communities through digital innovation

CATHLEEN MATHEW AND VIBHUTI ARYA AMIRFAR

In this era of digital everything, community pharmacy practice is joining the world of delivering convenience to patients with the touch of a fingertip. In this column, we've covered mobile apps for adherence and medication reminders, as well as those that track and chart your activity, medication use behavior, and symptoms—among many other permutations of health care in a smartphone.

What's next, you ask?

Now, big pharmacy businesses are strategizing on how to incorporate these new tools and technologies into patient experiences without taking away the personal touch.

One is CVS Health, which recently changed its name from CVS Caremark Corporation and made the public health community happy by eliminating all tobacco products from its more than 7,600 stores nationwide as of October 1, 2014.

In 2010, CVS Health developed a mobile application for users to fill a prescription and check its history, cost, and status. In July 2013, a drug interaction checker was added. Also in 2013, CVS Health launched a "virtual pharmacy" iPad application through which users could manage their pharmacy and Minute Clinic experiences, similarly to the mobile application.

Telehealth visits with physicians at some of its MinuteClinics were also developed, in which text messages were sent to patients about their prescriptions and electronic health record data shared with select providers. These efforts to utilize technology have been well received, with more than 15 million users of the text messaging program receiving notifications when their prescriptions are ready for pick-up.

In November 2014, CVS Health announced its Digital Innovation Lab, to open in Boston.[1] Brian Tilzer, Senior Vice President and Chief Digital Officer for CVS Health, described the lab partly as an open workspace "that encourages idea-sharing and innovation to produce the next level of digital technology."[2] The Digital Innovation Lab plans to focus on developing mobile apps and other forms of digital technology to improve and enhance the patient experience, with a goal to help people on their path to better health, according to the company.[3]

From the independent pharmacy on the **corner to the major chains,** each practice has an opportunity to change the way it interfaces **with patients.**

Innovative uses of existing technology

Such efforts to integrate technology in everyday pharmacy practice may be just a harbinger of what's to come. Although these technological advances may be expensive to adopt systemwide, using existing tools in an innovative way may be worth looking at in pharmacy practice.

From the independent pharmacy on the corner to the major chains, each practice has an opportunity to change the way it interfaces with patients. Learning about patients' use of technology in our communities may provide us with ideas on how students, residents, and seasoned practitioners can work with patients to enhance their pharmacy experience.

Perhaps some of the features may be more automated than others, leaving us time to actually speak with our patients, address their concerns, and develop a longstanding relationship as partners in improving their health. Giving patients the ability to not only manage their pharmacy visits but also simplify these visits may increase patient satisfaction and encourage patients to be proactive about their health.

It's time to rethink the way we view technology and its role in pharmacy practice. Thinking of innovative ways to use the technology that already shapes our patients' everyday world may be an area of opportunity for pharmacists to further engage them.

HIGHLIGHTS

- Big pharmacy businesses are incorporating new tools and technologies into patient experiences.
- Automated features may give pharmacists more time to speak with patients, address their concerns, and develop a longstanding relationship with them.

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Cathleen Mathew, 2015 PharmD candidate, Northeastern University School of Pharmacy, Boston

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Pharmacogenomics: Emerging opportunity for pharmacists

LOREN BONNER

Pharmacogenomics is possible, but not a reality yet. That's the opinion of many experts in the field right now who see it as a service pharmacists should be aligned with, particularly within medication therapy management (MTM).

A study published in the March/April 2014 issue of ***JAPhA*** tested the feasibility of implementing pharmacogenomics services in a community pharmacy setting. The study, conducted in a single community chain pharmacy, found that prescribers are receptive to having community pharmacists perform pharmacogenetic testing, but key challenges remain around reimbursement and integrating pharmacogenomics into a pharmacist's existing workflow.

"Is it worth going over those hurdles? I think our study showed that it is," said Shanna K. O'Connor, PharmD, BCPS, one of the authors of the study and Assistant Professor in the Department of Pharmacy Practice and Science at the University of Arizona College of Pharmacy. "There was a high acceptance rate and a positive reaction from patients to what we were doing."

She said that once reimbursement and workflow integration are figured out, pharmacogenetic testing services in pharmacy clinical practice could really hit the ground running.

"Pharmacists understand the **mechanisms of drug** interactions **and can easily** grasp gene interactions."

Pharmacogenomics in MTM

Pharmacists are uniquely qualified to take a leadership role in pharmacogenomics, which is defined as identifying drug-to-gene interactions that can optimize drug therapy selection.

According to David Kisor, PharmD, Department Chair of Pharmaceutical Sciences at Manchester University College of Pharmacy in Indiana, pharmacogenomics can naturally fit into MTM.

"Pharmacists understand the mechanisms of drug interactions and can easily grasp gene interactions," said Kisor.

A case report published online before print in the *Journal of Pharmacy Practice* on February 23, 2014, led by Kisor, demonstrates specifically how pharmacists can use a patient's genetic information and make drug therapy choices for them.

The report details a community pharmacist who identified a 65-year-old patient with myocardial infarction for genetic testing to determine the most optimal antiplatelet medication for him. After undergoing percutaneous coronary intervention and stent placement, the patient was prescribed clopidogrel 75 mg. But during an MTM evaluation when the pharmacist determined the patient's cytochrome P450 (CYP)2C19 genotype, he found that he was an intermediate metabolizer of clopidogrel. The pharmacist recommended prasugel 10 mg for the patient going forward, which the cardiologist accepted.

"It fits perfectly with MTM because it's not cut and dry. Few drugs go through only one pathway, and so if one pathway is inhibited or completely shut down based on a genetic test result, other pathways might still work," said O'Connor.

Identifying drug-to-gene interactions is similar to the drug–drug, drug–allergy, and drug–disease checks that pharmacists already do. Incorporating pharmacogenomics into a pharmacist's workflow—and the databases already developed—would be easy theoretically, according to O'Connor.

The challenge of pharmacists getting paid for pharmacogenetic testing services is likely more difficult to overcome. Even if pharmacists gain provider status, O'Connor said that doesn't necessarily mean they get paid enough money to cover the time that goes into providing the service.

HIGHLIGHTS

- Prescribers are receptive to pharmacogenomics services in a community pharmacy setting, but challenges remain around reimbursement and existing workflow.
- Only a handful of community pharmacists currently offer pharmacogenetic testing services to patients.

Current landscape

Only a handful of community pharmacists currently offer pharmacogenetic testing services to patients. Theresa Tolle, BSPharm, FAPhA, Owner of Bay Street Pharmacy in Sebastian, FL, is one of them. She was approached by the genetic testing company Genelex almost 3 years ago to offer the service to patients in her pharmacy, send the cheek swab to a testing lab, and interpret the results for patients. Tolle said the process became easier and less time consuming after the initial implementation and investment in continuing education courses that got her up to speed.

David Bright, PharmD, BCACP, Assistant Professor in the Department of Pharmaceutical Sciences at Ferris State University College of Pharmacy, said that while there may be some initial fear from pharmacists in understanding genetics and relating that to pharmacokinetics, where dosing decisions are made, it's something they pick up quickly. He said there needs to be more focus on education not only for pharmacists, but for patients and physicians as well.

Currently, pharmacogenetic testing service in a pharmacy is mainly cash based since pharmacists can't bill for cognitive services, according to O'Connor.

Tolle said she has always used pharmacogenetic testing as a marketing opportunity and has not been paid because of concerns about kickback provisions within Medicare and Florida state law. She is hopeful pharmacogenetic testing will soon be billable as an MTM service.

Loren Bonner, MA, Reporter

Coping with stress: Job satisfaction in community pharmacies

BRUCE BUCKLEY

In more than a decade working as both community staff pharmacist and manager, Jennifer Davis, PharmD, has found at least one solution for countering the stress that inevitably follows a tension-producing incident like a misfill or an encounter with an upset customer: she presses the pause button.

"Those of you who were involved need to take a break," Davis, who is now a Fred Meyer Pharmacy manager in Beaverton, OR, will tell her staff. "You need to get off the floor, because the chance of making an error right now is very high."

Sounds like a simple prescription for limiting the toxic fallout from acute stress in a busy community pharmacy, but many pharmacists find it difficult to cope. And rather than promoting the challenges and professional rewards of community practice, many of them advise younger pharmacists to look elsewhere for career opportunities. That was what Mark A. Munger, PharmD, Senior Associate Dean and Professor of Pharmacology at the University of Utah College of Pharmacy, and colleagues discovered in a 2012 survey of more than 300 independent and community chain pharmacists, published in the May/June 2013 issue of ***JAPhA*** as "Community pharmacists' occupational satisfaction and stress: A profession in jeopardy?"

"These negative attributes have the ability to damage the profession for many years," Munger told ***Pharmacy Today***, "because we're going to lose the best and brightest minds, and oftentimes choosing a professional career is done at the grassroots level."

Reversing discouraging attitudes

Steps are being taken, though, to reverse these discouraging attitudes, said Munger, who is scheduled to lead a discussion, Pharmacist Occupational Satisfaction and Coping with Stress, at the 2015 APhA Annual Meeting & Exposition in San Diego in March (APhAMeeting.org).

In the year and a half since the study appeared, Munger said he had heard from both independent and chain pharmacies. Many of the chains, he said, "have developed internal oversight committees that handle their employee–pharmacist complaints or suggestions and then address them by building a culture that relates around appreciation for their individual work, the individual pharmacist's ideas, and empowers them to make more individualized decisions."

Munger added that many of them are also "building clinical services into their labor projections, which will no doubt improve the workplace environment, as we suggested in the paper, empowering pharmacists to make more clinical decisions. We think that was really one of the major emphases that we got from our survey."

Making clinical decisions

Making clinical decisions during medication therapy management (MTM) sessions in a high-volume pharmacy can be challenging, but not impossible, said Davis. She added, however, that pharmacists who want to do so need to choose their practice environments wisely. "Some situations are more easily adapted to doing things like that," she said, "Thankfully, I work in pharmacy where there are always at least two pharmacists on duty, so if one of us gets pulled out for an immunization or MTM session, it's not a big deal."

She also encouraged pharmacists to seek out resources like the Oregon State University (OSU) College of Pharmacy's Stress Management for Pharmacists continuing pharmacy education (CPE) course she completed about a year ago (https://pace.oregonstate.edu/catalog/stress-management-pharmacists). The course is the second of three OSU CPE courses that focus on pharmacy workplace issues. The others deal with management and human resources skills and with patient safety and medication error prevention.

Making clinical decisions in a **high-volume pharmacy can be challenging,** but not impossible.

Diplomacy works best

Davis has also learned that diplomacy works best when a patient with urgent needs demands time during a period when patients are lined up at the counter waiting for prescriptions or to be counseled. She will tell the patient: "I would love to spend time with you, but can't right now. Could I look into this and call you back at a better time?"

"Ninety-nine percent of the time, they're totally fine with that," she added.

Munger said that developing pharmacists' confidence in their ability to use such diplomatic skills in clinical practice needs to be a goal that community chain pharmacies embrace. "I think they have to be providing training and support for clinical services, along with academia and foundations helping them train these pharmacists," he said.

"This is happening in some places," Munger added, "but it will have to be nationwide, and because this is quite a change for pharmacies, especially in a community setting, we're going to have to be patient as a profession."

Bruce Buckley, contributing writer

HIGHLIGHTS

- Many pharmacists find it difficult to cope with acute stress in a busy community pharmacy.
- To counter stress following an incident, press the pause button.
- Diplomacy works best for patients with urgent needs demanding time.

North Carolina powerhouses partner to drive clinical pharmacy services

SONYA COLLINS

Three North Carolina–based organizations have joined forces to study pharmacist-driven models of care that focus on medication use. About one-half of all adults have at least one chronic medical condition. One-quarter of adults have two or more. This portion of the population relies on daily medication for continued health. Proper use of this medication is the key to controlling health care costs and achieving positive patient outcomes.

Over the next 2 years, Community Care of North Carolina (CCNC), GlaxoSmithKline (GSK) and the UNC (University of North Carolina) Eshelman School of Pharmacy will study the role of pharmacists in a variety of settings and care models to learn how they can make the greatest impact on medication use and how to pay for their interventions.

"Patients who have chronic illness take lots of medicine, and while they see a lot of physicians, they go to the pharmacy more than they see their physician," said Allen Dobson Jr., MD, President and CEO of CCNC. "Pharmacists represent an opportunity for a touch point in the care delivery system where we can really impact the patients."

integral part in each of these multidisciplinary care models.

"Someone once described it as Willy Wonka's factory of care coordination. It's like a laboratory testing grounds for these advanced pharmacy practices," said Troy Trygstad, PharmD, MBA, PhD, Vice President for Pharmacy Programs at CCNC.

CCNC also counts among its diverse models of care First in Health, a patient-centered medical home that the organization developed in collaboration with GSK for its employees. CCNC is also the backbone of North Carolina's Community Pharmacy Enhanced Services Network, which brings in community pharmacists as members of the patient care team. The program, funded by a CMS Center for Medicare & Medicaid Innovation (CMMI) Health Care Innovation Award, provides the pharmacists with the resources, information, and technology they need to be full participants in patient care. (For more information on the CMMI grant, see page 49 of December's ***Pharmacy Today***.)

"Pharmacists will work in a new **practice concept with other health care** providers in primary care."

Care coordination

CCNC is a physician-led, community-based managed care organization that contracts with the state to care for the majority of its Medicaid population. Comprising regional networks of health care providers across all disciplines, health care facilities, social services and community resources, the organization coordinates the care of its patients through care managers and information sharing in a medical home model.

The organization's numerous clinical programs include coordination of ongoing patient care in the community, inpatient care, hospital-to-home transitions, behavioral and mental health care, and palliative care. Pharmacists play an

"Over the last 20 years, we've taken pharmacy away from the rest of the health care system," Dobson said. "We've lost a health care provider with a lot of knowledge to give."

Across its many clinical programs, CCNC gives pharmacists access to crucial patient health information through its informatics center and North Carolina's health information exchange.

"In the past, in most open-ended health care delivery systems, community pharmacists have been pretty much in the dark as it relates to the challenges or problems that patients might have and the critical laboratory and/or health information that's necessary in order to have an appropriate pharmacist–patient intervention," said Robert Blouin, PharmD, Dean of UNC Eshelman School of Pharmacy.

GSK, UNC Eshelman School of Pharmacy, and CCNC will collaborate to study, assess, and improve all of these diverse care models.

Predictive analytics

CCNC pharmacists can make a variety of interventions based on the patient's needs. GSK devised a predictive analytics tool called Care Triage that helps predict which patients need what type of intervention.

"As we started thinking about what was needed within this patient-centered medical home, First in Health, we realized that we had data scientists and statisticians, and CCNC had population health experts," said Jon Easter, BSPharm, Senior Director of Policy at GSK. So we began to devise additional tools that would help the medical home work better."

The result was Care Triage, a health information technology tool that attempts to provide with relatively small data sets the same insights about CCNC patients that big data sets can provide about larger populations. Using information such as a patient's diagnoses, medication list, and discharge data from the patient's most recent hospitalization, Care Triage can compare the patient to similar patients and predict the risk of certain adverse events.

"So then is there something that we can do at the pharmacy, based on this predictive data, that will make a meaningful impact? Because pharmacists see the patients a heck of a lot more than I do as a physician," said Dobson. "So it's really an exciting opportunity to change how pharmacy is practiced."

Best practices

As the collaboration brings together pharmacists from diverse settings and puts to work innovative models of care, UNC will advise on best practices. The school of pharmacy will offer its expertise in putting research into practice to inform care delivery and practice transformation.

"Over the next few years there is going to be a dramatic change in the way health care is delivered in this country, including how pharmacy and pharmacists interact within that health care system, moving away from a pay-for-service model toward a pay-for-value model," said Blouin.

"We will be helping each of the pharmacies and pharmacists in developing the models of care and keeping them up to date on the constantly changing best practices associated with a wide array of disease and/or drug therapy protocols, so that the pharmacists are always in a position to offer the patient contemporary best practice."

The collaboration is an opportunity for pharmacists to work with physicians, nurse practitioners, physician assistants, and other health care providers to create a new model of care, he said. "This isn't just a model for pharmacists, but a model for how pharmacists will work in a new practice concept with other health care providers primarily involved in the execution of primary care."

Analyzing outcomes

UNC Eshelman School of Pharmacy will analyze the outcomes of CCNC's diverse pharmacy practice models. "We will systematically study the various outcomes of pharmacists' interventions along with those of the other accompanying health care providers, and then evaluate the potential cost–benefit ratio of instituting such a new program," said Blouin.

Together, the three organizations aim to determine which pharmacist interventions are most effective to improve patient outcomes; the resources pharmacists need to execute these interventions; and how to pay pharmacists for this type of care. They will measure the interventions' success through metrics including total cost of care, hospital admissions, emergency department visits, avoidable hospitalizations, medication adherence, key chronic disease quality indicators, and patient experience.

All of this, Dobson hopes, will answer a more philosophical question: "How can we reintroduce the pharmacist into the health care team and use that to make a difference in patient care?"

Sonya Collins, MA, MFA, contributing writer

How pharmacists can help patients at risk for suicide

DIANA YAP

In 2003, C. Patrick Tharp, PhD, BSPharm, founded Pharmacists Preventing Suicides—a St. Louis–based group that focuses on suicide prevention education, research, training, lobbying, and promotion of tools—after he and his wife lost their youngest daughter, Tricia, to depression and suicide.

"We want pharmacists to know that this is not a difficult subject to master, and [that it] is not difficult to become comfortable with speaking to families and patients and even friends or families of your own that might be at risk for taking their own life," said Tharp. "My wife—my bride, Peggy—told us when we started that saving one life would be worth the effort. And we would like to see no other families have to go through what we went through."

In the United States, suicide claims approximately 30,000 lives each year, or slightly more than 1% of deaths; it is the most common psychiatric emergency, with close to 1 million Americans receiving treatment for suicidal thoughts, behaviors, or attempts on a yearly basis, according to the National Alliance on Mental Illness (NAMI) website. Internationally, more than 800,000 people die by suicide every year—around 1 person every 40 seconds, according to the World Health Organization's first global report on suicide prevention, published in September 2014.

"Suicide prevention is a humbling line of work. Really what I think we're talking about is the recognition of depression. Depression correlates highly," said Ken Duckworth, MD, Medical Director for NAMI. "Suicide prevention is every health professional's job to the best of their ability."

Duckworth added, "I would consider pharmacists to be on the health care team, and I would hope they'd be expanding their training, expanding their knowledge."

"We want pharmacists to know that this is **not a difficult** subject **to master."**

What are the pharmacist's responsibilities?

A pharmacist has two responsibilities related to suicide prevention, according to Glen Lewis Stimmel, PharmD, BCPP, Professor of Clinical Pharmacy and Psychiatry at the University of Southern California School of Pharmacy and Keck School of Medicine.

At a minimum, he said, all pharmacists need to get comfortable enough to be able to talk with patients about suicide. And the only responsibility of pharmacists who identify a possibly suicidal patient in their practice is to get that person connected to help—whether that's his or her physician, a family member, or the suicide hotline.

"Every pharmacy must have readily available—to any pharmacist working—the local and/or national suicide hotline number," Stimmel said. The only suicide hotline that NAMI publicizes is the crisis line of the American Association of Suicidology: 800-273-TALK (8255), which includes a prompt for veterans. The website (www.suicidology.org) also provides listings of state-by-state suicide crisis lines.

In terms of talking with a patient about suicide, it's better to say "thoughts of hurting yourself" rather than "suicide" or "killing yourself," emphasized Stimmel, a founding Member and Past President of the College of Psychiatric and Neurologic Pharmacists.

Pharmacists aren't trained to diagnose, but they can recognize if a patient is different than he or she was previously, and ask about that—not at the counter, but in a private counseling area, said Lawrence J. Cohen, PharmD, BCPP, FASHP, FCCP, FCP, Professor of Pharmacotherapy, Coordinator of Interprofessional Education, and Coordinator of Continuing Professional Education at the University of North Texas System College of Pharmacy.

"The best thing to do initially is to ask very open-ended questions of the individual," Cohen explained. "Ask in a very nonjudgmental way, 'You know, you seem to be a little off your game today,' or, 'You seem sad to me. Is there anything going on that you can talk to me about?'" Be caring, nonjudgmental, and don't jump to conclusions, he said.

"If you see things that are of concern as a health care provider, you can make sure the relevant practitioners and prescribers are made aware of what you've observed," said Cohen, a founding Member of the Board of Directors of the College of Psychiatric and Neurologic Pharmacists and Past President of the American College of Clinical Pharmacy. "While we may not be providing the direct treatment for it, we certainly can be involved with the treatment team in making sure they're aware so that they can make appropriate adjustments in treatment and psychotherapy."

Cohen cautioned that pharmacists should do what they can to make sure the patient is the one who initiates contact with the primary care provider or treating practitioner. "It is a much better scenario if you contact their physician with their permission on their behalf," he said. "You have a responsibility of not violating a patient's wishes, and if they don't want you to contact their physician, you've basically gotten yourself in pretty hot water." On the other hand, he said, pharmacists—as health professionals—have a duty to warn a patient's physician if the patient is a serious health risk.

Pharmacists can provide patients with good patient-focused information such as the NAMI website (www.nami.org) and the National Institute of Mental Health (NIMH) website (www.nimh.nih.gov), Cohen said.

Depression and suicide risk

A responsibility of all pharmacists is to learn how to recognize the common

signs and symptoms of depression. Community pharmacists, who are involved in filling all of the prescriptions for a patient, should be on the alert for changes in mood associated with depression, Cohen said.

Signs and symptoms of depression

Following are signs and symptoms of depression, according to the NIMH website (www.nimh.nih.gov/health/topics/depression/index.shtml#part1):

- Persistent sad, anxious, or "empty" feelings
- Feelings of hopelessness or pessimism
- Feelings of guilt, worthlessness, or helplessness
- Irritability, restlessness
- Loss of interest in activities or hobbies once pleasurable, including sex
- Fatigue and decreased energy
- Difficulty concentrating, remembering details, and making decisions
- Insomnia, early-morning wakefulness, or excessive sleeping
- Overeating, or appetite loss
- Thoughts of suicide, suicide attempts
- Aches or pains, headaches, cramps, or digestive problems that do not ease even with treatment

"People with depressive illnesses do not all experience the same symptoms," explained the NIMH website. "The severity, frequency, and duration of symptoms vary depending on the individual and his or her particular illness."

It's important to keep in mind some nuances of depression and suicide risk, according to Cohen. People may have a depressive disorder that's caused by other medical conditions. Many conditions may have symptoms of depression associated with them, but it can also be depressing to be given a diagnosis that indicates one's life may be shorter than one actually expected it would be.

People with chronic pain also may develop symptoms associated with depression. Cohen said that his patients who have chronic pain for more than 36 to 48 hours start to develop symptoms consistent with a diagnosis of depression. These patients feel "like the pain's never going to go away; it hurts any time you move, even during sleep; and it doesn't take very long for you to become depressed just because of that scenario," he said. "That's something that pharmacists in whatever setting, whatever their training is, should be sensitive to."

While antidepressants carry a black box warning from FDA on the risk of increased suicide, according to the NAMI website, "most people with depression or anxiety will be less likely to hurt themselves if they are taking an antidepressant medication." Cohen's opinion is that antidepressants do not cause people to commit suicide. But pharmacists may encounter a situation in which patients with both dysthymic disorder and major depressive disorder start taking antidepressants. They may start getting better in the areas of energy level, appetite, and sleep—which, Cohen said, may now give them the energy to act on suicidal impulses.

Alcohol and drugs are very dangerous for people at risk for suicide, according to the NAMI website. Addiction increases this risk and can worsen other mental illnesses, further increasing the risk. Also, people who are intoxicated or withdrawing from drugs or alcohol may be more impulsive—and impulsiveness can make people more likely to attempt suicide.

Why are pharmacists in a position to help?

"The role of the pharmacist is evolving as the health care system changes. People are thinking of pharmacists more as a clinical resource as opposed to a place that you get pills," said NAMI's Duckworth. "Pharmacists are being given more respect in terms of their capacity to provide resources to our members. They understand medicines really well."

In 2012, mental health medications represented the number two class of drugs in terms of spending, just behind oncology agents. Because medications play an important role in the management of mental illness, pharmacists must use their point of contact to help optimize medication therapy outcomes and manage risks, William M. Ellis, BSPharm, MS, Board of Pharmacy Specialties (BPS) Executive Director, and Maria Llana Posey, PharmD, Board Certified Psychiatric Pharmacist and BPS Board Member, wrote in a guest CEO Blog post on suicide prevention that was published on APhA's pharmacist.com in August 2014.

"As pharmacists continue to pursue provider status at the national level and see the expansion of their services across the country and globally," they wrote, "it is important to realize that part of a comprehensive medication therapy management service includes a plan to help patients with mental illness maximize their therapeutic outcomes."

Tharp, the founder of Pharmacists Preventing Suicides, said the idea was to teach others who would teach others about suicide prevention.

"We hope that state boards and schools of pharmacy [and] pharmacy organizations will all join in and encourage pharmacists to become knowledgeable and trained and active in preventing folks from taking their own life," he said. "That's where we're at, and we hope that the pharmacists of America are there also." For more information, visit the Pharmacists Preventing Suicides website (www.pharmacistspreventingsuicides.com).

Diana Yap, Editorial Director

Suicide in the military and among veterans

People with a history of trauma, such as childhood abuse, automobile accident, or combat experience, are at increased risk for suicide. One reason that suicides are seen in veterans is PTSD, or posttraumatic stress disorder, said Lawrence J. Cohen, PharmD, BCPP, FASHP, FCCP, FCP. In PTSD, a traumatic event is reexperienced in the patient's mind over and over again, like a video clip.

In July 2010, the active duty suicide rate was 22 per 100,000 in the U.S. Army and 24 per 100,000 in the U.S. Marine Corps, compared with 18 per 100,000 among the general population; and a report issued in the spring of 2010 estimated that 18 veterans die by suicide every day, according to the National Alliance on Mental Illness website. In 2011, the U.S. Department of Defense (DoD) established the Defense Suicide Prevention Office (www.suicideoutreach.org), which includes information for patients and caregivers.

Pharmacists' picks of the top OTCs

Pharmacy Today proudly presents APhA's Annual Over-the-Counter Product Survey. Conducted using a scientifically valid methodology, the survey determines those nonprescription products most often recommended by pharmacists in the United States to consumers.

Over a 4-week period beginning July 12, 2014, APhA e-mailed the OTC Product Survey to 12,635 randomly selected practicing community pharmacist recipients of *Pharmacy Today*. Overall, the survey achieved an 8% response rate after the initial invite and two reminder messages.

The survey consisted of eight introductory OTC questions and a series of 89 product categories, for which the recipients were asked to write in approximately how many times per week they had recommended each product. These 89 product categories were divided into three groups of questions, each of which was sent to one-third of participants. The top choices for each category are listed here along with an "other" category that combines products with few responses. The n value given for each category represents the total number of responding pharmacists' recommendations per week.

As initiated with the 2013 survey, results are grouped by organ system or general use of the products. The groupings were derived from the structure of APhA's *Handbook of Nonprescription Drugs*, the definitive source of professional information about OTC products. The *Handbook* is available in the Shop section of pharmacist.com and online at PharmacyLibrary.com.

SURVEY TABLE OF CONTENTS

The n listed is the total number of responding pharmacists' recommendations per week for each product category.

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Pain and fever disorders

Adult headache products
(n = 3,800)

Tylenol 30%
Advil 23%
Aleve 14%
Motrin IB 10%
Excedrin 7%
Ecotrin 3%
Other 14%

Sinus headache products
(n = 1,912)

Advil Cold & Sinus 21%
Sudafed 12 Hour Pressure + Pain 18%
Tylenol Sinus Congestion & Pain 11%
Sudafed PE Pressure + Pain 8%
Excedrin Sinus Headache 7%
Aleve-D Sinus & Cold 7%
Other 28%

Migraine headache products
(n = 2,286)

Aleve 28%
Motrin IB 26%
Excedrin Migraine 19%
Advil Migraine 7%
Bayer Migraine Formula 3%
BeKoool Migraine Soft Gel Sheets 0%
Other 17%

Pediatric analgesics and fever reducers
(n = 2,567)

Children's Tylenol 34%
Children's Motrin 24%
Children's Advil 14%
PediaCare Fever Reducer/Pain Reliever (acetaminophen) 9%
PediaCare Pain Reliever/Fever Reducer IB (ibuprofen) 7%
Little Remedies for Fevers Infant Fever/Pain Reliever 6%
Other 6%

Osteoarthritis pain—Oral products
(n = 3,215)

Aleve 24%
Tylenol 24%
Advil 22%
Motrin IB 14%
Other 16%

Osteoarthritis pain—Topical treatments
(n = 1,416)

Icy Hot 25%
Capzasin-P 20%
ThermaCare Muscle & Joint HeatWraps 19%
Bengay 16%
Aspercreme 15%
Other 6%

Thermal and pain care patches
(n = 769)

Salonpas Pain Relief Patch 32%
ThermaCare HeatWraps 29%
Icy Hot Patch 20%
Bengay Pain Relieving Patch 6%
WellPatch 1%
Other 13%

Bone and joint strengtheners
(n = 1,020)

Osteo Bi-Flex 30%
Cosamin DS 24%
Move Free Advanced 15%
Nature's Bounty Joint Support Complex 11%
Flex-a-min 11%
Arthri-Flex Advantage 1%
Other 7%

Pain with sleeplessness products
(n = 1,091)

Tylenol PM 45%
Advil PM 24%
Unisom PM Pain 10%
Motrin PM 7%
Excedrin PM 4%
Other 10%

Reproductive and genital disorders

Vaginal yeast infection treatments
(n = 592)

Monistat 81%
Vagistat 9%
Other 10%

Menstrual pain treatments
(n = 943)

Midol 22%
Advil 22%
Pamprin 17%
Aleve 13%
ThermaCare HeatWraps 11%
Motrin IB 9%
Other 7%

Respiratory disorders

Adult antihistamines
(n = 2,632)

Zyrtec 28%
Claritin 22%
Benadryl 19%
Allegra 17%
Chlor-Trimeton 6%
Alavert 2%
Other 7%

Adult cold—Liquid products
(n = 1,170)

Mucinex Cold, Flu & Sore Throat ... 24%
Tylenol Cold Multi-Symptom (Daytime) 16%
NyQuil 16%
Theraflu 14%
DayQuil 13%
Robitussin Peak Cold Multi-Symptom Cold 10%
Other 7%

Adult multisymptom cold or flu products
(n = 1,511)

Mucinex D 30%
Coricidin HBP Cold & Flu 21%
DayQuil Cold & Flu Multi-Symptom Relief 17%
Tylenol Cold Multi-Symptom (Daytime) 11%
Robitussin Peak Cold Multi-Symptom Cold 7%
Mucinex Fast-Max 4%
Other 11%

The n listed is the total number of responding pharmacists' recommendations per week for each product category. These data may not be used without the prior permission of the American Pharmacists Association.

Adult multisymptom cold or flu products—Nighttime
(n = 1,220)

NyQuil 23%
Tylenol Cold Multi-Symptom (Nighttime) 20%
Theraflu Nighttime Severe Cold & Cough 14%
Sudafed PE Day + Night Congestion ... 12%
Robitussin Peak Cold Nighttime Multi-Symptom Cold 12%
Alka-Seltzer Plus 10%
Other 9%

Adult multisymptom allergy and hay fever products
(n = 2,128)

Claritin-D 32%
Zyrtec-D 26%
Allegra-D 16%
Advil Allergy & Congestion Relief 6%
Advil Allergy Sinus 4%
Other 15%

Adult decongestants
(n = 1,390)

Sudafed 64%
Sudafed PE 22%
Other 15%

Adult topical decongestants
(n = 751)

Afrin 49%
Mucinex Sinus-Max Nasal Spray 13%
Neo-Synephrine 10%
Vicks VapoInhaler 10%
Vicks Sinex 12-Hour Decongestant Nasal Spray 5%
Sinol All-Natural Nasal Spray 1%
Other 12%

Pediatric antihistamines
(n = 1,299)

Children's Claritin Allergy 38%
Children's Benadryl Allergy 33%
Children's Allegra Allergy 10%
PediaCare Allergy 4%
Hyland's 4 Kids Complete Allergy 2%
Kids Relief Allergy 0%
Other 13%

Pediatric decongestants
(n = 598)

Children's Sudafed Nasal Decongestant Liquid 31%
Children's Mucinex Stuffy Nose & Cold 24%
Little Remedies for Noses Decongestant Nose Drops 22%
Triaminic Chest & Nasal Congestion 17%
Other 6%

Pediatric multisymptom cold, flu, or allergy products
(n = 935)

Children's Dimetapp 25%
Children's Mucinex 25%
Children's Triaminic 16%
Children's Robitussin Cough & Cold CF 16%
Children's Robitussin Cough & Cold Long-Acting 11%
Other 8%

Zinc-containing cold products
(n = 583)

Cold-Eeze 38%
Zicam Cold Remedy 28%
Airborne 22%
Halls Defense Harvest Cherry 11%
Other 2%

Nasal decongestants—Saline
(n = 1,120)

Ocean 41%
Simply Saline 21%
Ayr 15%
Little Remedies for Noses Saline 10%
Rhinaris 2%
Other 12%

Nasal irrigation systems
(n = 1,066)

Simply Saline 52%
NasaFlo Neti Pot 12%
SinuCleanse 8%
NasalCare 2%
Alkalol 2%
Rhinaris 2%
Other 21%

Adult antitussives—Dextromethorphan
(n = 1,573)

Delsym 41%
Mucinex DM 39%
Robitussin Lingering Cold Long-Acting Cough 7%
DayQuil Cough 5%
Vicks Nature Fusion Cough 2%
Vicks Formula 44 Custom Care Dry Cough Suppressant 1%
Other 5%

Adult expectorants
(n = 1,162)

Mucinex/Mucinex D/Mucinex DM ... 70%
Robitussin Peak Cold Cough + Chest Congestion DM 20%
Vicks Formula 44 Custom Care Chesty Cough 1%
Other 9%

Pediatric cough antitussives
(n = 1,146)

Delsym Children's 30%
Children's Mucinex Cough 25%
Children's Dimetapp Long Acting Cough Plus Cold 14%
Children's Robitussin Cough 14%
Children's Triaminic 8%
PediaCare Cough & Congestion 7%
Other 2%

Diabetic cough products
(n = 572)

Diabetic Tussin 71%
Robitussin Peak Cold Sugar-Free 12%
Safe Tussin 10%
Scot-Tussin 3%
Other 4%

Gastrointestinal disorders

Episodic heartburn treatments
(n = 2,218)

Zantac 22%
Pepcid AC 16%
Tums 15%
Maalox 13%
Mylanta 12%
Gaviscon 9%

The n listed is the total number of responding pharmacists' recommendations per week for each product category.

Pepcid Complete 7%
Other 7%

Frequent heartburn treatments
(n = 1,438)

Prilosec OTC 53%
Nexium 24HR 19%
Prevacid 24HR 14%
Zegerid OTC 3%
Other 10%

Antigas products
(n = 1,805)

Gas-X 36%
Infants' Mylicon Drops 19%
Mylanta Gas Maximum Strength 10%
Maalox Advanced 10%
Phazyme 7%
Beano 5%
Little Remedies for Tummys Gas Relief Drops 4%
PediaCare Gas Relief Drops 3%
Other 6%

Laxatives—Fiber (n = 1,646)

Metamucil 28%
Benefiber 20%
FiberCon 14%
Citrucel with SmartFiber 13%
Fiber Choice 11%
Fiber Smart 7%
Other 7%

Laxatives—Nonfiber (n = 1,901)

MiraLax 34%
Dulcolax 24%
Senokot 19%
Fleet 7%
Peri-Colace 7%
Ex-Lax 1%
Other 9%

Fiber supplements
(n = 777)

Metamucil 37%
Benefiber 30%
FiberCon 18%
Citrucel with SmartFiber 5%
Fiber Choice 5%
Other 5%

Stool softeners
(n = 1,697)

Colace 59%
Dulcolax Stool Softener 18%
Surfak Stool Softener 4%
Phillips' Stool Softener 2%
Other 17%

Antidiarrheal products
(n = 1,385)

Imodium A-D 61%
Pepto-Bismol 18%
Kaopectate 8%
Imodium Multi-Symptom Relief 7%
Other 6%

Hemorrhoidal treatments
(n = 890)

Preparation H 60%
Tucks 24%
Nupercainal 14%
Other 2%

Upset stomach and nausea treatments
(n = 1,176)

Emetrol 26%
Pepto-Bismol 22%
Tums 16%
Mylanta 14%
Maalox Multi-Action 9%
Gaviscon 5%
Other 8%

Motion sickness remedies
(n = 1,064)

Dramamine Less Drowsy (meclizine) 38%
Dramamine (dimenhydrinate) 26%
Bonine 25%
Sea-Band 6%
Other 4%

Nutrition and nutritional supplementation

Adult multivitamins
(n = 2,456)

Centrum 34%
One A Day 18%
Nature's Bounty 17%
Nature Made 15%
Vitafusion MultiVites 3%
Alive! Multi-Vitamin Adult Gummies 2%
Other 10%

Iron supplements
(n = 546)

Feosol 50%
Ferro-Sequels 16%
Vitron-C 10%
Pur-Absorb 1%
Other 23%

Calcium supplements
(n = 1,522)

Citracal 33%
Tums 22%
Caltrate 17%
Os-Cal 13%
Viactiv 3%
Vitafusion Calcium Gummy 2%
Other 9%

Children's multivitamins
(n = 1,025)

Poly-Vi-Sol 27%
Centrum Kids 25%
Flintstones 25%
One A Day Kids 7%
L'il Critters Gummy Vites 6%
Other 10%

Probiotic dietary supplements
(n = 1,561)

Culturelle 22%
Florastor 20%
Align 16%
Lactinex 15%
Phillips' Colon Health 10%
TruBiotics 9%
Other 8%

Infant formulas
(n = 189)

Enfamil 37%
Similac 24%
ProSobee 18%
Gerber Good Start 13%
Isomil 7%
Other 1%

The n listed is the total number of responding pharmacists' recommendations per week for each product category.

Diet aids
(n = 347)

Slim-Fast 22%
Alli 20%
Dexatrim 5%
Hydroxycut 4%
Xenadrine 1%
QuickTrim Extreme Burn 0%
Other 49%

Ophthalmic, otic, and oral disorders

Artificial tears
(n = 1,549)

Systane 28%
Refresh Tears 25%
Tears Naturale 16%
GenTeal 15%
Blink Tears 9%
Visine Tears Dry Eye Relief 4%
Other 3%

Eye washes
(n = 474)

Bausch & Lomb Advanced Eye Relief 49%
Collyrium for Fresh Eyes 30%
OcuFresh 12%
Other 9%

Ocular nutritional supplements
(n = 620)

Ocuvite 37%
PreserVision 26%
I-Caps 19%
OcuGuard Plus 1%
MaxiVision 0%
Other 17%

Allergy ophthalmic drops
(n = 1,369)

Zaditor 37%
Naphcon-A 18%
Visine-A 17%
Opcon-A 13%
Alaway 11%
Other 4%

Ophthalmic vasoconstrictors and decongestants
(n = 513)

Visine 46%
Clear Eyes 25%
Bausch + Lomb Advanced Eye Relief Redness 15%
Other 14%

Contact lens saline solutions
(n = 720)

Bausch & Lomb Sensitive Eyes Plus Saline Solution 34%
Opti-Free Replenish Contact Lens Solution 26%
Simply Saline Sterile Saline Solution for Contact Lenses 18%
Renu Sensitive Multi-Purpose Solution 12%
Unisol 4 Saline Solution 5%
Clear Care Cleaning & Disinfecting Solution 3%
Other 3%

Earwax removal products
(n = 744)

Debrox Earwax Removal Aid 74%
Murine Ear Wax Removal System 13%
Auro Earwax Removal Aid 5%
Similasan Ear Wax Relief 4%
Mack's ProRinse Earwax Removal System 1%
Other 4%

Tooth whitening systems
(n = 380)

Rembrandt Deeply White 2 Hour Whitening Kit 41%
Crest 3D White Whitestrips 38%
Aquafresh White Trays 14%
Plus White 5 Minute Speed Whitening System 2%
Dazzling White Professional Strength Whitening Pen 1%
Luster Pro Light 1%
Other 4%

Canker sore treatments
(n = 1,289)

Orajel for Canker Sores 25%
Gly-Oxide 21%
Anbesol 17%
Zilactin-B 16%
Colgate Orabase 12%
Kank-A Mouth Pain Liquid 5%
Other 5%

Cold sore treatments
(n = 1,186)

Abreva 60%
Orajel for All Mouth Sores 13%
Carmex 13%
Herpecin L 7%
Anbesol Cold Sore Therapy 3%
Zilactin 2%
Other 2%

Artificial saliva
(n = 563)

Biotene Oral Balance 63%
Oasis Dry Mouth Moisturizing Spray 9%
ACT Dry Mouth Lozenges 9%
Salivart 8%
Stoppers 4 Dry Mouth Spray 1%
Other 10%

Lip balms
(n = 1,031)

Carmex 28%
Blistex 19%
ChapStick 17%
Burt's Bees 11%
Neutrogena Lip Moisturizer SPF 15 ..... 11%
Vaseline Lip Therapy 10%
Other 5%

Dermatologic disorders

Itch associated with dry skin—Lotions and creams
(n = 1,788)

Eucerin 27%
AmLactin 19%
Aveeno 16%
Sarna 15%
CeraVe 11%
Gold Bond Medicated Body Lotion 8%
Other 5%

The n listed is the total number of responding pharmacists' recommendations per week for each product category.

Therapeutic skin care products
(n = 1,477)

Eucerin	**26%**
Aquaphor	21%
Aveeno	16%
Cetaphil	15%
AmLactin	11%
Lubriderm	9%
Other	3%

Moisturizing creams
(n = 1,544)

Eucerin	**28%**
Cetaphil	23%
AmLactin	15%
Lubriderm	13%
Aveeno	9%
Vaseline	6%
Other	7%

Poison ivy or oak remedies
(n = 1,733)

Cortizone-10	**32%**
Benadryl Cream/Spray	14%
Caladryl	11%
Zanfel	11%
Aveeno	9%
Ivy-Dry	8%
Cortaid	8%
Other	8%

Diaper rash treatments
(n = 1,149)

A+D Diaper Rash Cream	**41%**
Desitin Maximum Strength Original Paste	24%
Triple Paste Medicated Ointment	11%
Boudreaux's Butt Paste	10%
Balmex Diaper Rash Cream	6%
Aveeno Baby Soothing Relief Diaper Rash Cream	3%
Other	4%

Insect bite or sting remedies—Lotions and creams
(n = 2,327)

Cortizone-10	**26%**
Benadryl Itch Stopping Cream	20%
After Bite	14%
Caladryl	13%
Cortaid	11%
Aveeno Anti-Itch	8%
Other	8%

Head lice treatments
(n = 958)

Nix	**59%**
Rid	35%
LiceMD	2%
Licefreee!	1%
Quit Nits	0%
Vamousse Lice Treatment	0%
Other	3%

Minor burn and sunburn treatments
(n = 1,008)

Solarcaine	**31%**
Dermoplast	24%
A+D Original Ointment	15%
Bactine	8%
Lanacane	5%
Other	17%

Topical antibiotic ointments and creams
(n = 1,378)

Neosporin	**61%**
Bacitracin	18%
Polysporin	14%
Other	7%

Athlete's foot remedies
(n = 1,070)

Lotrimin AF	**33%**
Lamisil AT	31%
Lotrimin Ultra	12%
Tinactin	8%
Zeasorb Athlete's Foot	7%
Desenex Antifungal Powder	3%
Other	6%

Nail antifungal treatments
(n = 330)

Fungi-Nail	**42%**
Fungoid Tincture	18%
FungiCure	14%
Dr. Scholl's Fungal Nail Management Kit	12%
Kerasal Nail Fungal Nail Renewal Treatment	7%
Mycocide NS	3%
Other	3%

Jock itch products
(n = 981)

Lotrimin AF	**41%**
Lamisil AT	27%
Tinactin	9%
Zeasorb Jock Itch	7%
Other	17%

Wart removal products
(n = 1,025)

Compound W Freeze Off	**30%**
DuoFilm	21%
Dr. Scholl's Freeze Away	21%
Curad Mediplast	16%
Wartner	10%
Other	2%

General foot care products
(n = 683)

Dr. Scholl's	**39%**
Gold Bond	21%
Kerasal	17%
Zim's Crack Creme	10%
Flexitol Heel Balm	6%
Miracle Foot Repair Cream	3%
Other	4%

Other medical disorders

Oral glucose gels
(n = 270)

Insta-Glucose	**32%**
Dex4	23%
Glutose	12%
GlucoBurst	4%
Other	29%

Diabetic foot creams
(n = 386)

Eucerin	**47%**
DiabetiDerm	16%
Zim's Crack Creme	13%
Zostrix Diabetic Foot Pain Relieving Cream	12%
Kerasal	6%
TriDerma Diabetic Foot Defense Healing Cream	2%
Flexitol	0%

The n listed is the total number of responding pharmacists' recommendations per week for each product category.

Other 4%

Aspirin for cardioprotection
(n = 1,775)

Bayer 46%
Ecotrin 17%
St. Joseph 6%
Bufferin 1%
Other 30%

Sleep aids
(n = 956)

Unisom SleepGels (diphenhydramine) 18%
Unisom SleepTabs (doxylamine) 16%
Sominex 10%
ZzzQuil 9%
Nytol QuickCaps 2%
MidNite 1%
Other 44%

Antisnoring products
(n = 419)

Breathe Right Nasal Strips 91%
SnoreStop 5%
Other 4%

Smoking cessation products
(n = 455)

NicoDerm CQ 53%
Nicorette Gum 39%
Habitrol Nicotine Transdermal System 5%
Other 4%

Home medical equipment and tests

Home ovulation tests
(n = 333)

First Response Ovulation Test 39%
Clearblue Ovulation Test 26%
Answer Ovulation Test 22%
Accu-Clear Early Ovulation Predictor . 3%
Nexcare Basal Digital Thermometer ... 2%
Other 8%

Home cholesterol tests
(n = 190)

CholesTrak 70%
First Check Cholesterol Home Test ... 16%
CheckUp America Cholesterol Panel... 2%
Q.Steps Cholesterol BioMeter 1%
Other 13%

Diabetes management monitors
(n = 1,240)

OneTouch 33%
FreeStyle 21%
Accu-Chek 19%
Bayer Contour USB 10%
Bayer A1CNow 1%
iBGStar 0%
Other 16%

Digital thermometers
(n = 435)

BD Digital Thermometer 43%
Braun ThermoScan Ear Thermometer.. 19%
Vicks Digital Thermometer 17%
Omron Digital Thermometer 12%
Exergen Comfort Scanner Temporal Thermometer 4%
Other 4%

Home pregnancy tests
(n = 354)

e.p.t. 39%
First Response 39%
Clearblue 10%
Answer 4%
Fact Plus 2%
Other 7%

Home blood pressure monitors
(n = 463)

Omron 71%
LifeSource 8%
HoMedics 6%
Other 15%

Urinary tract infection tests
(n = 230)

AZO Test Strips 71%
Uristat UTI Test Strips 20%
VH Essentials UTI Home Test 5%
Other 4%

Incontinence products
(n = 466)

Depend 58%
Poise 15%
Tena Serenity 8%
Attends 7%
Other 13%

Complementary therapies

Flaxseed oil supplements
(n = 333)

Nature Made 55%
Nature's Bounty 19%
Nature's Way 11%
Sundown Naturals 7%
21st Century Flax Seeds 5%
Other 4%

Garlic supplements
(n = 410)

Nature's Bounty 34%
Nature Made 18%
Garlique 10%
Sundown Naturals 5%
Nature's Way 3%
Kyolic 3%
Other 27%

Omega-3/fish oil supplements
(n = 799)

Nature's Bounty 27%
Nature Made 21%
MegaRed 21%
Mason 4%
Sundown Naturals 4%
21st Century 2%
Nordic Naturals 2%
Other 19%

The n listed is the total number of responding pharmacists' recommendations per week for each product category.

Nicotine: Progress stalled, threats loom

CARL LABBE

Nicotine has always been a tough addiction to break, but tobacco opponents had one reliable strategy: get young people not to take up the habit. Today, with an explosion in devices for getting the drug into the body—especially the popular electronic cigarettes that mimic smoking so well—pharmacists and other health professionals must seek new and different ways of countering both advertising strategies and peer pressure when it comes to producing progress in stalled tobacco use rates.

Some professionals—and even the American Heart Association—are turning to e-cigarettes as the answer when other methods of getting people off tobacco don't work. With the safety of these new devices unclear, not everyone is on board with that approach.

"It's frustrating to start somebody on effective cessation therapy only to lose them to the e-cig marketplace," Karla Lodge, a physician assistant in the Phoenix area, told ***Pharmacy Today***. "Competent providers know that long-term success is much more likely when there is lasting behavior modification that results in a patient [who] is no longer dependent on nicotine."

Pharmacists are undoubtedly well positioned to help people stop using tobacco and nicotine, with high visibility, trust, and availability of nonprescription options. It takes some effort, though, and perseverance.

all the new nicotine delivery systems. E-cigarettes, vapor devices, strips, orbs, and snus are all marketed as cleaner versions of tobacco products and even hailed by some as tools for smoking cessation.

"It's frustrating to start somebody **on effective cessation therapy only to lose them** to the e-cig marketplace."

Nicotine as you like it

Smoking rates are at historic lows but are stalled after decades of decline. The explosion in availability of nicotine-delivery systems—and their popularity among teenagers and young adults, as reported in the 2013 National Youth Tobacco Survey[1]—suggests the need for prescription and OTC cessation products won't subside any time soon.

Constant vigilance and continuing education are required for pharmacists to maintain their credibility regarding

How you can help

Nicotine replacement therapy (NRT) products have been available for more than 30 years. The products produce higher quit rates than many other cessation techniques, are safe to use without a prescription, and are readily available to consumers.

Used as monotherapy or in combination, OTC nicotine patches, gum, and lozenges can triple quit rates, compared with placebo, according to the new edition of APhA's *Handbook of Nonprescription Drugs* (www.PharmacyLibrary.com). While about 14% of patients can achieve smoking abstinence with placebo, rates jump to 19% with gum, 23% with lozenges, and 27% with patches. Combining the patches with nonprescription gum or lozenges, or with prescription nicotine inhalers, enables 37% of patients to quit.

If NRT products are designed to put nicotine into patients' circulation, can the same end result be achieved through use of vaporized nicotine? Most health-related professional organizations, including APhA, want to see more research. The American Heart Association encourages "clinicians to use proven smoking cessation strategies as the first line of treatment for any patient," but "when repeated efforts with conventional treatment fail, [are] intolerant, or rejected by a patient, clinicians may support the patient's attempt to quit using e-cigarettes."[2]

The American Lung Association (ALA) takes a different tack. Even though 51 years have passed since smoking was linked to lung cancer by the U.S. Surgeon General, nearly half a million Americans die from smoking-related causes each year, and the habit costs society $333 billion for health care and lost productivity, ALA said. In calling for action by the federal government, the association emphasized the following three goals for the nation as a whole:

- Reduce smoking rates, currently at about 18%, to less than 10% by 2024.
- Protect all Americans from secondhand smoke by 2019.
- Ultimately eliminate the death and disease caused by tobacco use.

HIGHLIGHTS

- Nicotine replacement therapy products produce higher quit rates than many other techniques, are safe to use without a prescription, and are readily available to consumers.
- Most health-related professional groups, including APhA, want to see more research on e-cigarettes.

Old drug offers new option

Thanks to a recent article in the *New England Journal of Medicine*,[3] pharmacists may be getting questions about a plant extract from Eastern Europe, cytisine, for smoking cessation. Chemically similar to nicotine and varenicline, cytosine is currently manufactured as Tabex by a Bulgarian company, Sopharma, and marketed in Europe.

Compared with 8 weeks of NRT in 1,310 smokers, cytosine administered orally for 25 days produced significantly higher quit rates: 40% versus 31%. Adverse effects were more common in the cytisine group and included gastrointestinal problems and sleep disturbances.

Earlier studies have shown similar short-term results with cytisine, and one study stated a 12-month quit rate for cytisine as 8.4% versus 2.4% for NRT. Most of these studies provided minimal behavioral counseling.

Tabex is being shipped into the United States and is currently unregulated by FDA.

Another new tool would enable personalization of therapy by identifying slow metabolizers of nicotine. Slow metabolizers achieve higher quit rates with NRT patches, a Pfizer-sponsored study of 1,200 smokers showed, while normal metabolizers responded better to varenicline.

References

1. MMWR. 2014;63(45):1021
2. http://blog.heart.org/top-ten-things-to-know-aha-e-cigarette-policy-statement/
3. N Engl J Med. 2014; 371:2353–62

Carl Labbe, BSPharm, contributing writer

APhA policy on the use and sale of electronic cigarettes (e-cigarettes) (2014)

1. APhA opposes the sale of e-cigarettes and other vaporized nicotine products in pharmacies until such time that scientific data support the health and environmental safety of these products.
2. APhA opposes the use of e-cigarettes and other vaporized nicotine products in areas subject to current clean air regulations for combustible tobacco products until such time that scientific data support the health and environmental safety of these products.
3. APhA urges pharmacists to become more knowledgeable about e-cigarettes and other vaporized nicotine products.
4. APhA urges FDA to require the full disclosure of all ingredients in e-cigarettes and other vaporized nicotine products in both the pre-use and vapor states.

Source: J Am Pharm Assoc. 2014;54:358

Gray area: OTC use in pregnancy, lactation

L. MICHAEL POSEY

Now that FDA has moved to create better information about use of prescription agents during pregnancy and breastfeeding, what can be done for OTC products?

That is a question Rachel Katz–Galatt, MBA, is addressing on her own. Founder of the Healthy Mama line that is now expanding into several traditional chains and big-box stores, Katz–Galatt had questions during her first pregnancy about treating a common ailment. When she saw how confusing the available information about such a simple question could be, an obvious solution came to mind.

Question marks

Relying on the ABCDX system now retired by FDA (see page 30 of the January 2015 ***Pharmacy Today***), Appendix 1 in the new edition of APhA's *Handbook of Nonprescription Drugs* (available at PharmacyLibrary.com) provides a pregnancy risk category rating for six pages of common OTC medications. It is striking in its lack of As and Xs: doxylamine gets an A, along with several vitamins; the only X listed is for large amounts of ethanol used for prolonged periods.

The rest of the products get ratings of B, C, or D, meaning that the risks and benefits must be assessed for specific patients. "Medications should be used during pregnancy only under the supervision of a physician and only when the potential benefits outweigh the potential risks," *Handbook* editors wrote.

In Appendix 2, a few natural products are rated X: juniper tea, red rice yeast, and saw palmetto. Many other products are "not recommended" based on lack of data or indicators of problems in limited studies.

The information for the two appendices is compiled from manufacturers' recommendations, textbooks, and drug information compendia.

Confusion—and a wrong choice

When Katz–Galatt experienced symptoms one weekend, she did what every pregnant patient is supposed to do. "I called my doctor," Katz–Galatt recalled. "She didn't get back to me. I went online and found all kinds of conflicting information. I was astounded."

Living in Manhattan just above a pharmacy, Katz–Galatt thought that surely the pharmacist would know what she could take. Instead of a clear answer, though, Katz–Galatt got a confusing answer about the antiquated pregnancy risk ratings. She and her husband ended up "going up and down the aisles looking at labels."

"Why isn't there a section in retail **that only contains products pregnant** and breastfeeding women can **use safely?**"

That's when "the light went on." Katz–Galatt translated her 18 years in brand development to verbalize a simple idea: "Why isn't there a section in retail that only contains products pregnant and breastfeeding women can use safely?"

Through Healthy Mama, Katz–Galatt is intent on creating that new section, one that busy health professionals can point patients toward. She and her husband picked an unsafe medication that day in New York. She wants to help women avoid such errors—and the anxiety and angst that accompanied the situation.

MORE ONLINE

- More information about Healthy Mama: www.healthymamabrand.com
- Management of the pregnant patient, in the *Handbook of Nonprescription Drugs, 18th ed.*, Chapter 2: PharmacyLibrary.com

Engaging pharmacists

In addition to enabling the creation of a prenatal section in pharmacies, Katz–Galatt wants to educate pharmacists, obstetricians–gynecologists, midwives, and other health professionals about what they can tell pregnant and breastfeeding patients. "I want to simplify the experience for other women," she said. "Women who gave birth 5 years ago have told me, 'God, I wish this brand had been available. I was so uncomfortable, but I didn't know that I could take anything.'"

Katz–Galatt is also looking at ways to generate better information about use of nonprescription medications and nutritional products during pregnancy and breastfeeding. If successful, the results will be finding ways for professionals and patients "to make sure that women have the information they need at their fingertips."

Healthy, full-term pregnancies

While not clearly linked to her wrong medication choice, Katz–Galatt delivered her first daughter early—very early. That has given her and her company a central mission: helping women have healthy, full-term pregnancies.

"I delivered my first daughter at a mere 24 weeks, so we're very tied in with the March of Dimes to create and provide education to women so they don't experience the plight I experienced," Katz–Gatall said. "If I can help one woman—one woman—I'll feel like I've done something amazing."

L. Michael Posey, BSPharm, MA, Editor

Infections and infestations	bronchitis, gastroenteritis, gastroenteritis viral, influenza, nasopharyngitis, sinusitis, urinary tract infection
Injury, poisoning and procedural complications	fall, muscle strain
Metabolism and nutrition disorders	decreased appetite
Musculoskeletal and connective tissue disorders	arthralgia, back pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity
Nervous system disorders	lethargy, migraine, sedation
Psychiatric disorders	anxiety, depression, insomnia
Respiratory, thoracic and mediastinal disorders	cough, nasal congestion, oropharyngeal pain
Skin and subcutaneous tissue disorders	hyperhidrosis, pruritus, rash
Vascular disorders	hot flush, hypertension

Other less common adverse reactions that were seen in <1% of the patients in the HYSINGLA ER chronic pain clinical trials include the following in alphabetical order: abdominal discomfort, abdominal distention, agitation, asthenia, choking, confusional state, depressed mood, drug hypersensitivity, drug withdrawal syndrome, dysphagia, dyspnea, esophageal obstruction, flushing, hypogonadism, hypotension, hypoxia, irritability, libido decreased, malaise, mental impairment, mood altered, muscle twitching, edema, orthostatic hypotension, palpitations, presyncope, retching, syncope, thinking abnormal, thirst, tremor, and urinary retention.

7 DRUG INTERACTIONS **7.1 Drugs Affecting Cytochrome P450 Isoenzymes** *Inhibitors of CYP3A4* Co-administration of HYSINGLA ER with ketoconazole, a strong CYP3A4 inhibitor, significantly increased the plasma concentrations of hydrocodone. Inhibition of CYP3A4 activity by inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. Caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*. *Inducers of CYP3A4* CYP3A4 inducers may induce the metabolism of hydrocodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration with HYSINGLA ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*. **7.2 Central Nervous System Depressants** The concomitant use of HYSINGLA ER with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and HYSINGLA ER for signs of respiratory depression, sedation and hypotension. When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Warnings and Precautions (5.4)]*. **7.3 Interactions with Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics** Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist analgesics (buprenorphine) may reduce the analgesic effect of HYSINGLA ER or precipitate withdrawal symptoms in these patients. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving HYSINGLA ER. **7.4 MAO Inhibitors** HYSINGLA ER is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between hydrocodone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate. **7.5 Anticholinergics** Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention and constipation in addition to respiratory and central nervous system depression when HYSINGLA ER is used concurrently with anticholinergic drugs. **7.6 Strong Laxatives** Concomitant use of HYSINGLA ER with strong laxatives (e.g., lactulose), that rapidly increase gastrointestinal motility, may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. If HYSINGLA ER is used in these patients, closely monitor for the development of adverse events as well as changing analgesic requirements.

8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** *Pregnancy Category C Risk Summary* There are no adequate and well-controlled studies of HYSINGLA ER use during pregnancy. Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. In animal reproduction studies with hydrocodone in rats and rabbits no embryotoxicity or teratogenicity was observed. However, reduced pup survival rates, reduced fetal/pup body weights, and delayed ossification were observed at doses causing maternal toxicity. In all of the studies conducted, the exposures in animals were less than the human exposure (see Animal Data). HYSINGLA ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Clinical Considerations* Fetal/neonatal adverse reactions Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*. *Data* Animal Data No evidence of embryotoxicity or teratogenicity was observed after oral administration of hydrocodone throughout the period of organogenesis in rats and rabbits at doses up to 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). However, in these studies, reduced fetal body weights and delayed ossification were observed in rat at 30 mg/kg/day and reduced fetal body weights were observed in in rabbit at 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). In a pre- and post-natal development study pregnant rats were administered oral hydrocodone throughout the period of gestation and lactation. At a dose of 30 mg/kg/day decreased pup viability, pup survival indices, litter size and pup body weight were observed. This dose is approximately 0.1-fold the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons. **8.2 Labor and Delivery** Opioids cross the placenta and may produce respiratory depression in neonates. HYSINGLA ER is not recommended for use in women immediately prior to and during labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. HYSINGLA ER may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. **8.3 Nursing Mothers** Hydrocodone is present in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue HYSINGLA ER, taking into account the importance of the drug to the mother. Infants exposed to HYSINGLA ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped. **8.4 Pediatric Use** The safety and effectiveness of HYSINGLA ER in pediatric patients have not been established. Accidental ingestion of a single dose of HYSINGLA ER in children can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*. HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) when exposed to water or other fluids. Pediatric patients may be at increased risk of esophageal obstruction, dysphagia, and choking because of a smaller gastrointestinal lumen if they ingest HYSINGLA ER *[see Warnings and Precautions (5.9)]*. **8.5 Geriatric Use** In a controlled pharmacokinetic study, elderly subjects (greater than 65 years) compared to young adults had similar plasma concentrations of hydrocodone *[see Clinical Pharmacology (12.3)]*. Of the 1827 subjects exposed to HYSINGLA ER in the pooled chronic pain studies, 241 (13%) were age 65 and older (including those age 75 and older), while 42 (2%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received HYSINGLA ER. Hydrocodone may cause confusion and oversedation in the elderly. In addition, because of the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease and concomitant use of CNS active medications, start elderly patients on low doses of HYSINGLA ER and monitor closely for adverse events such as respiratory depression, sedation, and confusion. **8.6 Hepatic Impairment** No adjustment in starting dose with HYSINGLA ER is required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*. **8.7 Renal Impairment** No dose adjustment is needed in patients with mild renal impairment. Patients with moderate or severe renal impairment or end stage renal disease have higher plasma concentrations than those with normal renal function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in these patients and monitor closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE **9.1 Controlled Substance** HYSINGLA ER contains hydrocodone bitartrate, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, abuse, addiction and criminal diversion. The high drug content in the extended-release formulation adds to the risk of adverse outcomes from abuse and misuse. **9.2 Abuse** All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get "high," or the use of steroids for performance enhancement and muscle build up. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal. "Drug-seeking" behavior is very common to addicts and drug abusers. Drug seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers, people with untreated addiction, and criminals seeking drugs to sell. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction. HYSINGLA ER can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by law, is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs. Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk is increased with concurrent use of HYSINGLA ER with alcohol or other central nervous system depressants. *Risks Specific to Abuse of HYSINGLA ER* HYSINGLA ER is for oral use only. Abuse of HYSINGLA ER poses a risk of overdose and death.. Taking cut, broken, chewed, crushed, or dissolved HYSINGLA ER increases the risk of overdose and death. With parenteral abuse, the inactive ingredients in HYSINGLA ER can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV. Abuse Deterrence Studies *Summary* The *in vitro* data demonstrate that HYSINGLA ER has physical and chemical properties that are expected to deter intranasal and intravenous abuse. The data from the clinical abuse potential studies, along with support from the *in vitro* data, also indicate that HYSINGLA ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed. However, abuse of HYSINGLA ER by the intravenous, intranasal, and oral routes is still possible. Additional data, including epidemiological data, when available, may provide further information on the impact of HYSINGLA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate. HYSINGLA ER contains hydrocodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, addiction, and criminal diversion *[See Warnings and Precautions (5.1) and Drug Abuse and Dependence (9)]*. **9.3 Dependence** Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects. Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. HYSINGLA ER should be discontinued by a gradual downward titration *[see Dosage and Administration (2.6)]*. If HYSINGLA ER is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate. Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.3)]*.

10 OVERDOSAGE **10.1 Symptoms** Acute overdosage with opioids is often characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, pulmonary edema, bradycardia, hypotension, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. **10.2 Treatment** In the treatment of HYSINGLA ER overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression that may result from opioid overdosage. Nalmefene is an alternative opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of HYSINGLA ER may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling, as needed, to maintain adequate respiration. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on HYSINGLA ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

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U.S. Patent Numbers: 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

This brief summary is based on Hysingla ER Prescribing Information 303511-0B, Revised 11/2014 (A)

Pharmacist license revocation reversed

DAVID B. BRUSHWOOD

Regulatory agencies require pharmacists to follow specific rules as a condition of licensure. Likewise, these agencies are required to follow specific rules when they take action against a pharmacist's license. A court in Rhode Island recently held that a state agency had violated procedural rules in revoking a pharmacist's license on the basis of an inadvertent error.

HIGHLIGHTS

- Inadvertent error does not justify license revocation.
- Pharmacy errors are a part of the learning process for pharmacists.

Background

While compounding an oral liquid preparation for an infant, the pharmacist mistakenly adulterated the preparation with morphine instead of a flavoring that had a similar color and packaging. The patient became lethargic, and the compounding error was discovered after the patient was hospitalized. The patient's mother submitted a complaint to the Board of Pharmacy.

Investigators determined that the pharmacy compounding area was "very cluttered and disorganized" and that the error was caused by "not quarantining inactives and active ingredients." They explained that when ingredients similar in appearance and packaging are placed next to each other, there exists "a definite concern of a mix-up or switch."

The pharmacist's license was placed on suspension. A hearing officer was selected to hear evidence and to recommend an appropriate permanent punishment. The hearing officer recommended that the pharmacist be given a 30-month license suspension with 15 months stayed, and a 2-year probationary period with continuing education included.

The Director of the State Department of Health rejected this recommendation and revoked the pharmacist's license. From this revocation the pharmacist appealed to a court.

Rationale

The reviewing court noted that "where a hearing officer is able to examine evidence and live testimony firsthand, the law accords more weight to his or her findings than to a reviewing administrative official who does not hear such testimonial evidence." The court took issue with the Director's conclusion that the hearing officer had not considered the seriousness of the error, and that the pharmacist had not agreed to implement remedial measures to prevent future errors of the same kind. In fact, the hearing officer had noted the seriousness of the error, and the pharmacist had agreed to adopt remedial measures.

The court commented that "pharmacists **cannot be held to a standard** of perfection."

The court noted that the hearing officer "sought to impose a sanction commensurate with past discipline and the severity of the violations." However, "in contrast, the Director, for the first time in Rhode Island's history, revoked a pharmacist's license for a dispensing error."

The court commented that "pharmacists cannot be held to a standard of perfection" and that "dispensing errors do occur and are expected to be a part of the learning process for a pharmacist." The court commented also that "the distinction between intentional and unintentional conduct is absolutely relevant to the severity of the sanction."

The court ruled that the Director had "acted in excess of his statutory authority and abused his discretion in revoking [the pharmacist's] license to practice pharmacy." Because the pharmacist's license had been suspended for 33 months since the error occurred, the court ordered that his license "be immediately reinstated, and the two-year probationary period with continuing education classes shall commence forthwith."

Discussion

Inadvertent pharmacy errors are significant, and they warrant administrative discipline geared toward quality improvement. On the other hand, if the license of every pharmacist who made an inadvertent error were revoked, there would soon be no licensed pharmacists. Licensure revocation as punishment for error does nothing to improve systems that set up pharmacists for error. License suspension, with required continuing education to address deficiencies, and a detailed plan to promote patient safety, is the most stringent reasonable regulatory response to inadvertent error by a pharmacist.

Based on: *Blais v Rhode Island Department of Health*, 2014 R.I.Super. 172 (December 22, 2014)

David B. Brushwood, BSPharm, JD, column coordinator, and Professor Emeritus of Pharmaceutical Outcomes and Policy, University of Florida College of Pharmacy, Gainesville

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National Governors Association paper: States should integrate pharmacy into health care system

DIANA YAP

Ringing in the new year with more good news for pharmacist provider status efforts, the National Governors Association (NGA) yesterday released a paper, "The Expanding Role of Pharmacists in a Transformed Health Care System," on how states can integrate pharmacists more fully into the health care system.

"To better integrate pharmacists into the health care delivery system and allow them to practice to the full scope of their professional training, states should review the laws and regulations affecting the profession and consider actions to expand pharmacists' scope of practice," noted the NGA news release.

The greatest challenges pharmacists face include restrictions in collaborative practice agreements, "recognition of pharmacists as health care providers to ensure compensation for direct patient care services," and access to health information technology (IT) systems, the report concluded.

The issue brief, fourth in a series examining ways that states can expand their health care workforce—others focused on physician assistants, dental hygienists, and nurse practitioners—was funded by the Health Resources and Services Administration, the federal agency within the U.S. Department of Health & Human Services.

National pharmacy groups react

National pharmacy associations were pleased by the news.

"This is a significant addition to the list of government and nongovernment entities recognizing the value of pharmacists and their patient care services," wrote APhA Executive Vice President and CEO Thomas E. Menighan, BSPharm, MBA, ScD (Hon), FAPhA, in a CEO Blog post on pharmacist.com.

"APhA is thrilled that the National Governors Association cites the use of pharmacists and their patient care services as an opportunity for states to provide more effective and efficient health care. The report lays out for state governments what our profession and our patients already know—that pharmacists and their patient care services are an integral part of the patient's health care team because of the value they bring to patients and the health care system," said Stacie Maass, BSPharm, JD, APhA Senior Vice President of Pharmacy Practice and Government Affairs.

"This is a significant addition to the **list of government and nongovernment** entities recognizing the value of pharmacists and their **patient care** services."

"The recently published report from the National Governors Association reaffirms what has been shown in research and in practice: when pharmacists are included on the health care team, outcomes improve and costs go down," said Krystalyn K. Weaver, PharmD, National Alliance of State Pharmacy Associations Director of Policy and State Relations. "The policy considerations put forth in the paper support the efforts by state pharmacy associations to advance state-level provider status by integrating pharmacists' patient care services into state-provided health benefits and aligning state scope of practice laws and regulations with pharmacist training and education."

NGA: Integrating pharmacists helps meet goals

The report included sections on pharmacists' clinical training and expertise; current scope of practice, including advanced practice designations; the evolving role of pharmacists, including integration into chronic care delivery teams; state-specific models of team-based care using pharmacists; challenges and barriers to maximizing the effectiveness of pharmacists within the health care system, including variation in state laws governing collaborative practice agreements, recognition of professional services and related payment fees, and access to health IT systems.

Integrating pharmacists into chronic care delivery teams has the potential to improve health outcomes because of the critical role medication management plays in treating chronic disease, according to the NGA news release.

"As the health care system undergoes a major transformation in both finance and the delivery of services, states are focusing on improved quality and health outcomes," NGA Executive Director Dan Crippen said in his statement. "Integrating pharmacists, who represent the third largest health profession, into the health care delivery system is one way to meet these goals."

Diana Yap, Editorial Director

Provider status in this issue

Policy 101: What are medically underserved communities?

DIANA YAP

Federal provider status recognition legislation was introduced as H.R. 4190 in the last Congress by Reps. Brett Guthrie (R-KY), G.K. Butterfield (D-NC), and Todd Young (R-IN) on March 11, 2014, and is expected to be reintroduced—with a new bill number—in this Congress. The legislation would amend Title XVIII of the Social Security Act to enable patient access to, and coverage for, Medicare Part B services by all state-licensed pharmacists who practice in "medically underserved communities."

What are medically underserved communities? The legislation specifically references Medically Underserved Areas (MUAs), Medically Underserved Populations (MUPs), or Health Professional Shortage Areas (HPSAs), which are defined and designated by the Health Resources and Services Administration (HRSA) in the U.S. Department of Health & Human Services.

Pharmacists can find out if they practice in an MUA, MUP, or HPSA on the HRSA website (http://datawarehouse.hrsa.gov/GeoAdvisor/ShortageDesignationAdvisor.aspx).

Shortage designation: Combination of factors

The HRSA designations aren't just about not enough physicians. Rather, they are the result of a combination of factors, according to the HRSA website (www.hrsa.gov/shortage/).

MUAs and MUPs are areas or populations that have too few primary care providers, high infant mortality, high poverty, and/or high older adult population. In MUAs—including a whole county, a group of contiguous counties, a group of county or civil divisions, or a group of urban census tracts—residents have a shortage of personal health services. MUPs may include groups of persons within an area of residence who face economic, cultural, or linguistic barriers to health care.

HPSAs have shortages of primary medical care, dental, or mental health providers and may be geographic (a county or service area), demographic (low-income population), or institutional (comprehensive health center, federally qualified health center, or other public facility). In short, HPSAs may be urban or rural areas, population groups, or medical or other public facilities.

Medically underserved communities aren't just very remote or rural. Many areas throughout the country, including inner-city urban areas, fall into MUAs, MUPs, and HPSAs. The areas so designated will likely increase as the shortage of primary care providers worsens as projected.

Practicing in an underserved community

El Rio Health Center—which serves the greater Tucson area and southern Arizona with 18 locations—is located in an area that HRSA designates as MUA, MUP, and HPSA (primary care, as well as mental health and dental provider shortages).

"As health care continues to shift to outcomes-driven care, it is especially critical to have access to care for patients to hit quality outcomes, goals, and safety," said Sandra Leal, PharmD, MPH, Vice President for Innovation at SinfoniaRx, former Medical Director of Clinical Pharmacists/Broadway Clinic at El Rio, and a longtime advocate for pharmacist provider status.

"This legislation is critical for us because pharmacists can help fill gaps in care to improve access to care for patients," said Leal. "This legislation will create opportunities for pharmacists to help alleviate the shortages that are currently happening in HPSA areas and MUA areas. Some of these areas are in remote rural areas where pharmacists are sometimes one of the few providers available to help patients."

Health Partners of Western Ohio (HPWO) has four locations that are designated as primary care, mental health, and dental MUA, MUP, and HPSA, said Jenny Clark, BSPharm, HPWO Director of Pharmacy Services. "With Medicaid expansion in Ohio and patients getting insurance through the marketplace, more patients are presenting for care at a time when there are fewer primary care providers to meet their needs," Clark said.

"We are in medically underserved areas, so most of the time we don't have physicians. We're dealing with mostly nurse practitioners and physician assistants. So pharmacists are really able to integrate into the team," said Josh Ebbing, PharmD, a clinical pharmacist at one of the clinics. "This legislation is vital to continue our incorporation into the health care team."

"At our organization, we have people come in who have not seen a family provider in over 20 years, due to the lack of care in the community in which they live. This legislation would allow more patients the opportunity to get the care that they have been missing out on for a long time," said Kyle Glasgow, PharmD, BCACP, a Clinical Pharmacy Manager and Residency Coordinator at another of the clinics.

"Practicing with this community, it really allows you to form a unique bond with your patient because a lot of these patients have been failed so many other times in their lives," Glasgow continued. "Once they do open up to you, it's amazing how much they show you what you mean to them; how appreciative they are that they finally have a group of people who care about them. It makes it easy to go to work every day knowing the impact you can have on somebody's life."

Diana Yap, Editorial Director

Disease state management provided at FQHC in North Carolina

SONYA COLLINS

"Mary's" physician had tried several different medications for her hard-to-control diabetes. While one medication would cause intolerable adverse effects, another would have no impact on her disease state at all. Mary couldn't lose weight, her blood pressure was out of control, and her glycosylated hemoglobin (A1C) wouldn't budge below 8.7. That's when Mary's physician referred her to clinical pharmacist practitioner Jennifer Smith, PharmD.

Physicians simply do not have sufficient time to provide the amount of education that patients need to live successfully with diabetes and other chronic conditions. Fortunately, under North Carolina's collaborative practice agreement, the state medical board authorizes Smith to provide disease state management to patients with a number of conditions at Wilson Community Health Center, a federally qualified health center (FQHC) in Wilson, NC. In the hour she spends with patients with diabetes, Smith has the time to learn about any possible barriers to patients' reaching their treatment goals.

But Smith can't always address those barriers. "Where my hands are tied is that I can't provide comprehensive care to patients that receive Medicaid or Medicare," she said.

Patient access to comprehensive care?

Because CMS does not recognize pharmacists as health care providers, as other stories in this series show, Smith cannot always give patients the comprehensive care that the state medical board authorizes her to provide. Yet in a federally qualified health center where a significant portion of the patient population is living with chronic disease that is controlled with chronic medication, pharmacists could greatly ease the burden on physicians, who are already in short supply and high demand.

"Pharmacists are uniquely placed and trained to provide that disease state education and management," Smith said.

Ninety-five percent of the patients the clinic sees live within 200% of the federal poverty level. Sixty percent are uninsured, and most of the others are on Medicare or Medicaid. And 25% have diabetes. Low health literacy and general low literacy mean patients at Wilson Community Health Center need additional guidance in self-management.

Jennifer Smith

"Many people might think an hour is way too long, but our patients need it," Smith said.

'The patient was so excited'

During a typical diabetes appointment, Smith downloads the data from the patient's glucose meter. They discuss diet, exercise, and lifestyle changes. She reviews all their medications for drug interactions, redundant medications, and new prescriptions. She adjusts medications as needed.

In her appointment with Mary, Smith learned that Mary's medications weren't working for her. Because Mary had seen no change in her weight, blood glucose levels, or blood pressure with her medications, she'd lost the motivation to keep trying. When Smith started Mary on a sodium–glucose cotransporter 2 inhibitor, everything changed.

"When she had a little bit of weight loss, a drop in blood sugar and blood pressure, she was ecstatic," Smith said. "So it motivated her to start doing some exercise, because she was just so excited that she was finally starting to lose weight."

Time for teaching patients

Smith needed to monitor Mary's kidney function and potassium levels after she started her new medication. But CMS doesn't allow pharmacists to monitor patients' labs, nor can pharmacists order a patient's diabetes testing supplies.

For these common components of diabetes management—that the state medical board authorizes Smith to do—Smith had to track down Mary's physician. "It takes time away from me, from her provider, and from her," Smith said, slowing down the momentum that Smith and Mary had gained.

This may seem like a minor inconvenience, Smith says, until you multiply that delay in care by the number of adults with a chronic disease. One-half of U.S. adults have at least one chronic disease. More than 12% of adults have two or more chronic diseases.

"Physicians have maybe 15 minutes. You're not going to be able to teach patients disease self-management and address their medication issues, and also examine them and carry out everything else the provider has to do," Smith said. "Pharmacists could be providing some of those services. We are trained to be disease state educators and medication managers."

Provider status stories

Pharmacists are health care providers. In a series of profiles appearing in ***Pharmacy Today*** and on pharmacist.com, pharmacists explain how their patients would benefit from provider status. And as part of our campaign for provider status, APhA has asked pharmacists to share their story of how they provide care to their patients and how provider status will improve health care. These stories are collected on the APhA YouTube channel at https://www.youtube.com/user/aphapharmacists/playlists. If you would like to share your story, please visit PharmacistsProvideCare.com.

Sonya Collins, MA, MFA, contributing writer

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ACA in 2015 and beyond: What pharmacists need to know

LOREN BONNER

Pharmacists are likely seeing more patients under the Affordable Care Act's (ACA) expansion of health insurance coverage. About 10 million American have gained insurance coverage through ACA, according to the latest numbers from the Obama administration. Some have signed up for plans through state and federal health insurance exchanges that began operating on October 1, 2013, while others qualified for coverage through expanded state Medicaid programs or employer-based insurance.

HIGHLIGHTS

- Pharmacists involved in medication therapy management in accountable care organizations are providing a variety of services.
- Care delivery and payment models have been tested with grants from CMS's Center for Medicare & Medicaid Innovation.

Open enrollment for 2015 began on December 15, 2014, and ends February 15, 2015, with the goal of enrolling 9.1 million Americans. According to U.S. Department of Health & Human Services (HHS) Secretary Sylvia Mathews Burwell, 6.8 million Americans have so far selected coverage or reenrolled in a plan for 2015 through the online health insurance exchanges. Figures from HHS also show that an overwhelming majority—87%—of people signing up or renewing their plans qualified for federal subsidies to help them offset the cost of insurance premiums.

Efforts to shut down ACA

While the main provisions of the ACA have been phased in at this point, the law isn't totally safe from Republicans who have been fighting to repeal the law since it was passed nearly 5 years ago.

This spring, the U.S. Supreme Court will hear oral arguments in a case that could eradicate the subsidies and tax credits for consumers in states without their own health insurance exchange. Language in the law says that subsidies can only be paid out by state-run health insurance exchanges. But 36 states deferred setting up a health insurance exchange to the federal government because they either refused to do it or could not. Opponents argue that this language means that consumers in states with federally run state health insurance exchanges are ineligible for subsidies or tax credits.

Republicans are also targeting the employer mandate in the law, which was delayed for 1 year and which requires employers to offer health insurance coverage to full-time employees or pay a penalty. The requirement is scheduled to begin this year for business with 100 or more employees, and in 2016 for employers with 50 to 99 employees.

"We are seeing increasing integration of **pharmacists in these new models** of care."

Using a strategy to eradicate the law piece by piece, Republicans are trying to pass a bill that would change the definition of a full-time employee under ACA from someone who works 30 hours per week to someone who works 40 hours per week. The concern is that employers are likely to drop employees below 40 hours to meet the threshold, and the 30-hour limit was set originally in the law to minimize lowering hours.

President Barack Obama said he would veto any bill if it reached him.

SHOP for small employers

Additionally, small employers will still be able to buy health coverage for their employees through the Small Business Health Options Program (SHOP), although some states offer only a few plan choices.

While some of these potential changes could have implications for pharmacies' bottom lines, differences in what may be available to patients on the plan level as determined by drug formularies should also be of interest to pharmacists.

Health insurance exchange plans

The proposed rule on benefit parameters for health insurance exchange plans for 2016 released by CMS in November 2014 could affect essential health benefits (EHB) and network adequacy, among other areas.

EHB, determined on the federal level in 10 categories defined in the law, must be included in health insurance exchange plans for individuals and small businesses. One of the categories consists of a pharmacy drug formulary, but differences can pop up in determining what is in that formulary, said Jillanne Schulte, JD, APhA Director of Regulatory Affairs.

According to the proposed rule from CMS, health insurance exchange plans may be required to adopt a pharmacy and therapeutics committee—although, if adopted, any such requirement would not go into effect until 2017.

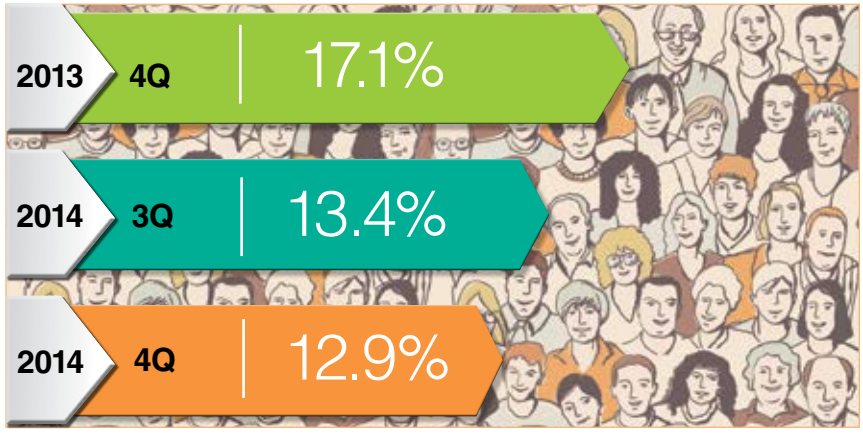
"It's what's done for a lot of private plans. But it hasn't been required on the exchange, and could possibly have some repercussions," said Schulte.

The proposed rule also seeks to replace the United States Pharmacopeia (USP) standard, or the USP Model Guidelines 5.0, with the American Hospital Formulary Service, which Schulte said should be noted.

"USP standards are used broadly throughout the health care community, so we have some concerns about switching to a new standard without significant stakeholder discussion regarding potential risks and benefits," she said.

Other parts of the proposed rule are welcome news. Some pharmacists have had long-standing concern that some patients were not able to adequately determine what's included on their health insurance exchange plan's

Figure 1: Uninsured rate among U.S. adults



Source: www.galloup.com/poll/180425/uninsured-rate-sinks.aspx

prescription drug coverage. Language in the proposed rule said it would increase transparency regarding plan formularies.

Community vs. mail-service pharmacies

APhA, along with other pharmacy stakeholders such as the National Community Pharmacists Association, also supports the proposed requirement that enrollees be provided with the option to access their prescription drug benefit through brick-and-mortar pharmacies, instead of being limited by mail-service–only prescription drug benefits in their plan.

Pharmacist integration into new models of care

ACOs. The proliferating number of accountable care organizations (ACOs) has been accelerated through ACA. ACOs are a network of health care providers that share responsibility for a patient's care. ACOs are incentivized for keeping costs down and patients healthy. Some quality metrics that ACOs have to meet in order to qualify for financial incentives are affected by patients' medications.

"Pharmacists can have an impact on these new systems," said Anne Burns, BSPharm, APhA Vice President for Professional Affairs.

Today, more than 600 private, Pioneer, and Medicare ACOs exist. In some cases, pharmacists are formally involved in the ACOs, but there are still not adequate data on how many ACOs include pharmacists as members of the team.

"We are seeing increasing integration of pharmacists in these new models of care, but don't have hard data on the total number," said Burns.

Pharmacists involved in medication therapy management (MTM) in ACOs are providing a variety of services. Burns said pharmacists manage complex therapies, sometimes under collaborative practice agreements, and may be hired to help with care transitions and medication adherence; they also manage chronic conditions where medications play an important role. Or pharmacists are incorporated to conduct Medicare annual wellness visits, which include medication reconciliation.

Pharmacists' roles often evolve over time. For example, the pharmacist may be hired or contracted to provide patient education and medication adherence services and then responsibilities are expanded gradually as other health care providers on the team see their capabilities.

While pharmacists could also help manage the drug spend and achieve savings and financial incentives for an ACO, the Medicare Part D prescription drug benefit is explicitly excluded in Medicare ACOs, and prescription drug costs are also excluded from many private sector ACOs. In other words, ACOs are responsible for managing the patient, but not the patient's medication costs—although CMS is exploring integration of the Part D benefit into Medicare ACOs, according to Burns.

"The question is: How much are ACOs paying attention to medications and their appropriate use?" said Burns.

For now, the reaction is mixed. Some say that ACOs are not liable for medication costs and patients should be prescribed the best therapy to meet clinical goals, with pharmacists helping to manage the patient's medications to meet those goals. But others criticize this thinking, saying the focus on medications is not as strong as it would be if ACOs had to manage the drug spend along with everything else.

CMMI grants. Other care delivery models have been tested with grants from CMS's Center for Medicare & Medicaid Innovation (CMMI), which was established through the law in 2011.

"Some CMMI grants have a specific focus on care delivery and payment models where pharmacists are managing medications and helping to improve health care," said Burns.

Several examples include a 2012 grant, which just wrapped up after 3 years, led by the University of Southern California School of Pharmacy. The $12 million project brought pharmacists into safety net clinics in southern California to provide MTM, medication reconciliation, and referrals to preventive care programs in order to reduce avoidable hospitalizations and emergency visits. (For more information, see page 46 in September 2012's ***Pharmacy Today***.)

Also during the 2012 funding round, the Wisconsin Pharmacy Quality Collaborative (WPQC) was chosen to expand its program across the state, where pharmacists collaborate with physicians as medication therapy managers. One of the program's objectives was to "achieve professional recognition and compensation for pharmacists based upon the development and implementation of pharmacy practice services which improve the use and safety of medications," according to WPQC literature. (For more information, see page 57 in January 2015's ***Today***.)

A more recent project headed by Community Care of North Carolina (CCNC), which won funding in 2014, will demonstrate how community pharmacists can reduce costs by integrating pharmacists into CCNC's multidisciplinary teams and equipping them with technology to communicate and share information. (For more information, see page 49 of the December 2014 issue and page 50 of this issue of ***Today***.)

Burns said APhA looks forward to the publication of the results from these projects.

Loren Bonner, MA, Reporter

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Hepatitis C therapy: Looking toward interferon-sparing regimens

Trang H. Au, Christopher J. Destache, and Renuga Vivekanandan

Abstract

Objective: To describe chronic hepatitis C virus (HCV) infection, including its epidemiology and pathophysiology; review current treatment options for HCV infection; recognize investigational agents being studied as part of interferon-free therapy; and summarize clinical trials for the new agents.

Data sources: PubMed for 2004 through August 2014 using search terms *hepatitis C, American Association for the Study of Liver Diseases, sofosbuvir, simeprevir,* and as needed specific names of other agents in development during this time; news articles and news releases about company actions with regard to clinical trials and filings for marketing approval in the United States.

Study selection: At the discretion of the author based on clinical relevance of study and relevance to national guidelines for HCV therapy.

Results: HCV infection is an important medical and public health problem in the United States and worldwide that can cause cirrhosis, hepatocellular carcinoma, and liver failure. The advent of newly developed targeted therapies is changing the treatment paradigm for this disease. Although traditional therapy with pegylated interferon and ribavirin remain therapeutic options, direct-acting agents such as sofosbuvir (Sovaldi—Gilead) and simeprevir (Olysio—Janssen) are producing faster, earlier, and improved treatment response with fewer adverse effects. The combination of anti-HCV agents and the duration of treatment are based on genotype, patient treatment status, and patient risk factors. The dramatic and sustained clearance of the virus with these drugs makes sustained virologic response a reality for patients who are unable to tolerate pegylated interferon. The downside is their high cost, which may make them economically unsustainable. However, for patients infected with HCV, the potential for a cure and improved quality of life may now be a reality.

Conclusion: HCV, a well-known blood-borne disease associated with significant morbidity and mortality worldwide, can be effectively and safely treated with new anti-HCV agents such as SOF. While these new medications are in their early days of real-world practice, they offer hope that cure is truly possible.

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Development: This home-study CPE activity was developed by the American Pharmacists Association.

Learning objectives

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

- Describe chronic hepatitis C virus (HCV) infection, including its epidemiology and pathophysiology.
- Review current treatment options for HCV infection.
- Recognize investigational agents being studied as part of interferon-free therapy.
- Summarize clinical trials for the new agents.

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

1. Which is a risk factor for HCV infection?
   a. Breastfeeding
   b. Kissing
   c. History of incarceration
   d. Hugging

2. Which is a correct statement about HCV?
   a. HCV is a single-stranded deoxyribonucleic acid virus.
   b. HCV is a single-stranded ribonucleic acid virus.
   c. HCV is a double-stranded deoxyribonucleic acid virus.
   d. HCV is a double-stranded ribonucleic acid virus.

3. Which group is considered a unique population for HCV treatment?
   a. Health professionals
   b. Patients with renal dysfunction (CrCL < 60 mL/min)
   c. Patients with HIV/HCV coinfection
   d. Patients with significant alcohol use

Hepatitis C virus (HCV) is a contagious, blood-borne viral pathogen associated with significant morbidity and mortality. HCV infections can cause liver inflammation and progress to cirrhosis, hepatocellular carcinoma, and liver failure. Since the 1988 discovery of viral antigens specific for HCV (previously called non-A, non-B hepatitis), substantial advances in molecular biology and sequence data have enabled identification and isolation of the virus. More recently, targeted therapies with a favorable efficacy and safety profile compared with other therapies are becoming available. These direct-acting agents (DAAs) and their inclusion in current treatment guidelines are transforming the treatment and management of HCV infections.

Table 1 lists current common abbreviations and acronyms used in the literature for HCV.

Objectives

The purpose of this article is to describe chronic HCV infection, including its epidemiology and pathophysiology; review current treatment options; recognize investigational agents being studied as part of interferon-free therapy; and summarize clinical trials for the new agents.

Search methodology

To identify relevant literature, PubMed was searched for the years 2004 through August 2014 using the terms *hepatitis C, American Association for the Study of Liver Diseases, sofosbuvir, simeprevir,* and other specific agents as needed. Landmark clinical trials were identified and reviewed, with attention to those cited in nationally recommended guidelines for management of HCV infections. News articles, news releases, and other sources of current information were used to determine actions of companies such as filings with the Food and Drug Administration (FDA) for approval of agents used in treating HCV infections.

Table 1. Common abbreviations and acronyms used in hepatitis C virus literature

Abbreviations / acronyms	Terms
BOC	Boceprevir
DAA	Direct-acting agent
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IFN	Pegylated interferon
IL-28B	Interleukin-28B
MSM	Men who have sex with other men
RBV	Ribavirin
RNA	Ribonucleic acid
SMV	Simeprevir
SOF	Sofosbuvir
STAT-C	Specifically targeted antiviral therapy
SVR	Sustained virologic response
SVR12	SVR at 12 weeks after stopping therapy
SVR24	SVR at 24 weeks after stopping therapy
TVR	Telaprevir

Epidemiology

HCV causes acute and chronic infection primarily affecting the liver. Approximately 130 million to 150 million people worldwide have a diagnosis of chronic HCV.[1] In the United States, HCV is the most common blood-borne viral infection; an estimated 4.1 million U.S. persons have been exposed to HCV, and 3.2 million have chronic disease.[2] HCV has an annual age-adjusted mortality rate of 4.58 per 100,000 deaths[3,4] and is the leading cause of liver transplantation in the United States. Other complications include coinfection with human immunodeficiency virus (HIV), steatosis, insulin resistance, diabetes, and renal disease. Concomitant HIV infection exacerbates HCV disease and makes spontaneous clearance of HCV less likely.[5]

Despite the decline in HCV incidence in the last decade, chronic HCV infection accounts for more disease burden and death than infections of hepatitis B virus or HIV.[4,6] Evaluation of long-term morbidity and mortality in patients with HCV has demonstrated that risk of death is reduced by 45% and risk of liver complications by 27% among patients who achieve viral load suppression,[7] defined as the absence of HCV ribonucleic acid (RNA) in serum by a sensitive test at the end of treatment.[3] Sustained virologic response (SVR) is defined as viral load suppression at the end of treatment and again at 6 months.[3]

Chronic HCV infections are caused by six major genotypes and more than 40 subtypes. Genotypes 1, 2, and 3 are common in Western countries; genotypes 1, 4, and 5 are common in Africa; and genotype 6 predominates in Asia.[8] Genotypes 1a and 1b are generally considered more difficult to treat, which may be explained by the absence of the favorable-treatment polymorphism associated with interleukin-28B (IL-28B). The favorable genetic variant shown to be the most important predictor of SVR is the CC variant (a genetic

subtype of IL-28B).[9,10] In the United States, genotype 1 represents 73% of infections, although the prevalence of genotypes 4 to 6 is increasing because of the growth in cultural diversity.[3,6]

Among persons in the United States who are chronically infected with HCV, an estimated 45% to 85% are unaware of their infection.[3] This presents a challenge for appropriate identification of HCV cases and highlights the importance of recognizing risk factors for infection. The single most important risk factor for HCV infection is injection drug use, which accounts for more than 60% of acute infections. Intranasal illicit drug use is another risk factor for HCV infection. Other risk factors include long-term hemodialysis; tattoos inked in an unregulated setting; exposure to HCV-infected blood from needlestick, sharps, or mucosal injury; children born to HCV-positive women; and prior blood transfusions or organ transplants. HIV infection and unexplained chronic liver disease with elevated liver enzymes can also increase risk for HCV infection.

In addition to significant mortality and morbidity, HCV disease is associated with a significant economic burden. Analysis of a data pool of 30 U.S. managed care organizations showed that patients with HCV have higher all-cause costs, mean inpatient costs, and prescription drug costs. In addition, hospitalization rates of HCV patients are significantly higher than those of people without HCV (24% vs. 7%, respectively).[11]

Transmission

The primary mode of HCV transmission is by percutaneous exposure to infected blood. The virus is not transmitted by hugging, kissing, sharing utensils, or breastfeeding.[3] Blood, tissue, and organ donation account for many of the chronic HCV infections among those born between 1945 and 1965, commonly called the "baby boomer" generation. However, this source of infection has been of less concern since improved interviewing techniques and laboratory screening tests became available in 1992. According to current estimates, 1 in 1 million blood products may transmit HCV.[6] Although injection drug use is at the center of the present HCV epidemic, it remains difficult to study. A new group of injection drug users is attracting attention for characteristics unseen in previous cohorts: 24 years of age or younger, white, nonminority, nonurban, and prior use of opioids.[6]

Among women with HCV, approximately 5% transmit the virus to their child. Perinatal transmission has the highest risk at the time of birth. The risk of mother-to-infant transmission is twice as high among women coinfected with HCV and HIV compared with women who have HCV infection alone.[3]

Epidemiologic studies have identified HIV infection as an independent risk factor for HCV infection.[5] Because people with HIV and HCV coinfection appear to be less likely to clear the HCV virus, they may be more infectious than those who have HCV infection alone.[5] On the whole, sexual transmission of HCV occurs less commonly than perceived, but the incidence of acute HCV infection is increasing in the HIV-positive cohort of men who have sex with men.

Highly active antiretroviral therapy has successfully extended the life expectancy of HIV-infected individuals, but it may also contribute to the misperception that unprotected sex is less risky in the setting of controlled HIV infection. The practice of decision-making about sexual behavior according to same HIV status is also known as serosorting. Serosorting is associated with increased incidence of sexually transmitted diseases such as herpes and syphilis, which increases susceptibility to HCV infection.[5,6]

Pathophysiology

HCV is a single-stranded, enveloped RNA virus of the *Flaviviridae* family that replicates at a rate of 1010–1012 virions per day.[12] The genetic diversity of HCV is attributed to its rapid replication rate and the poor fidelity of its RNA polymerase. The lack of proofreading by RNA-dependent RNA polymerase leads to mutant viruses with genetic heterogeneity. A high rate of genetic substitutions occurs during acute infection and decreases with continuous infection.[12] The main reason for these high rates of genetic substitution is the selective pressure exerted by antibodies and activated T cells during acute infection. This mechanism may also explain why HCV infection resolves spontaneously in some patients. The HCV genome includes 3,000 amino acids. Host and viral proteases are involved in producing components of the capsid, envelope, and viral enzymes required for replication and virion assembly.

Though HCV was discovered approximately 15 years ago, its life cycle is not fully understood because small animal models do not exist and the virus does not replicate in cell culture.[13] Researchers have hypothesized that the complex, multistep pathway of viral entry into hepatocyte involves lipid metabolism and host factors.[14] Glycoproteins on the viral envelope bind to the cellular receptor proteins on the cell surface, among which the CD81 molecule has been the most studied. Internalization occurs by endocytosis in a low pH–dependent manner. The exact mechanism by which the viral genome is released from the nucleocapsid into the host cell is unknown.[14] After replication and assembly, the virions that carry the viral genome are released into the extracellular space. Overall, the replication process is similar to that of HIV.

HCV-induced chronic inflammation of the liver involves a host of immune cells, including T and B lymphocytes, macrophages (Kuffer cells), natural killer cells, pro-inflammatory cytokines, and neutrophils. Tumor necrosis factor can cause liver damage by apoptosis-mediated death of hepatocytes and fibrosis formation. With prolonged infection, antibody-mediated cytotoxicity further contributes to fibrosis progression. The exact mechanism by which HCV causes hepatic cell carcinoma is unknown.[15,16] Although HCV is not thought to be oncogenic per se, an HCV-associated oncogenic effect cannot be ruled out. The proliferative potential of HCV proteins in vitro, including the core, NS3, NS5A, and NS5B proteins, is hypothesized to possess oncogenic potential. More specifically, HCV viral proteins may interfere with cellular proteins,

such as cyclin and cyclin-dependent kinase, which regulate cell cycle control. Cell cycle dysregulation produces an imbalance of tumor suppressor genes and oncogene activity.[15]

Screening

Current guidelines recommend comprehensive screening for patients who have increased risk for HCV infection, with risk factors grouped by behaviors, exposures, and comorbid medical conditions. One-time testing for HCV is recommended in persons who meet the following criteria:

1. Behaviors—history of injection or intranasal illicit drug use regardless of frequency or duration
2. Exposures—long-term hemodialysis, tattoos received in an unregulated setting, health care workers who have had needlestick injury or mucosal exposure to HCV-positive blood, children born to HCV-infected mothers, receipt of blood or blood product transfusion or organ transplant before July 1992, and history of incarceration
3. Comorbid medical conditions—HIV infection, unexplained chronic liver disease, or chronic hepatitis (including elevated alanine aminotransferase levels)[3]

In addition, the Centers for Disease Control and Prevention recommends HCV testing at least once in the lifetime of persons born between 1945 and 1965.[17] All testing should be done using one of the seven tests approved by FDA, which include manual and automated laboratory assays or a point-of-care assay.

Serologic and molecular assays are used to diagnosis and manage HCV infection. A positive serologic HCV test result may be interpreted in three different ways: current and active infection that may be acute or chronic, prior infection that is now resolved, or a false-positive result. The delay of several months between exposure to HCV and development of detectable antibodies to the virus can lead to a false-reacting screening test that does not discriminate between resolved and chronic infection.

To confirm test results, an HCV nucleic acid test is performed. Molecular qualitative assays with real-time polymerase chain reaction and transcription-mediated amplification are used to detect viral nucleic acid. Presence of viremia confirms a current and active infection. False-positive results are more likely in patients who have low risk for HCV infection.[17]

A second test may be performed with a different FDA-approved test for a questionable false-positive serologic test result. Absence of laboratory evidence for active HCV infection is defined as a positive serologic test and negative molecular test, such as an HCV RNA test. For patients who have negative laboratory evidence despite the presence of risk factors for HCV, repeating the HCV RNA test may be considered.

Clinical presentation

The majority of patients with acute HCV are asymptomatic, and researchers have estimated that as many as 85% of patients with chronic HCV are unaware of their infection.[3] Table 2 lists common patient categories and their usual response to therapy.

Table 2. Definitions of types of patients with hepatitis C virus

Patient types	Definitions
Treatment-naive	Has never been treated with anti-HCV
Treatment-experienced	Has been treated with anti-HCV therapy
Nonresponder	Has a reduced response to anti-HCV therapy
Null responder	Nonresponder who does not have a 2 log 10 IU/mL reduction of hepatitis C RNA by week 12 of therapy
Partial responder	Nonresponder who has a 2 log 10 IU/mL reduction of hepatitis C RNA by week 12 of therapy

Abbreviation used: HCV, hepatitis C virus; RNA, ribonucleic acid.

Symptomatic patients with HCV infections may present with fatigue, appetite loss, jaundice, dark urine, clay-colored stool, nausea, and abdominal pain, particularly right upper quadrant pain. Symptoms may appear 2 weeks to 6 months after exposure. With chronic HCV infections, most people do not have symptoms until liver damage has developed. Elevated liver function enzymes are often found inadvertently during routine blood tests, leading to further testing. However, liver enzyme levels can and often do fluctuate between normal or near normal and high. Thus, liver enzyme tests are sometimes needed several times as part of the diagnostic work-up.

Because HCV is often asymptomatic, identifying patients and diagnosing infection is particularly challenging. Among the patients found to have acute infection, 60% to 70% progress to chronic infection. Among patients with chronic infection, up to 20% develop cirrhosis over several decades, and up to 5% die of cirrhosis or hepatocellular carcinoma.

The inherent difficulty in identifying patients with HCV infection underscores the importance of recognizing patients with risk factors that warrant screening for antibodies to the virus. Approximately 20% to 25% of patients with acute infection clear the virus spontaneously and do not progress to chronic status. The reason for this spontaneous clearance remains unknown.[17,18] Characteristics that favor spontaneous clearance are being female, younger than 40 years of age, and symptomatic.

Diagnosis

An accurate diagnosis of HCV requires both serologic and molecular assays to determine the degree of viremia in the circulating blood. The appearance of viral RNA may occur as early as 1 month after exposure, and antibodies to the virus may be detected approximately 2 months after exposure. A quantitative HCV RNA test to establish baseline viremia is necessary before treatment is initiated. The relative decline of subsequent measures of viremia is compared to the baseline viral load to assess efficacy of treatment. In addition, severity of liver damage is evaluated, usually by liver biopsy to assess degree of fibrosis.

In patients for whom liver biopsy is not possible, imaging by ultrasound, computer tomography, and liver elastography and use of noninvasive clinical markers, such as ami-

notransferase enzymes, albumin, bilirubin, international normalized ratio, Model for End-Stage Liver Disease score, and Child–Pugh score, may be used. In addition, aspartate aminotransferase-to-platelet ratio index or fibrosis-4 index (FIB-4) can identify HCV patients most likely to have a more severe degree of fibrosis.[19]

Liver biopsy is an invasive procedure that can provide objective information about the degree of hepatic scar tissue, liver inflammation, and steatosis. The Metavir assessment is commonly used to stage fibrosis (scored from F0 to F4).[3] Although liver biopsy is considered the gold standard diagnostic tool, it is not without complications, of which bleeding is the most common. Additional risks include puncture of other internal organs and underdiagnosis of cirrhosis due to sampling error.[20] Furthermore, liver biopsy is expensive, and the interpretation of histopathology samples requires expert analysis.

Determination of HCV genotype is important because treatment regimens are based on genotype. HCV genotypes respond differently to therapy, and certain regimens have been effective for particular genotypes. Historically, combination therapy with pegylated interferon (IFN) and ribavirin (RBV) was initiated. The advent of specifically targeted antiviral therapy (STAT-C) compounds has broadened therapeutic options.[21] Therefore, patients are not necessarily restricted to the RBV–IFN regimen, which is associated with an extensive adverse effect profile that can be so intolerable that it limits treatment.

Patients who have a confirmed diagnosis of HCV should be given comprehensive counseling about preventing further liver damage and spreading the disease. Most importantly, patients should be educated about cessation of alcohol intake and, if necessary, provided with support to achieve abstinence. Alcohol consumption in the setting of HCV infection can accelerate liver fibrosis, progress to cirrhosis, and contribute to higher incidence of hepatocellular cancer. Patients with HCV who abuse alcohol have decreased survival compared with patients who are HCV-positive without alcohol intake or those who are HCV-negative and abuse alcohol.[22] The deterioration of HCV status secondary to alcohol abuse is hypothesized to occur by increased oxidative stress, cytotoxicity, immune system dysfunction, and enhanced viral replication. Abstinence may help reverse these effects.[23]

In addition to intensive, complete education about alcohol cessation, medical conditions that may exacerbate liver fibrosis, such as hepatitis B and HIV infection, should be evaluated. Vaccination against hepatitis A and hepatitis B is also recommended, as well as patient education about how to avoid transmitting HCV. More specifically, patients should be advised on the following: do not share dental or shaving equipment; cover bleeding wounds; cease illicit drug use, but if this is continued do not share drug paraphernalia; do not donate blood or fluid products; use barrier precautions to prevent sexual transmission; and clean any blood spills at home with diluted bleach and water (1:9 ratio) while wearing gloves.

Treatment

Several agents are FDA-approved for treatment of HCV (Table 3). In the following sections we discuss IFN, RBV, boceprevir (BOC; Victrelis—Merck), telaprevir (TVR; Incivek—Vertex), sofosbuvir (SOF; Sovaldi—Gilead), and simeprevir (SMV; Olysio—Janssen), with a focus on information that is relevant to real-world practice. Current American Association for the Study of Liver Diseases (AASLD) guidelines state that treatment should be given to patients with advanced fibrosis (Metavir F3), patients with compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C. Table 4 reviews the criteria for patient types in whom HCV therapy should be initiated.[3]

Pegylated interferon

Treatment with IFN is a mainstay of HCV therapy.[24,25] Two IFN products, IFN alpha-2a and IFN alpha-2b, are currently available in the United States. As its name indicates, interferon interferes with viral replication. The polyethylene glycol moiety that was added to interferon beginning in the 1980s has improved the tolerability of IFN therapy and increased its half-life. As a result, the drug remains in the body for a longer time and requires less frequent dosing. IFN alpha-2a is dosed according to weight, whereas IFN alpha-2b is given as a fixed dose. When used to treat HCV, both products are administered as weekly subcutaneous injections.

Despite the improved adverse effect profile of IFN, tolerance can still be a barrier to treatment. Influenza-like symptoms can be treatment limiting. Bone marrow suppression resulting in anemia, neutropenia, and thrombocytopenia, as well as psychiatric problems such as depression, irritability, insomnia, and moodiness, may occur and could halt treatment. Because IFN is a subcutaneous injection that must be self-administered, some patients are not interested in receiving this therapy.

Ribavirin

RBV is a nucleoside analog drug that inhibits the ability of HCV to replicate.[26,27] It is not as effective as monotherapy but appears to boost cure rates and reduce risk of relapse when added to HCV treatment regimens. A twice-daily oral medication available in tablet, capsule, or solution formulation, RBV is dosed according to weight, with a 75-kg threshold for dose adjustment. Its major adverse effect is dose-dependent anemia, which may be managed successfully by either lowering the dose or supplementing it with red blood cell growth factors. Other adverse effects reported include cardiac problems, depression, skin rash, fatigue, diarrhea, dizziness, and gastrointestinal disturbances such as nausea and vomiting.

Overall, combination RBV–IFN produced an average SVR of 35% to 40% in most clinical trials. Given the overwhelming number of patients requiring HCV therapy, this response rate was too low, and a search for molecular therapies that produce higher SVRs began.

Table 3. Summary of approved medications for treating hepatitis C virus infections

Product labeling sections	IFN	RBV	BOC	TVR	SMV	SOF
Drug class	Interferon	Nucleoside analog	Protease inhibitor	Protease inhibitor	Protease inhibitor	Polymerase inhibitor
Mechanism of action	Interferes with viral replication	Inhibits viral replication	Inhibits NS3A/4	Inhibits NS3A/4	Inhibits NS3A/4	NS5B
Dose or dose range	IFN alpha-2a: 180 mcg weekly IFN alpha-2b: 6 mcg/kg weekly	<75 kg: 1,000 mg twice daily >75 kg: 1,200 mg twice daily	800 mg three times daily	1,125 mg twice daily	150 mg once daily	400 mg once daily
Administration	Subcutaneous injection	Oral (tablet, capsule, solution)	Oral (200-mg tablets); take with food	Oral (375-mg tablets); take with food	Oral (150-mg tablet)	Oral (400-mg tablet)
Renal adjustment	Combined with RBV, IFN alpha-2a: 135 mcg if CrCL < 30 mL/min IFN alpha-2b: discontinue if SCr > 2 mg/dL	Tablet: alternate 200 mg and 400 mg EOD when CrCL is 30–50 mL/min (or not recommended when CrCL < 50 mL/min; see package insert). Capsule/solution: contraindicated for CrCL < 50 mL/min	None	Not studied for CrCl < 50 mL/min	Not studied for CrCl < 30 mL/min	Not studied for CrCl < 30 mL/min
Hepatic adjustment	IFN alpha-2a: 135 mcg if LFTs are rising IFN alpha-2b: Discontinue if hepatic decompensation or Child-Pugh B or C	CI with hepatic decompensation	None	Not recommended with hepatic decompensation	Not recommended with hepatic decompensation	Not studied in decompensated cirrhosis
Adverse effects	Influenza-like symptoms, anemia, neutropenia, thrombocytopenia, bone marrow suppression, psychiatric disorders	Dose-dependent hemolytic anemia, cardiac, pruritus, depression	Anemia, neutropenia, fatigue, decreased kidney function	Itchy rash, anemia, nausea, vomiting, fatigue, decreased kidney function	Pruritus, rash, photosensitivity, nausea	Fatigue, headache, nausea, insomnia, pruritus
Interactions with hepatic metabolic isoenzymes	CYP1A2	None	CYP3A4/5	CYP3A	CYP3A4	None
Pregnancy category	C	X	B X (with RBV)	X	X	B X (with RBV–IFN)

Abbreviations used: BOC, boceprevir; CrCl, creatinine clearance; CYP, cytochrome P450; EOD, every other day; IFN, pegylated interferon; LFT, liver function test; MOA, mechanism of action; RBV, ribavirin; SCr, serum creatinine; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir

Table 4. Categories of patients who qualify for newly developed therapies for hepatitis C virus infections

Highest priority with highest risk for severe complications	High priority with high risk for complications
Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)	Fibrosis (Metavir F2)
Organ transplant	HIV-1 coinfection
Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations	Other coexistent liver disease
Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis	HBV coinfection
	Debilitating fatigue
	Type 2 diabetes
	Porphyria cutanea tarda

Abbreviations used: HBV, hepatitis B virus; HIV-1, human immunodeficiency virus type 1.
Source: American Association for the Study of Liver Diseases guidelines, 2014

Boceprevir and telaprevir

First-generation DAAs include BOC and TVR.[28,29] Both agents were approved in 2011 for treatment in combination with IFN and RBV for HCV genotype 1 infection. BOC and TVR inhibit the viral NS3/4A protease, which is responsible for cleaving HCV viral protein into mature proteins. Phase III clinical trials that formed the foundation for FDA approval demonstrated SVR rates of approximately 65% after 24 to 48 weeks of therapy.[30] Factors that predicted SVR with BOC included low viral load, IL-28B genotype, absence of cirrhosis, and race other than black.[31] In the latest guidelines, neither of these drugs is recommended for treatment of any HCV genotype.[3]

Although treatment with BOC and TVR can improve SVR, not all patients achieve SVR, nor is treatment without complications. One single-center study reported an SVR rate of 57% and 59.7% with BOC and TVR, respectively.[32] These results suggest that in almost one-half of patients treated in the real-world setting with BOC or TVR with RBV–IFN, BOC and TVR are not as effective at controlling the disease as anticipated. Furthermore, anemia is the most common treatment-limiting adverse effect of BOC. Dermatologic responses, particularly a persistently itchy rash, have developed in patients with HCV. Severe rash with death has occurred in some patients, prompting FDA to issue a new warning to discontinue TVR if a rash develops.[28,29]

These adverse effects compound those associated with RBV and especially IFN. BOC and TVR can also cause decreased kidney function, as evidenced by a decrease in MELD score (a scoring system for assessing the severity of chronic liver disease).[32] The greater concern with BOC and TVR therapy is the emergence of viral resistance to these medications. More specifically, mutations at amino acid 54 were seen with BOC treatment, and mutations at amino acid 36 and/or 155 were seen with TVR treatment.[33]

Simeprevir

SMV was the third DAA to be approved for HCV and the first of the new-generation DAAs.[34] SMV is a highly specific, potent NS3/4A protease inhibitor used with RBV and IFN in patients with HCV genotype 1. Biochemical assays have shown that SMV can inhibit the NS3/4A protease of genotypes 1a and 1b, which are traditionally considered difficult to treat.[35] Unlike BOC and TVR, which have a high pill burden, SMV is dosed as a convenient, once-daily 150-mg tablet to be taken with food. Overall, adverse effects of SMV combined with RBV–IFN are similar to those of RBV–IFN except there is milder, reversible jaundice.[35]

Approval of SMV was based on the results of a series of Phase III trials, including QUEST 1 and 2, PROMISE, and ASPIRE. The pooled analysis of QUEST 1 and 2 studies showed that among 521 treatment-naive patients with HCV genotype 1, 88% achieved an SVR at 12 weeks after being treated with SMV combined with RBV–IFN. The PROMISE trial was a randomized, double-blind, placebo-controlled study examining 260 patients with HCV genotype 1 who relapsed after prior IFN-based therapy. In the intention-to-treat analysis, 93% of patients were found to have an SVR at 12 weeks after receiving SMV+IFN+RBV.[36]

The ASPIRE trial evaluated patients with HCV genotype 1 who were prior relapsers, partial responders, or null responders. Results indicated that genotype 1a and 1b patients who received SMV+RBV+IFN achieved SVR rates of 47% and 77% at 24 weeks compared with RBV–IFN SVR rates of 13% and 7% at 24 weeks, respectively. In addition, the SVR at 24 weeks was 72.9% for patients treated with SMV 150 mg daily and RBV–IFN, 65.5% for patients treated with SMV 100 mg daily and RBV–IFN, and 22.7% for patients treated with placebo and RBV–IFN.

SMV is currently approved for treatment of patients with HCV genotype 1, including those with cirrhosis. FDA noted that SMV is less effective in genotype 1a patients who have an NS3 Q80k polymorphism at baseline. Therefore, screening patients for this polymorphism is strongly recommended, and alternative therapy should be considered for affected patients. Table 5 summarizes the clinical studies that led to approval of SMV.

Sofosbuvir

SOF is a second-generation DAA that received FDA approval a few months after SMV was approved.[37] As a class, second-generation DAAs have been shown to be superior to BOC and TVR for improved SVR, better tolerability, and substantially reduced pill burden. SOF is a nucleotide analogue that inhibits the NS5B polymerase inhibitor. More specifically, it is a prodrug with an active metabolite that acts as a chain terminator in HCV replication. It has been evaluated for HCV genotypes 1 through 6 among patients with HCV infections who were treatment-naive, had previously discontinued IFN for intolerance, or had previously failed IFN because of lack of efficacy.

Table 5. Summary of key clinical trials for simeprevir

Trial characteristics	ASPIRE	PROMISE	QUEST-1	QUEST-2
Participants	Failed RBV–IFN	Relapse with prior IFN	Treatment-naive	Treatment-naive
Genotype	G1	G1	G1	G1
Study design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
Study site	81 international	71 international	71 international	76 international
Regimen	SMV/placebo with RBV–IFN	SMV/placebo with RBV–IFN	SMV/placebo with RBV–IFN	SMV/placebo with RBV–IFN
Treatment duration (weeks)	48	12	24 or 48	24 or 48
SVR	SVR24	SVR12	SVR12	SVR12
SVR rate(s)	SMV 150 mg 72.9% (n = 199) SMV 100 mg 65.5% (n = 197) Placebo 22.7% (n = 66)	SMV 79.2% (n = 260) Placebo 36.1% (n = 133)	SMV 80% (n = 264) Placebo 50% (n = 130)	SMV 81% (n = 257) Placebo 50% (n = 134)

Abbreviations used: IFN, pegylated interferon; G, genotype; RBV, ribavirin; SMV, simeprevir; SVR, sustained virologic response; SVR12, sustained virologic response at 12 weeks; SVR24, sustained virologic response at 24 weeks.

Table 6. Summary of key clinical trials for sofosbuvir

Trial characteristics	NEUTRINO	FISSION	POSITRON	FUSION	VALENCE
Participants	Treatment-naive	Treatment-naive	Previously discontinued IFN	Failed IFN	G2, G3
Genotype	G1, G4, G5, G6	G2, G3	G2, G3	G2, G3	G2, G3
Study design	Open label	Randomized, open-label, noninferiority	Blinded, placebo-controlled	Blinded, active-controlled	Randomized, placebo-controlled
Study site	56 U.S.	97 international	63 international	63 international	77 international
Regimen	SOF + RBV + IFN	SOF + RBV + IFN	SOF + RBV	SOF + RBV	SOF + RBV
Treatment duration (weeks)	12	12	12	12 or 16	12 or 24
SVR	SVR12	SVR12	SVR12 SVR24	SVR12	SVR12
SVR rate(s)	G1 89% (n = 291) G4 96% (n = 28) G5 100% (n = 1) G6 100% (n = 6)	G2 97% (n = 73) G3 63% (n = 183)	G2 100% (n = 109) G3 98% (n = 98)	G2 86% for 12 weeks (n = 39); 94% for 16 weeks (n = 64) G3 30% for 12 weeks (n = 39); 62% for 16 weeks (n = 63)	G2 93% (n = 73) G3 86% (n = 261)

Abbreviations used: IFN, pegylated interferon; G, genotype; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; SVR12, sustained virologic response at 12 weeks; SVR24, sustained virologic response at 24 weeks.

The SVR rates seen with RBV–IFN and SOF combination therapy have been remarkable, as evidenced by an SVR of more than 85% for the more difficult-to-treat genotype 1 and a higher SVR for genotypes 4, 5, and 6 at 12 weeks from the end of treatment (SVR12).[38] In addition, IFN discontinuation is historically 10% to 14% with dual therapy because of adverse effects, whereas discontinuation was 2% with RBV–IFN and SOF combination therapy.[13] Results from the FUSION trial combining SOF with only RBV produced remarkable SVR rates of 86% at 12 weeks and 94% at 16 weeks in patients who previously failed IFN therapy.[39] Table 6 provides a summary of key studies that have evaluated SOF in HCV.[38–40]

Overall, SOF has been shown to be effective for achieving SVR in many genotypes, different patient populations, various regimens, and different durations of treatment. It produces a viral load reduction in a few days and is associated with a high resistance barrier. Its pharmacokinetics is unaffected by food, age, gender, body mass index, race, or cirrhosis status. It has an approximate 60% binding to serum proteins. In addition, it has no clinically relevant interactions with antiretroviral agents, which is particularly important given the not-uncommon coinfection of HCV with HIV.

SOF is currently approved for HCV genotypes 1 and 4 in combination with RBV and IFN and for HCV genotypes 2 and 3 with RBV alone. It is the first anti-HCV combination therapy to exclude IFN and may lead the way for new regimens that achieve SVR without the intolerability of IFN. SOF is conveniently administered as a 400-mg daily oral tablet. Its most commonly cited adverse effects are fatigue, headache, nausea, insomnia, and pruritus.

Treatment guidelines

AASLD and the Infectious Diseases Society of America maintain a "living" Practice Guideline about testing, managing, and treating HCV.[3] Given the rapid rate at which the understanding of HCV is unfolding, this guideline is updated as new information becomes available. Here we summarize the first-line recommendations for HCV treatment in newly diagnosed patients (Table 7) and refer the reader to the guidelines for alternative treatment options.

The Practice Guideline recommendations include grades based on level of scientific evidence, strength of evidence, and expert opinion. To summarize, Class I represents conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective; Class II represents conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment; Class IIa represents the weight of evidence and/or opinion in favor of usefulness and efficacy; Class IIb represents usefulness and efficacy that are less well established and/or opinion; and finally, Class III represents conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or in some cases may be harmful.[3]

Strength of evidence is graded based on the following characteristics: Level A, data derived from multiple randomized clinical trials, meta-analyses, or equivalent; Level B, data derived from a single randomized trial, nonrandomized studies, or equivalent and Level C, consensus opinion or experts, case studies, or standard of care.[3]

After a diagnosis of HCV and before the discussion about which type of treatment to pursue, a commitment to treatment should be confirmed with the patient. Cost is an important factor: a 12-week regimen of SOF currently costs $84,000, which is equivalent to $1,000 per tablet. Given that a course of combined IFN and RBV costs $65,000, the total for the recommended triple-drug regimen of SOF, IFN, and RBV for HCV exceeds $100,000.41 While cure rates are exceeding 90% in most genotypes, and cost-effectiveness analysis of SOF+RBV+IFN combination therapy appears favorable in the long term, the high price associated with treatment should be well understood by the health professional and patient.[41,42] The pharmacoeconomic assessment of SOF is currently undergoing considerable debate.[43]

Once pursuit of treatment is elected, patients should have an established baseline quantification of their HCV RNA viral load to allow for a relative comparison with future measures of viremia. Viral genotyping is also very important, as this will be used to determine the HCV regimen. Different combinations of anti-HCV agents of various treatment durations are recommended for each genotype.

Throughout the guidelines, various combinations of anti-HCV therapies are recommended. In some cases, duration of therapy depends on whether the patient is eligible or ineligible for IFN treatment. Ineligibility for IFN treatment is defined as intolerance to IFN; having comorbid autoimmune disorder, decompensated hepatic disease, depression, or cardiac disease; and having baseline laboratory values of neutrophil count less than 1,5000/µL, platelet count less than 90,000/µL, and hemoglobin less than 10 g/dL. For all genotypes, monotherapy with RBV, IFN, or a DAA is not recommended because these agents used alone are not effective.

Table 7. Summary of recommended hepatitis C virus therapy for treatment-naive patients

Genotype	Regimen (grade of evidence supporting recommendation)
G1	SOF + RBV–IFN for 12 weeks if IFN eligible (IA) SOF + SMV + RBV for 12 weeks if IFN ineligible (IB)
G2	SOF + RBV for 12 weeks (IA)
G3	SOF + RBV for 24 weeks (IB)
G4	SOF + RBV–IFN for 12 weeks if IFN eligible (IIaB) SOF + RBV for 24 weeks if IFN ineligible (IIbB)
G5 or G6 (limited data)	SOF + RBV–IFN for 12 weeks (IIaB)

Abbreviations used: IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir

Treatment-naive patients

Table 7 provides a summary of recommendations for HCV treatment-naive patients. Among patients who are treatment-naive, patients with genotypes 1 or 4 should receive SOF+RBV–IFN treatment with duration of therapy dependent on the patient's IFN eligibility status. For patients with genotype 1 who are IFN ineligible, the duration is unchanged, but SMV replaces IFN. IFN-free therapy with SOF and RBV is recommended for genotypes 2 and 3.

Treatment-experienced patients

Treatment-experienced patients may be considered relapsers or nonresponders. Relapsers are defined as being HCV RNA negative at the end of treatment but thereafter have disease relapse. The NEUTRINO study evaluated SOF+RBV+IFN treatment in treatment-naive patients with genotypes 1, 4, 5, and 6.[34] Using the findings from this study, FDA has extrapolated the results to relapsers, concluding that relapsers have a similar treatment response as treatment-naive persons and should be treated similarly.

Nonresponders are patients who have a reduced treatment response and can be further classified as being null responders or partial responders. Similar to the therapy recommendations for treatment-naive patients, those for patients in whom prior RBV–IFN treatment has not been effective are as follows: 12 weeks of SOF+SMV+RBV for those with genotype 1; 12 weeks of SOF–RBV for genotype 2 (extend to 16 weeks for patients with cirrhosis); 24 weeks of SOF–RBV for genotype 3; and 12 weeks of SOF+RBV+IFN for genotypes 4, 5, and 6.

Unique patient populations

Four groups of persons with HCV are considered unique given the challenges associated with effective treatment for

them: patients with HIV/HCV coinfection, cirrhosis, recurrent HCV infection after liver transplantation, and renal impairment.

Treatment of HCV in HIV/HCV coinfected individuals is particularly challenging because of lower response rates, adverse events with IFN, limited treatment options, and complex drug interactions among the antiviral medications for both conditions. As demonstrated in a small cohort study, rapid onset of fibrosis from HCV infection in HIV-positive persons should be not considered a benign development. Decompensated cirrhosis and death within 2 to 8 years have ensued. Liver histopathophysiology at death revealed that liver destruction was secondary to HCV infection. In addition, the rate of liver failure may be related to the degree of the HIV-induced immunocompromise, which further complicates treatment and management in this population.[44]

In a Phase III trial evaluating SOF+RBV in treatment-naive HIV/HCV coinfected persons with well-controlled HIV, the SVR at 12 weeks was 76% in patients with HCV genotype 1 (n = 114), 88% in genotype 2 (n = 26), and 67% in genotype 3 (n = 42), results that improve upon the 25% to 30% SVR seen with RBV–IFN therapy. The mean CD4 counts of the patients were 559–636 cells/µL. Patients were treated with the antiretroviral agents efavirenz, atazanavir–ritonavir, darunavir–ritonavir, raltegravir (Isentress—Merck), and rilpivirine with tenofovir–emtricitabine (Complera—Gilead).[45]

Table 8 provides a general summary of the regimens recommended for HIV/HCV coinfection. SOF can be used with antiretroviral agents except didanosine, zidovudine, or tipranavir. Concurrent antiretroviral agents with SMV are limited to raltegravir, rilpivirine, maraviroc (Selzentry—Viiv Healthcare), enfuvirtide (Fuzeon—Roche), tenofovir, emtricitabine, lamivudine, and abacavir.

HCV-positive patients who have cirrhosis are considered to have compensated or decompensated liver damage. Treatment is the same for patients with compensated cirrhosis as for treatment-naive patients without cirrhosis. For patients with decompensated cirrhosis, the guidelines recommend referral to a liver transplant center (strength of recommendation, IC) or treatment with SOF+RBV for 48 weeks (IIbB). Unfortunately, cirrhosis is a predictor for treatment failure, which underscores the importance of providing excellent patient education about preventing further liver damage.

Patients who develop posttransplantation HCV infections may be treated according to the following first-line recommendations: SOF–SMV with or without RBV for compensated allograft genotype 1 and SOF–RBV for compensated allograft genotypes 2 or 3 with close monitoring of creatinine clearance (CrCL) and hemoglobin. Neither BOC nor TVR should be used in this patient population because these first-generation DAAs have toxicities and drug interactions with calcineurin inhibitors.

The fourth unique group of HCV-positive patients is those with renal impairment, defined as having a CrCL less than 30 mL/min or end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis. SOF has an inactive metabolite that is almost entirely renally eliminated via glomerular filtration and active tubular secretion. No dosage adjustment of SOF is necessary for those with higher CrCL rates. Because no dosing data exist for CrCL below 30 mL/min, SOF is not recommended in patients with ESRD.

Table 8. Summary of recommended therapy for coinfections of hepatitis C virus and human immunodeficiency virus

Genotype	Regimen (grade of evidence supporting recommendation)
G1	*Treatment-naive or RBV–IFN relapsers* SOF + RBV–IFN for 12 weeks if IFN eligible (IB) SOF + RBV for 24 weeks (IB) or SOF + SMV +/- RBV for 12 weeks (IIaC) if IFN ineligible *RBV–IFN nonresponders* SOF + SMV +/- RBV for 12 weeks (IIaC)
G2	SOF + RBV for 12 weeks (IB)
G3	SOF + RBV for 24 weeks (IB)
G4, G5, G6	Treat as recommended for HCV monoinfection for treatment-naive and treatment-experienced patients

Abbreviations used: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir

Unlike with SOF, renal clearance represents less than 1% of elimination of SMV and its metabolites; therefore, concern for renal accumulation is not important and renal adjustment is not required. While SMV exposure was calculated to be higher in patients with ESRD, no clinically important difference was noted in SMV protein plasma binding. For RBV and IFN therapy, the guidelines recommend that practitioners follow FDA-approved product labeling recommendations for patients with renal impairment, ESRD, or hemodialysis.

Hemoglobin must be monitored closely when RBV is used in this patient population. This is particularly relevant to pharmacists involved in the care of hemodialysis patients. The incidence of acute HCV infection among hemodialysis patients is high because of the risk for nosocomial infections. If RBV is to be given, practitioners should prescribe low doses (200 mg daily), monitor hemoglobin levels weekly, administer epoetin alfa to manage anemia, and provide iron intravenously to promote erythropoietin activity.

Next steps

Traditionally, HCV has been treated with combination RBV and interferon. While this dual regimen was effective in approximately one-half of patients treated, many patients were left with limited treatment options. Among those who benefited from RBV and interferon, management of adverse effects was an ongoing challenge. In this setting, agents such as SOF and SMV offer people worldwide a chance for cure. Evidence from clinical trials suggests that these agents are highly effective. In addition, the combination of SOF and SMV has been evaluated in HCV genotype 1 nonresponders to RBV–IFN and found to be effective and well tolerated.[46]

These positive findings add to the growing body of positive evidence regarding IFN-free regimens. In October 2014, the first combination once-daily tablet of ledipasvir and SOF (Harvoni—Gilead) without need for concomitant RBV–IFN

was approved by FDA for genotype 1 infection.[47,48] Similarly, once-daily SMV has received expanded approval to be given in combination with once-daily SOF as an all-oral, IFN-free, and RBV-free treatment for genotype 1 chronic HCV infection.[49] In addition, combination ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A protease inhibitor), ritonavir, and dasabuvir (NS5B polymerase inhibitor) was just approved for HCV genotype 1 infection, including compensated cirrhosis, as Viekira Pak (AbbVie).[50] The various mechanisms of action inherent in this combination therapy appear to be effective for genotypes 1a and 1b in treatment-naive and treatment-experienced patients.[51] (Of note, since the writing of this review article, Vertex has stopped sales of telaprevir in the United States.[52]) Current ongoing Phase III clinical studies include fixed-combination daclatasvir, asunaprevir, and BMS-791325 for chronic HCV genotype 1 infection and fixed-dose grazoprevir–elbasvir for genotypes 1, 4, or 6.[53,54]

Conclusion

HCV is a well-known blood-borne disease associated with substantial morbidity and mortality worldwide. The leading risk factor for HCV is injection drug use. Screening, testing, and patient education are important components to successful treatment and management of the disease. No vaccine for HCV is available, and effective treatment has eluded the medical community until recently.

Though new anti-HCV agents such as SOF, which is the backbone of current treatment recommendations, are in their early days of real-world practice, they offer hope that cure is truly possible. The combination of anti-HCV agents and the duration of treatment are based on genotype, patient treatment status, and patient risk factors. Monotherapy with interferon, RBV, or any DAA is not recommended for any genotype. Given the estimated rise in chronic HCV infection over the next few decades, the emergence of potent targeted therapies is welcome. In addition, the rapid development of interferon-free regimens is broadening treatment options and is especially relevant for patients who cannot tolerate IFN.

The long-term effects of these novel therapies remains to be seen. In the meantime, we can hope they will perform in the real-world setting as remarkably as they did in clinical trials.

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CPE assessment

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

1. Which is a risk factor for HCV infection?
a. Breastfeeding
b. Kissing
c. History of incarceration
d. Hugging

2. Which is a correct statement about HCV?
a. HCV is a single-stranded deoxyribonucleic acid virus.
b. HCV is a single-stranded ribonucleic acid virus.
c. HCV is a double-stranded deoxyribonucleic acid virus.
d. HCV is a double-stranded ribonucleic acid virus.

3. When should the hepatitis C vaccine be given?
a. When a person becomes sexually active
b. Before a patient receives blood transfusion or organ transplant
c. When a patient is considered high risk for infection
d. There is no vaccine for HCV.

4. On which enzyme does SOF act?
a. NS5A
b. NS5B
c. NS3
d. NS4

5. Who should be tested for HCV?
a. A 60-year-old man who tried intranasal illicit drug once during college
b. A child whose adopted mother is HCV-positive and adopted father is HCV-negative
c. A 49-year-old man with cirrhosis due to a long history of alcohol abuse
d. A motor vehicle crash patient who needs emergent hemodialysis

6. Which genotype is the most common in the United States and traditionally considered the most difficult to treat?
a. Genotype 1
b. Genotype 3
c. Genotype 4
d. Genotype 6

7. Regarding which practice should patients who are HCV-positive receive intensive education?
a. Sexual abstinence
b. Avoiding crowds
c. Alcohol cessation
d. Avoiding sharing utensils

8. What is the mechanism of action of BOC and TVR?
a. NS3/4A polymerase inhibitor
b. NS5B polymerase inhibitor
c. NS3/4a protease inhibitor
d. NS5B protease inhibitor

9. Which currently approved direct-acting agent is less effective in those with the Q80k polymorphism?
a. SOF
b. SMV
c. TVR
d. BOC

10. Which of the following is a true statement?
a. IFN alpha-2a is given as a fixed dose.
b. IFN alpha-2b is given as a weight-adjusted dose.
c. Both IFN products are given as weekly subcutaneous injections.
d. Both IFN products are given as daily subcutaneous injections.

CPE information

To obtain 2.0 contact hours (0.2 CEUs) of CPE credit for this activity, you must complete the online assessment and evaluation. A Statement of Credit will be awarded for a passing grade of 70% or better on the assessment. You will have two opportunities to successfully complete the assessment. Pharmacists who successfully complete this activity before February 1, 2018, can receive CPE credit. Your Statement of Credit will be available upon successful completion of the assessment and evaluation and will be stored in your 'My Training Page' and on CPE Monitor for future viewing/printing.

CPE instructions:

1. Log in or create an account at pharmacist.com and select LEARN from the top of the page; select Continuing Education, then Home Study CPE to access the Library.
2. Enter the title of this article or the ACPE number to search for the article and click on the title of the article to start the home study.
3. To receive CPE credit, select Enroll Now or Add to Cart from the left navigation and successfully complete the assessment (with randomized questions) and evaluation.
4. To get your Statement of Credit, click "Claim" on the right side of the page. You will need to provide your NABP e-profile ID number to obtain and print your Statement of Credit.

■ Live step-by-step assistance is available Monday through Friday from 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing education@aphanet.com.

11. What is the major dose-dependent adverse effect of RBV?
a. Cardiac arrhythmias
b. Anemia
c. Diarrhea
d. Gastrointestinal problems

12. What is the recommended dosing schedule for SOF?
a. 400-mg oral tablet taken daily
b. 400-mg oral tablet taken twice daily
c. 150-mg oral tablet taken daily
d. 150-mg oral tablet taken twice daily

13. What is the approximate cost for a regimen of SOF, IFN, and RBV?
a. $25,000–$50,000
b. $50,000–$75,000
c. $75,000–$100,000
d. More than $100,000

14. Which two-drug combination was recently submitted to FDA for approval as the first INF-sparing regimen?
a. BOC+SOF
b. SOF+SMV
c. RBV+SOF
d. TVR+SOF

15. Which group is considered a unique population for HCV treatment?
a. Health professionals
b. Patients with renal dysfunction (CrCL < 60 mL/min)
c. Patients with HIV/HCV coinfection
d. Patients with significant alcohol use

16. SOF has drug interactions involving which cytochrome P450 (CYP) isoenzyme?
a. CYP3A4
b. CYP1A2
c. CYP3A4/5
d. SOF has no interactions involving the CYP isoenzymes.

17. Which anti-HCV agent acts as a nucleoside analogue?
a. BOC
b. SMV
c. RBV
d. IFN

18. How is sustained virologic response defined?
a. 50% reduction in viral load
b. 80% reduction in viral load
c. Nondetectable virologic response at a certain time after anti-HCV therapy begins
d. Nondetectable virologic response at a certain time after anti-HCV therapy ends

19. Below which CrCL was SMV not studied?
a. 60 mL/min
b. 50 mL/min
c. 40 mL/min
d. 30 mL/min

20. For treatment-naive patients with genotype 1 who are IFN eligible, what is the recommended first-line treatment?
a. SOF + RBV–IFN for 12 weeks
b. SOF + SMV–IFN for 12 weeks
c. SOF + RBV–IFN for 24 weeks
d. SOF + SMV–IFN for 24 weeks

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In directions to patients, be clear and explicit

INSTITUTE FOR SAFE MEDICATION PRACTICES

Recently, a 67-year-old man, who appeared well educated and knowledgeable about his health care, arrived at the emergency department (ED) with hypotension, tachycardia, gray vision, and lightheadedness. The patient's EKG showed an abnormal sinus rhythm resembling atrial fibrillation. The patient's cardiologist recommended starting him on digoxin and increasing his current metoprolol dose.

During the medication reconciliation interview with the pharmacist, the patient described taking tamsulosin (Flomax—Boehringer Ingelheim) 0.4 mg with meals, three times a day. The patient had started the tamsulosin 2 weeks before admission and had taken 0.4 mg three times a day the entire time. The pharmacy-generated label on the tamsulosin bottle read "Take daily after a meal," but the patient had interpreted it as "Take daily after *each* meal."

The ED physician and pharmacist decided to hold the tamsulosin and not increase the metoprolol or start digoxin. The patient's sinus rhythm, blood pressure, and heart rate returned to normal by the next morning. Upon discharge, the patient received proper education about taking tamsulosin once daily and not three times a day.

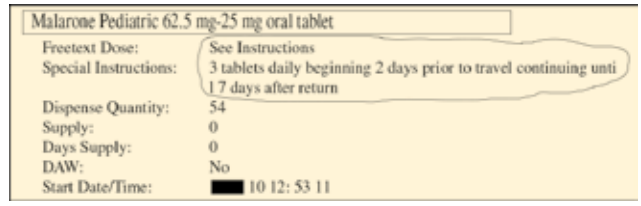

Figure 1. The letter "l" in "until" dropped to the next line and was misunderstood as the number "1," changing the directions on the label from 7 to 17 days.

Pharmacy-generated label instructions must be clear and explicit to reduce the risk of this type of error. When instructing a patient to take a medication with a meal, the label may refer to a specific meal but should always read once daily (e.g., "Take one capsule by mouth once daily after lunch"). Because low health literacy continues to be an issue, pharmacy-generated labels should contain simple, clear instructions conveying the most essential information patients need to use the medication safely and appropriately and adhere to the prescribed medication regimen.

Twice a week or twice a month?

In American parlance, the word "biweekly" is sometimes used to indicate once every 2 weeks, and "bimonthly" usually means once every 2 months. However, alternate meanings of each of these words can lead to confusion. According to available online and print dictionaries, "biweekly" is also used loosely to mean twice a week or semiweekly, and "bimonthly" can also indicate twice a month.

So, for clarity when ordering medications, avoid using these words. Instead, use terms such as "twice a week," "every other week" (or "every 2 weeks"), or "every other month."

Figure 1 shows an interesting example of a potential error caused by an electronically generated prescription that was faxed to a community pharmacy from a physician's office. Apparently, space ran out on the first line of the directions, and the word "until" was split so that the lowercase "l" appeared on the second line. The pharmacy technician mistook the letter "l" as the number 1 and entered the directions into the pharmacy computer incorrectly.

Fortunately, the pharmacist caught the error and corrected it before the prescription was dispensed to the patient. This type of error may not be easily identified and could result in an incorrect dose or wrong instructions for the patient. Electronic prescription vendors need to design systems so that words won't truncate in unconventional ways. Considering that these systems must be able to "talk" to each other, it is important for information to translate consistently.

The Institute for Safe Medication Practices (ISMP) has voiced this concern previously because many vendors become certified by organizations that do not take into account safety concerns about transfer of necessary information from the prescriber to the pharmacist. ISMP will continue tracking errors like this one and share them with computer system vendors, certifying organizations, and oversight agencies.

Patient counseling most important component

Prescription labeling practices that are well thought out must be part of an overall strategy to improve medication adherence and reduce medication errors. The prescription label cannot and should not replace critical pharmacist care responsibilities, such as appropriately identifying the patient at the time of dispensing and providing patient counseling. The single most effective component to increasing and improving patient compliance and avoiding medication errors, as documented in numerous studies, is appropriate patient counseling. The prescription label is designed to supplement this critical pharmacist responsibility and not replace it in any way.

To review ISMP's recommendations for pharmacy-generated labels, see www.ismp.org/tools/guidelines/labelFormats/comments/default.asp.

Institute for Safe Medication Practices, Horsham, PA

Have you experienced a medication error or close call? Report such incidents in confidence to ISMP's National Medication Errors Reporting Program (MERP) at www.ismp.org, ismpinfo@ismp.org, or 800-324-5723 to activate an alert system that reaches manufacturers, the medical community, and FDA. Your information may also be published anonymously to alert your professional colleagues.

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BRIEF SUMMARY

CELECOXIB CAPSULES

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WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISKS

Cardiovascular Risk

- **Celecoxib capsules may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. *(5.1, 14.6)***
- **Celecoxib capsules are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. *(4, 5.1)***

Gastrointestinal Risk

- **NSAIDs, including celecoxib, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal (GI) events. *(5.4)***

1 INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of celecoxib capsules and other treatment options before deciding to use celecoxib capsules. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

1.1 Osteoarthritis (OA)

Celecoxib capsules are indicated for relief of the signs and symptoms of OA [*see Clinical Studies (14.1)*].

1.2 Rheumatoid Arthritis (RA)

Celecoxib capsules are indicated for relief of the signs and symptoms of RA [*see Clinical Studies (14.2)*].

1.3 Juvenile Rheumatoid Arthritis (JRA)

Celecoxib capsules are indicated for relief of the signs and symptoms of JRA in patients 2 years and older [*see Clinical Studies (14.3)*].

1.4 Ankylosing Spondylitis (AS)

Celecoxib capsules are indicated for the relief of signs and symptoms of AS [*see Clinical Studies (14.4)*].

1.5 Acute Pain (AP)

Celecoxib capsules are indicated for the management of AP in adults [*see Clinical Studies (14.5)*].

1.6 Primary Dysmenorrhea (PD)

Celecoxib capsules are indicated for the treatment of PD [*see Clinical Studies (14.5)*].

4 CONTRAINDICATIONS

Celecoxib capsules are contraindicated:

- In patients with known hypersensitivity to celecoxib, aspirin, or other NSAIDs.
- In patients who have demonstrated allergic-type reactions to sulfonamides.
- In patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe anaphylactoid reactions to NSAIDs, some of them fatal, have been reported in such patients [*see Warnings and Precautions (5.7, 5.13)*].
- For the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Chronic use of celecoxib may cause an increased risk of serious adverse cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. In the APC (Adenoma Prevention with Celecoxib) trial, the hazard ratio for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 to 8.5) for celecoxib 400 mg twice daily and 2.8 (95% CI 1.1 to 7.2) with celecoxib 200 mg twice daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 3% (20/671 subjects) and 2.5% (17/685 subjects),
respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction [*see Clinical Studies (14.6)*]. All NSAIDs, both COX-2 selective and non-selective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with celecoxib, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and celecoxib does increase the risk of serious GI events [*see Warnings and Precautions (5.4)*].

Two large, controlled, clinical trials of a different COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [*see Contraindications (4)*].

5.2 Hypertension

As with all NSAIDs, celecoxib can lead to the onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including celecoxib, should be used with caution in patients with hypertension.

Blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy. The rates of hypertension from the CLASS trial in the celecoxib, ibuprofen and diclofenac-treated patients were 2.4%, 4.2% and 2.5%, respectively [*see Clinical Studies (14.6)*].

5.3 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs, including celecoxib [*see Adverse Reactions (6.1)*]. In the CLASS study [*see Clinical Studies (14.6)*], the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on celecoxib 400 mg twice daily (4 fold and 2 fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively. Celecoxib should be used with caution in patients with fluid retention or heart failure.

5.4 Gastrointestinal (GI) Effects Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including celecoxib, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS trial, and 2.19% for the subgroup on low-dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA [*see Clinical Studies (14.6)*]. With longer duration of use of NSAIDs, there is a trend for increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10 fold increased risk for developing a GI bleed compared to patients with neither of these
risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest duration consistent with individual patient treatment goals. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during celecoxib therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

5.5 Hepatic Effects

Borderline elevations of one or more liver-associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including celecoxib [*see Adverse Reactions (6.1)*]. In controlled clinical trials of celecoxib, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for celecoxib and 5% for placebo, and approximately 0.2% of patients taking celecoxib and 0.3% of patients taking placebo had notable elevations of ALT and AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), celecoxib should be discontinued.

5.6 Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs.

No information is available from controlled clinical studies regarding the use of celecoxib in patients with advanced renal disease. Therefore, treatment with celecoxib is not recommended in these patients with advanced renal disease. If celecoxib therapy must be initiated, close monitoring of the patient's renal function is advisable.

5.7 Anaphylactoid Reactions
As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to celecoxib. In postmarketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving celecoxib. Celecoxib should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs [*see Contraindications (4), Warnings and Precautions (5.7)*]. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

5.8 Skin Reactions
Celecoxib is a sulfonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

5.9 Pregnancy
In late pregnancy, starting at 30 weeks gestation, celecoxib should be avoided because it may cause premature closure of the ductus arteriosus [*see Use in Specific Populations (8.1)*].

5.10 Corticosteroid Treatment
Celecoxib cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

5.11 Hematological Effects
Anemia is sometimes seen in patients receiving celecoxib. In controlled clinical trials the incidence of anemia was 0.6% with celecoxib and 0.4% with placebo. Patients on long-term treatment with celecoxib should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. Celecoxib does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages [*see Clinical Pharmacology (12.2)*].

5.12 Disseminated Intravascular Coagulation (DIC)
Celecoxib should be used only with caution in pediatric patients with systemic onset JRA due to the risk of disseminated intravascular coagulation.

5.13 Preexisting Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, celecoxib should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

5.14 Laboratory Tests
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have a CBC and a chemistry profile checked periodically. If abnormal liver tests or renal tests persist or worsen, celecoxib should be discontinued.

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving celecoxib compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

5.15 Inflammation
The pharmacological activity of celecoxib in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

5.16 Concomitant NSAID Use
The concomitant use of celecoxib with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

6 ADVERSE REACTIONS
Of the celecoxib-treated patients in the premarketing controlled clinical trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients received a total daily dose of celecoxib of 200 mg (100 mg twice daily or 200 mg once daily) or more, including more than 400 treated at 800 mg (400 mg twice daily). Approximately 3,900 patients received celecoxib at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

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 adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

6.1 Premarketing Controlled Arthritis Trials
Table 1 lists all adverse events, regardless of causality, occurring in ≥ 2% of patients receiving celecoxib from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group. Since these 12 trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

Table 1: Adverse Events Occurring in ≥ 2% of Celecoxib Patients From Premarketing Controlled Arthritis Trials

	Celecoxib N = 4146	Placebo N = 1864	NAP N = 1366	DCF N = 387	IBU N = 345
Gastrointestinal					
Abdominal Pain	4.1%	2.8%	7.7%	9%	9%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6%	3.4%	6.7%
Body as a Whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral Edema	2.1%	1.1%	2.1%	1%	3.5%
Injury-Accidental	2.9%	2.3%	3%	2.6%	3.2%
Central, Peripheral Nervous System					
Dizziness	2%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5%	4.3%	4%	5.4%	5.8%
Upper Respiratory Tract Infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

Celecoxib = Celecoxib 100 to 200 mg twice daily or 200 mg once daily;
NAP = Naproxen 500 mg twice daily;
DCF = Diclofenac 75 mg twice daily;
IBU = Ibuprofen 800 mg three times daily.

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving celecoxib and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the celecoxib treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of celecoxib patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The following adverse reactions occurred in 0.1 to 1.9% of patients treated with celecoxib (100 to 200 mg twice daily or 200 mg once daily):

Gastrointestinal: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, vomiting

Cardiovascular: Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction

General: Allergy aggravated, allergic reaction, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

Central, peripheral nervous system: Leg cramps, hypertonia, hypoesthesia, migraine, paresthesia, vertigo

Hearing and vestibular: Deafness, tinnitus

Heart rate and rhythm: Palpitation, tachycardia

Liver and biliary: Hepatic function abnormal, SGOT increased, SGPT increased

Metabolic and nutritional: BUN increased, CPK increased, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increased, creatinine increased, alkaline phosphatase increased, weight increased

Musculoskeletal: Arthralgia, arthrosis, myalgia, synovitis, tendinitis

Platelets (bleeding or clotting): Ecchymosis, epistaxis, thrombocythemia

Psychiatric: Anorexia, anxiety, appetite increased, depression, nervousness, somnolence

Hemic: Anemia

Respiratory: Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia

Skin and appendages: Alopecia, dermatitis, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria

Application site disorders: Cellulitis, dermatitis contact

Urinary: Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus

The following serious adverse events (causality not evaluated) occurred in < 0.1% of patients (cases reported only in postmarketing experience are indicated *in italics*):

Cardiovascular: Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, *vasculitis, deep venous thrombosis*

Gastrointestinal: Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus

Liver and biliary: Cholelithiasis, *hepatitis, jaundice, liver failure*

Hemic and lymphatic: Thrombocytopenia, *agranulocytosis, aplastic anemia, pancytopenia, leucopenia*

Metabolic: *Hypoglycemia, hyponatremia*

Nervous: Ataxia, suicide, *aseptic meningitis, ageusia, anosmia, fatal intracranial hemorrhage* [*see Drug Interactions (7.1)*]

Renal: Acute renal failure, *interstitial nephritis*

Skin: *Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis*

General: Sepsis, sudden death, *anaphylactoid reaction, angioedema*

6.2 The Celecoxib Long-Term Arthritis Safety Study [see *Special Studies* (*14.6*)]

Hematological Events: The incidence of clinically significant decreases in hemoglobin (> 2 g/dL) was lower in patients on celecoxib 400 mg twice daily (0.5%) compared to patients on either diclofenac 75 mg twice daily (1.3%) or ibuprofen 800 mg three

times daily 1.9%. The lower incidence of events with celecoxib was maintained with or without ASA use [*see Clinical Pharmacology (12.2)*].

Withdrawals/Serious Adverse Events: Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for celecoxib, diclofenac and ibuprofen were 24%, 29%, and 26%, respectively. Rates for serious adverse events (i.e., causing hospitalization or felt to be life-threatening or otherwise medically significant), regardless of causality, were not different across treatment groups (8%, 7%, and 8%, respectively).

6.3 Juvenile Rheumatoid Arthritis Study

In a 12 week, double-blind, active-controlled study, 242 JRA patients 2 years to 17 years of age were treated with celecoxib or naproxen; 77 JRA patients were treated with celecoxib 3 mg/kg BID, 82 patients were treated with celecoxib 6 mg/kg BID, and 83 patients were treated with naproxen 7.5 mg/kg BID. The most commonly occurring (≥ 5%) adverse events in celecoxib treated patients were headache, fever (pyrexia), upper abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrhea and vomiting. The most commonly occurring (≥ 5%) adverse experiences for naproxen-treated patients were headache, nausea, vomiting, fever, upper abdominal pain, diarrhea, cough, abdominal pain, and dizziness (**Table 2**). Compared with naproxen, celecoxib at doses of 3 and 6 mg/kg BID had no observable deleterious effect on growth and development during the course of the 12 week double-blind study. There was no substantial difference in the number of clinical exacerbations of uveitis or systemic features of JRA among treatment groups.

In a 12 week, open-label extension of the double-blind study described above, 202 JRA patients were treated with celecoxib 6 mg/kg BID. The incidence of adverse events was similar to that observed during the double-blind study; no unexpected adverse events of clinical importance emerged.

Table 2: Adverse Events Occurring in ≥ 5% of JRA Patients in Any Treatment Group, by System Organ Class (% of patients with events)

	All Doses Twice Daily		
System Organ Class Preferred Term	**Celecoxib 3 mg/kg N = 77**	**Celecoxib 6 mg/kg N = 82**	**Naproxen 7.5 mg/kg N = 83**
Any Event	**64**	**70**	**72**
Eye Disorders	**5**	**5**	**5**
Gastrointestinal	**26**	**24**	**36**
Abdominal pain NOS	4	7	7
Abdominal pain upper	8	6	10
Vomiting NOS	3	6	11
Diarrhea NOS	5	4	8
Nausea	7	4	11
General	**13**	**11**	**18**
Pyrexia	8	9	11
Infections	**25**	**20**	**27**
Nasopharyngitis	5	6	5
Injury and Poisoning	**4**	**6**	**5**
Investigations[a]	**3**	**11**	**7**
Musculoskeletal	**8**	**10**	**17**
Arthralgia	3	7	4
Nervous System	**17**	**11**	**21**
Headache NOS	13	10	16
Dizziness (excl vertigo)	1	1	7
Respiratory	**8**	**15**	**15**
Cough	7	7	8
Skin & Subcutaneous	**10**	**7**	**18**

a Abnormal laboratory tests, which include: Prolonged activated partial thromboplastin time, Bacteriuria NOS present, Blood creatine phosphokinase increased, Blood culture positive, Blood glucose increased, Blood pressure increased, Blood uric acid increased, Hematocrit decreased, Hematuria present, Hemoglobin decreased, Liver function tests NOS abnormal, Proteinuria present, Transaminase NOS increased, Urine analysis abnormal NOS

6.4 Other Pre-Approval Studies

Adverse Events from Ankylosing Spondylitis Studies: A total of 378 patients were treated with celecoxib in placebo- and active-controlled AS studies. Doses up to 400 mg once daily were studied. The types of adverse events reported in the AS studies were similar to those reported in the OA/RA studies.

Adverse Events from Analgesia and Dysmenorrhea Studies: Approximately 1,700 patients were treated with celecoxib in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose of study medication. Doses up to 600 mg/day of celecoxib were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies.

6.5 The APC and PreSAP Trials

Adverse reactions from long-term, placebo-controlled polyp prevention studies:

Exposure to celecoxib in the APC and PreSAP trials was 400 to 800 mg daily for up to 3 years [*see Special Studies Adenomatous Polyp Prevention Studies (14.6)*]

Some adverse reactions occurred in higher percentages of patients than in the arthritis premarketing trials (treatment durations up to 12 weeks; *see Adverse events from celecoxib premarketing controlled arthritis trials*, above). The adverse reactions for which these differences in patients treated with celecoxib were greater as compared to the arthritis premarketing trials were as follows:

	Celecoxib (400 to 800 mg daily) N = 2285	**Placebo N = 1303**
Diarrhea	10.5%	7.0%
Gastroesophageal reflux disease	4.7%	3.1%
Nausea	6.8%	5.3%
Vomiting	3.2%	2.1%
Dyspnea	2.8%	1.6%
Hypertension	12.5%	9.8%

The following additional adverse reactions occurred in ≥ 0.1% and < 1% of patients taking celecoxib, at an incidence greater than placebo in the long-term polyp prevention studies, and were either not reported during the controlled arthritis premarketing trials or occurred with greater frequency in the long-term, placebo-controlled polyp prevention studies:

Nervous system disorders: Cerebral infarction

Eye disorders: Vitreous floaters, conjunctival hemorrhage

Ear and labyrinth: Labyrinthitis

Cardiac disorders: Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy

Vascular disorders: Deep vein thrombosis

Reproductive system and breast disorders: Ovarian cyst

Investigations: Blood potassium increased, blood sodium increased, blood testosterone decreased

Injury, poisoning and procedural complications: Epicondylitis, tendon rupture

7 DRUG INTERACTIONS

General: Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Coadministration of celecoxib with drugs that are known to inhibit CYP2C9 should be done with caution. Significant interactions may occur when celecoxib is administered together with drugs that inhibit CYP2C9.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6.

7.1 Warfarin

Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing celecoxib therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily 2 to 5 mg doses of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in postmarketing experience, serious bleeding events, some of which were fatal, have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving celecoxib concurrently with warfarin.

7.2 Lithium

In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg twice daily with celecoxib 200 mg twice daily as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

7.3 Aspirin

Celecoxib can be used with low-dose aspirin. However, concomitant administration of aspirin with celecoxib increases the rate of GI ulceration or other complications, compared to use of celecoxib alone [*see Warnings and Precautions (5.1, 5.4) and Clinical Studies (14.6)*]. **Because of its lack of platelet effects, celecoxib is not a substitute for aspirin for cardiovascular prophylaxis [*see Clinical Pharmacology (12.2)*].**

7.4 ACE-Inhibitors and Angiotensin II Antagonists

Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors and angiotensin II antagonists. This interaction should be given consideration in patients taking celecoxib concomitantly with ACE-inhibitors and angiotensin II antagonists [*see Clinical Pharmacology (12.2)*].

7.5 Fluconazole

Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole [*see Clinical Pharmacology (12.3)*]. Celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole.

7.6 Furosemide

Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

7.7 Methotrexate

In an interaction study of rheumatoid arthritis patients taking methotrexate, celecoxib did not have an effect on the pharmacokinetics of methotrexate [*see Clinical Pharmacology (12.3)*].

7.8 Concomitant NSAID Use

The concomitant use of celecoxib with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy category C. Pregnancy category D from 30 weeks of gestation onward.

Teratogenic Effects

Celecoxib at oral doses ≥ 150 mg/kg/day (approximately 2 fold human exposure at 200 mg twice daily as measured by AUC0-24), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed 6 fold human exposure based on the $AUC_{0\text{-}24}$ at 200 mg twice daily) throughout organogenesis. There are no studies in pregnant women. Celecoxib should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Celecoxib produced pre-implantation and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages ≥ 50 mg/kg/day (approximately 6 fold human exposure based on the $AUC_{0\text{-}24}$ at 200 mg twice daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are

they expected at clinical exposures. No studies have been conducted to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. Therefore, use of celecoxib during the third trimester of pregnancy should be avoided.

8.2 Labor and Delivery

Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7 fold human exposure as measured by the AUC_{0-24} at 200 mg BID). The effects of celecoxib on labor and delivery in pregnant women are unknown.

8.3 Nursing Mothers

Limited data from 3 published reports that included a total of 12 breastfeeding women showed low levels of celecoxib in breast milk. The calculated average daily infant dose was 10 to 40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year-old child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events. Caution should be exercised when celecoxib is administered to a nursing woman.

8.4 Pediatric Use

Celecoxib is approved for relief of the signs and symptoms of Juvenile Rheumatoid Arthritis in patients 2 years and older. Safety and efficacy have not been studied beyond six months in children. The long-term cardiovascular toxicity in children exposed to celecoxib has not been evaluated and it is unknown if long-term risks may be similar to that seen in adults exposed to celecoxib or other COX-2 selective and non-selective NSAIDs [*see BOXED WARNING, Warnings and Precautions (5.12), and Clinical Studies (14.3)*].

The use of celecoxib in patients 2 years to 17 years of age with pauciarticular, polyarticular course JRA or in patients with systemic onset JRA was studied in a 12 week, double-blind, active controlled, pharmacokinetic, safety and efficacy study, with a 12 week open-label extension. Celecoxib has not been studied in patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), and in patients with active systemic features. Patients with systemic onset JRA (without active systemic features) appear to be at risk for the development of abnormal coagulation laboratory tests. In some patients with systemic onset JRA, both celecoxib and naproxen were associated with mild prolongation of activated partial thromboplastin time (APTT) but not prothrombin time (PT). NSAIDs including celecoxib should be used only with caution in patients with systemic onset JRA, due to the risk of disseminated intravascular coagulation. Patients with systemic onset JRA should be monitored for the development of abnormal coagulation tests [see *Dosage and Administration (2.3), Warnings and Precautions (5.12), Adverse Reactions (6.3), Animal Toxicology (13.2), Clinical Studies (14.3)*].

Alternative therapies for treatment of JRA should be considered in pediatric patients identified to be CYP2C9 poor metabolizers [see *Poor Metabolizers of CYP2C9 Substrates (8.8)*].

8.5 Geriatric Use

Of the total number of patients who received celecoxib in pre-approval clinical trials, more than 3,300 were 65 to 74 years of age, while approximately 1,300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers. However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous postmarketing reports of fatal GI events and acute renal failure in the elderly than in younger patients [*see Warnings and Precautions (5.4, 5.6)*].

8.6 Hepatic Insufficiency

The daily recommended dose of celecoxib capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. The use of celecoxib in patients with severe hepatic impairment is not recommended [*see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)*].

8.7 Renal Insufficiency

Celecoxib is not recommended in patients with severe renal insufficiency [*see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)*].

8.8 Poor Metabolizers of CYP2C9 Substrates

Patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers (i.e., CYP2C9*3/*3). Alternative management should be considered in JRA patients identified to be CYP2C9 poor metabolizers [*see Dosage and Administration (2.6) and Clinical Pharmacology (12.5)*].

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Important Safety Information (continued)

WARNINGS AND PRECAUTIONS: As with all NSAIDs, celecoxib can lead to the onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. Blood pressure should be monitored closely while patients are taking celecoxib. Fluid retention and edema have been observed in some patients taking NSAIDs. Use celecoxib with caution in patients with fluid retention or heart failure. Celecoxib should be used only with caution in pediatric patients with systemic onset JRA due to the risk of disseminated intravascular coagulation.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or GI bleeding. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. Concurrent use of aspirin, oral corticosteroids or anticoagulants with celecoxib does increase the risk of serious GI events, as does a longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Fatal GI events are most common in elderly or debilitated patients. Patients on long-term treatment with celecoxib should be monitored for signs and symptoms of GI bleeding, and receive periodic assessments of CBC and chemistry profile. Borderline elevations of one or more liver-associated enzymes and rare cases of severe hepatic reactions have been reported. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib. It may be necessary to discontinue celecoxib therapy.

Renal papillary necrosis and other renal injury may occur with long term use of celecoxib. Patients at greatest risk of deterioration of renal function while taking celecoxib are those with impaired renal function, heart failure, liver dysfunction; those taking diuretics, angiotensin converting enzyme (ACE)-inhibitors, or angiotensin II receptor antagonists; and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Treatment with celecoxib is not recommended in patients with advanced renal disease. If celecoxib therapy must be initiated in these patients, close monitoring of the patient's renal function is advisable. Elevated BUN has occurred more frequently in patients receiving celecoxib than placebo.

Celecoxib should not be given to patients with the aspirin triad. Celecoxib is not a substitute for corticosteroids nor should it be used to treat corticosteroid insufficiency. However, the pharmacological activity of celecoxib in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions. Celecoxib is a sulfonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which can be fatal. Inform patients about the signs and symptoms of serious skin manifestations, and discontinue celecoxib at the first appearance of skin rash or any other sign of hypersensitivity.

Celecoxib should be used during pregnancy only if the potential benefit justifies the potential risk of teratogenic effects. Starting at 30 weeks gestation, celecoxib use should be avoided.

Anemia is sometimes seen in patients receiving celecoxib. Check hemoglobin or hematocrit if patients on long-term celecoxib therapy exhibit any signs or symptoms of anemia or blood loss.

Celecoxib metabolism is mediated by CYP2C9, and it has shown *in vitro* activity of inhibiting CYP2D6. Significant interactions may occur when celecoxib is administered together with drugs that inhibit CYP2C9 (e.g., fluconazole), or with drugs that are metabolized by CYP2D6.

The most common adverse reactions were abdominal pain, diarrhea, dyspepsia, flatulence, peripheral edema, accidental injury, dizziness, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, and rash.

For more information, please see full Prescribing Information, including Boxed Warnings.

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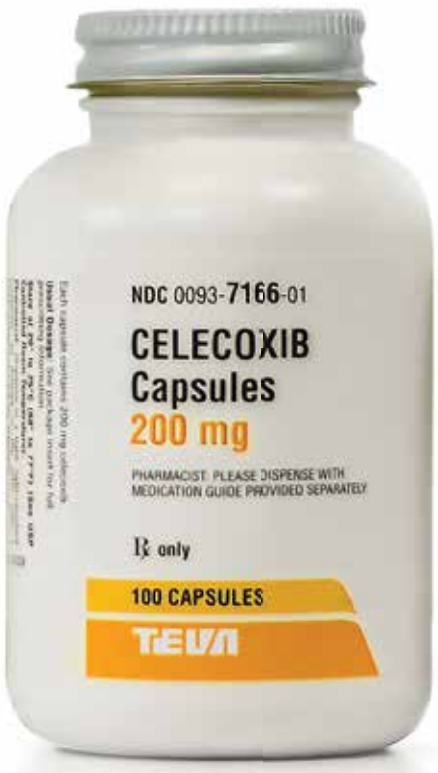

Celecoxib Capsules		
Strength	**Size**	**NDC**
50 mg	60	00093-7306-06
100 mg	100	00093-7165-01
	500	00093-7165-05
200 mg	100	00093-7166-01
	500	00093-7166-05
400 mg	60	00093-7170-06

INDICATIONS

Celecoxib capsules for oral use are a non-steroidal anti-inflammatory drug (NSAID) indicated for relief of the signs and symptoms of osteoporosis, rheumatoid arthritis, juvenile rheumatoid arthritis (JRA) in patients 2 years of age and older, and ankylosing spondylitis. Celecoxib capsules are also indicated for the management of acute pain and for the treatment of primary dysmenorrhea. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

IMPORTANT SAFETY INFORMATION

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISKS

Cardiovascular Risk

- **Celecoxib capsules may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with CV disease or risk factors for CV disease may be at greater risk.**
- **Celecoxib capsules are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.**

Gastrointestinal Risk

- **NSAIDs, including celecoxib, cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious GI events.**

CONTRAINDICATIONS: Celecoxib capsules are contraindicated in patients with known hypersensitivity to celecoxib, aspirin, or other NSAIDs; in patients who have demonstrated allergic-type reactions to sulfonamides; and in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs, as severe anaphylactoid reactions to NSAIDs, some of them fatal, have been reported in such patients. Celecoxib capsules are contraindicated for the treatment of peri-operative pain in the setting of CABG surgery.

Please see continued Important Safety Information and brief summary of Prescribing Information, including **Boxed Warnings**, continued on adjacent page.

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