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The pharmacist's role 19

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APREMILAST
New option for plaque psoriasis PG. 30

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VOL. 159 NO. 01

Voice of the Pharmacist DrugTopics.com January 2015

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2015 SALARY SURVEY

Incomes Hold Steady

PHARMACISTS PLEASED with COMPENSATION, BENEFITS

page 22

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MTM opportunities in caring for the patient with CVD Page 40

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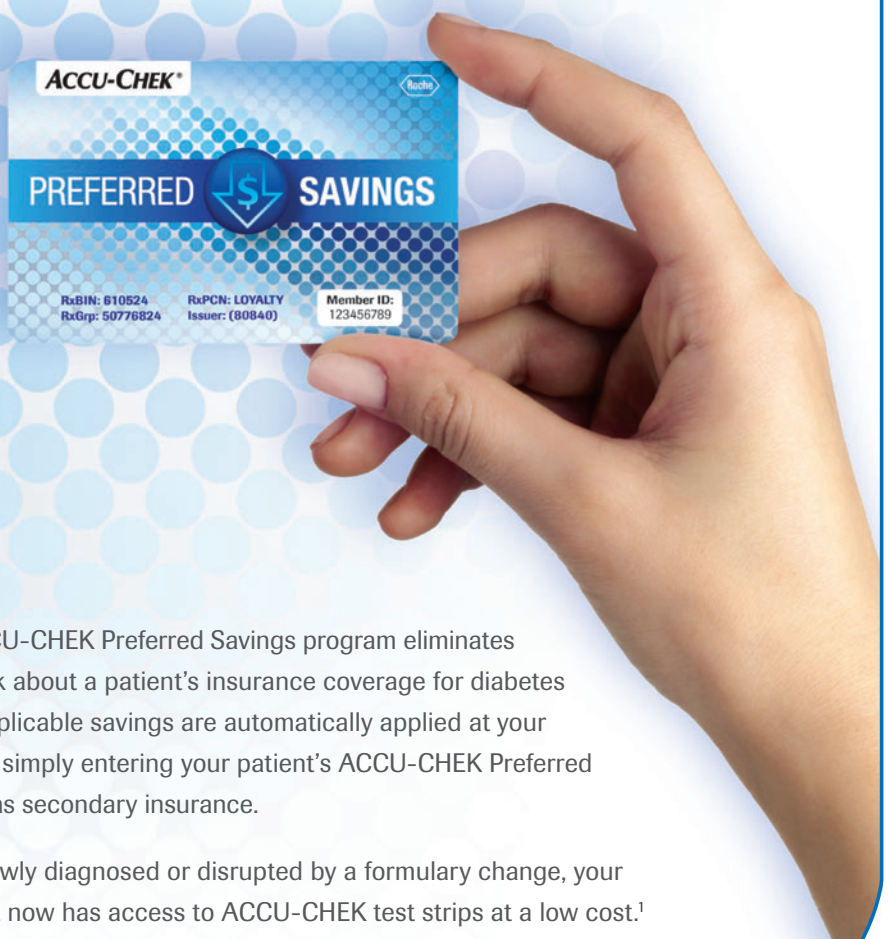

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JANUARY 2015

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VOL. 159 NO. 1

COVER STORY

Incomes hold steady

2015 SALARY SURVEY

Drug Topics' 2015 salary survey finds that satisfaction among pharmacists remains high, thanks in part to favorable compensation and benefits packages. PAGE 22

PRESCRIBED READING

Wole Williams, PharmD
Allow for the possibility PAGE 8

David Stanley, RPh
What's the holdup? PAGE 10

Sharrel Pinto, PharmD
STOMPPING for adherence PAGE 14

Andrew Faust, PharmD
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Warning of Secondary Exposure to Testosterone: Virilization has been reported in children who were secondarily exposed to testosterone gel. Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel. Healthcare providers should advise patients to strictly adhere to recommended instructions for use.

Indication: Testosterone Gel 1% is used as a replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Safety and efficacy of testosterone gel in males less than 18 years old have not been established. Testosterone Gel 1% is not intended for use in women. Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure.

Important Safety Information

What is the most important information I should know about testosterone gel?

Testosterone gel can transfer from your body to others. Women and children should avoid contact with the unwashed or unclothed area where testosterone gel has been applied to your skin. Early signs and symptoms of puberty have happened in young children who were accidentally exposed to testosterone through contact with men using testosterone gel. Stop using testosterone gel and call your healthcare provider right away if you see any signs and symptoms in a child or a woman that may have occurred through accidental exposure to testosterone gel. Signs and symptoms of exposure to testosterone gel in children may include:

- enlarged genitals or early development of pubic hair
- increased erections, sex drive or aggressive behavior

Signs and symptoms of exposure to testosterone gel in women may include:

- changes in body hair
- a large increase in acne

To lower the risk of transfer of testosterone gel from your body to others, you should follow these important instructions:

- Apply testosterone gel only to areas that will be covered by a short sleeve T-shirt. These areas are your shoulders and upper arms, or stomach area (abdomen), or shoulders, upper arms and stomach area.
- Wash your hands right away with soap and water after applying testosterone gel.
- After the gel has dried, cover the application area with clothing. Keep the area covered until you have washed the application area well or have showered.
- If you expect to have skin-to-skin contact with another person, first wash the application area well with soap and water.
- If a woman or child makes contact with the testosterone gel application area, that area on the woman or child should be washed well with soap and water right away.

Who should not use testosterone gel?

Do not use testosterone gel if you:

- have breast cancer
- have or might have prostate cancer
- are pregnant or may become pregnant or breast-feeding. Testosterone gel may harm your unborn or breast-feeding baby. Women who are pregnant or who may become pregnant should avoid contact with the area of skin where testosterone gel has been applied.

Talk to your healthcare provider before taking this medicine if you have any of the above conditions.

What are the possible side effects of testosterone gel?

Testosterone gel can cause serious side effects including:

- If you already have enlargement of your prostate gland your signs and symptoms can get worse while using testosterone gel. This can include:
  - increased urination at night
  - trouble starting your urine stream
  - having to pass urine many times during the day
  - having an urge that you have to go to the bathroom right away
  - having a urine accident
  - being unable to pass urine or weak urine flow
- Possible increased risk of prostate cancer. Your healthcare provider should check you for prostate cancer or any other prostate problems before you start and while you use testosterone gel.
- In large doses testosterone gel may lower your sperm count.
- Swelling of your ankles, feet, or body, with or without heart failure.
- Enlarged or painful breasts.
- Have problems breathing while you sleep (sleep apnea).
- Blood clots in the legs. This can include pain, swelling or redness of your legs.

The most common side effects of testosterone gel include:

- acne
- skin irritation where testosterone gel is applied
- lab test changes
- increased prostate specific antigen (a test used to screen for prostate cancer)

Other side effects include more erections than are normal for you or erections that last a long time.

Call your healthcare provider right away if you have any side effects listed above or that does not go away.

These are not all the possible side effects of testosterone gel. For more information, ask your healthcare provider or pharmacist.

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

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Please see additional patient information on adjacent page.

MEDICATION GUIDE

Testosterone Gel (tes-TOS-te-rone gel) CIII Rx Only

Read this Medication Guide that comes with testosterone gel before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about testosterone gel?

1. **Early signs and symptoms of puberty have happened in young children who were accidentally exposed to testosterone through contact with men using testosterone gel.**

Signs and symptoms of early puberty in a child may include:

- enlarged penis or clitoris
- early development of pubic hair
- increased erections or sex drive
- aggressive behavior

Testosterone gel can transfer from your body to others.

2. **Women and children should avoid contact with the unwashed or unclothed area where testosterone gel has been applied to your skin.**

   Stop using testosterone gel and call your healthcare provider right away if you see any signs and symptoms in a child or a woman that may have occurred through accidental exposure to testosterone gel.

Signs and symptoms of exposure to testosterone gel in children may include:

- enlarged penis or clitoris
- early development of pubic hair
- increased erections or sex drive
- aggressive behavior

Signs and symptoms of exposure to testosterone gel in women may include:

- changes in body hair
- a large increase in acne

To lower the risk of transfer of testosterone gel from your body to others, you should follow these important instructions:

- **Apply testosterone gel only to areas that will be covered by a short sleeve T-shirt.** These areas are your shoulders and upper arms, or stomach area (abdomen), or shoulders, upper arms and stomach area.
- **Wash your hands right away** with soap and water after applying testosterone gel.
- **After the gel has dried, cover the application area with clothing.** Keep the area covered until you have washed the application area well or have showered.
- **If you expect to have skin-to-skin contact with another person, first wash the application area well with soap and water.**
- **If a woman or child makes contact with the testosterone gel application area, that area on the woman or child should be washed well with soap and water right away.**

What is testosterone gel?

Testosterone gel is a prescription medicine that contains testosterone. Testosterone gel is used to treat adult males who have low or no testosterone.

Your healthcare provider will test your blood before you start and while you are using testosterone gel.

It is not known if testosterone gel is safe or effective in children younger than 18 years old. Improper use of testosterone gel may affect bone growth in children.

Testosterone gel is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your testosterone gel in a safe place to protect it. Never give your testosterone gel to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and is against the law.

Testosterone gel is not meant for use in women.

Who should not use testosterone gel?

Do not use testosterone gel if you:

- have breast cancer
- have or might have prostate cancer
- are pregnant or may become pregnant or breast-feeding. Testosterone gel may harm your unborn or breast-feeding baby.

  Women who are pregnant or who may become pregnant should avoid contact with the area of skin where testosterone gel has been applied.

Talk to your healthcare provider before taking this medicine if you have any of the above conditions.

What should I tell my healthcare provider before using testosterone gel?

Before you use testosterone gel, tell your healthcare provider if you:

- have breast cancer
- have or might have prostate cancer
- have urinary problems due to an enlarged prostate
- have heart problems
- have liver or kidney problems
- have problems breathing while you sleep (sleep apnea)
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using testosterone gel with certain other medicines can affect each other.

Especially, tell your healthcare provider if you take:

- insulin
- corticosteroids
- medicines that decrease blood clotting

Know the medicines you take. Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

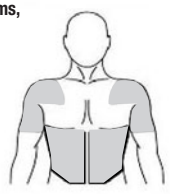
How should I use testosterone gel?

- It is important that you apply testosterone gel exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much testosterone gel to apply and when to apply it.
- Your healthcare provider may change your testosterone gel dose. **Do not** change your testosterone gel dose without talking to your healthcare provider.
- **Testosterone gel is to be applied to the area of your shoulders, upper arms, or abdomen that will be covered by a short sleeve t-shirt. Do not** apply testosterone gel to any other parts of your body such as your penis, scrotum, or back.
- Apply testosterone gel at the same time each morning. Testosterone gel should be applied after showering or bathing.
- **Wash your hands right away** with soap and water after applying testosterone gel.
- Avoid showering, swimming, or bathing for at least 5 hours after you apply testosterone gel.
- Testosterone gel is flammable until dry. Let testosterone gel dry before smoking or going near an open flame.
- Let the application areas dry before putting on a t-shirt.

Applying testosterone gel:

Testosterone gel comes in a pump or in packets.

- **Before applying testosterone gel, make sure that your shoulders, upper arms, and abdomen are clean, dry, and there is no broken skin.**
- The application sites for testosterone gel are the shoulders, upper arms, or abdomen that will be covered by a t-shirt (See Figure A).



(Figure A)

If you are using the testosterone gel pump:

- Before using a new bottle of testosterone gel for the first time, you will need to prime the pump. To prime the testosterone gel pump, slowly push the pump all the way down 3 times.
- **Do not** use any testosterone gel that came out while priming. Wash it down the sink to avoid accidental exposure to others. Your testosterone gel pump is now ready to use.
- Remove the cap from the pump. Then, position the nozzle over the palm of your hand and slowly push the pump all the way down. Apply testosterone gel to the application site. You may also apply testosterone gel directly to the application site.
- **Wash your hands with soap and water right away.**
- Your healthcare provider will tell you the number of times to press the pump for each dose.

If you are using testosterone gel packets:

- Tear open the packet completely at the dotted line. Squeeze from the bottom of the packet to the top.
- Squeeze all of the testosterone gel out of the packet into the palm of your hand. Apply testosterone gel to the application site. You may also apply testosterone gel from the packet directly to the application site.
- Testosterone gel should be applied right away.
- **Wash your hands with soap and water right away.**

What are the possible side effects of testosterone gel?

Testosterone gel can cause serious side effects including:

- See "What is the most important information I should know about testosterone gel?"
- **If you already have enlargement of your prostate gland your signs and symptoms can get worse while using testosterone gel.** This can include:
  - increased urination at night
  - trouble starting your urine stream
  - having to pass urine many times during the day
  - having an urge that you have to go to the bathroom right away
  - having a urine accident
  - being unable to pass urine or weak urine flow
- **Possible increased risk of prostate cancer.** Your healthcare provider should check you for prostate cancer or any other prostate problems before you start and while you use testosterone gel.
- **In large doses testosterone gel may lower your sperm count.**
- **Swelling of your ankles, feet, or body, with or without heart failure.**
- **Enlarged or painful breasts.**
- **Have problems breathing while you sleep (sleep apnea).**
- **Blood clots in the legs or lungs.** Signs and symptoms of a blood clot in your leg can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.

Call your healthcare provider right away if you have any of the serious side effects listed above.

The most common side effects of testosterone gel include:

- acne
- skin irritation where testosterone gel is applied
- lab test changes
- increased prostate specific antigen (a test used to screen for prostate cancer)

Other side effects include more erections than are normal for you or erections that last a long time.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of testosterone gel. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store testosterone gel?

- Store testosterone gel between 68°F to 77°F (20°C to 25°C).
- Safely throw away used testosterone gel in household trash. Be careful to prevent accidental exposure of children or pets.
- Keep testosterone gel away from fire.

Keep testosterone gel and all medicines out of the reach of children.

General information about the safe and effective use of testosterone gel.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use testosterone gel for a condition for which it was not prescribed. Do not give testosterone gel to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about testosterone gel. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about testosterone gel that is written for health professionals.

For more information, go to www.perrigo.com or call 1-866-634-9120

What are the ingredients in testosterone gel?

Active ingredient: testosterone

Inactive ingredients: carbomer 980, ethyl alcohol 67.0%, isostearic acid, purified water and sodium hydroxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Integrated Care Models and Pharmacy

In order for ICMs to work, pharmacies must be in the middle of the information equation. David Yakimischak, executive VP and general manager, Surescripts, explains how pharmacies should position themselves to take advantage of this trend.

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JANUARY 2015 **Drug Topics** Voice of the Pharmacist VOL. 159 NO. 1

CPE **CONTINUING EDUCATION**

MTM for the CVD patient

Highly accessible and knowledgeable pharmacists can provide many services to patients with cardiovascular disease, including MTM and instruction in self-care. **PAGE 40**

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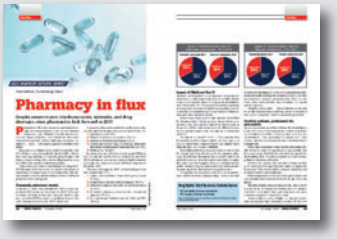

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DISPENSED AS WRITTEN Oluwole Williams, BS Pharm, PharmD

After the pharmacy: Employment alternatives for pharmacists

Optimism is an admirable state of mind. When reality, no matter how stressful, is clearly presented in facts and figures, an optimist might greet it as a bringer of opportunity. A community pharmacist who can hold onto optimism despite becoming a casualty in the ongoing "war against gray-hairs" in retail chain pharmacy might say, "Well, when one door closes another opens."

Today, all too often, senior colleagues with 30 years or more of retail chain experience are suddenly being shown the door, facing the grim reality of unemployment at age 60. What to do? Where to go? How to fend for themselves and their families? They face mortgage payments, car payments, children's college expenses — the list goes on and on.

Questions to ask

The most important questions to pose at this time are:

- What other services could an experienced community pharmacist render to the public for economic gain?
- Where should a former retail pharmacist offer his/her services outside of pharmacy?
- What other sphere(s) of human economic endeavor would suit the qualifications of a pharmacist?
- How should he/she invest a payout or gratuity?
- How could he/she offer services for pharmacy work overseas?
- What are the options for beneficial employment in early retirement?
- What are the employment opportunities for a 60-year-old pharmacist today?

Think outside the box

To the adventurous and enterprising among us, fascinating opportunities exist for a progressive, pharmacy-oriented occupation. An incurable optimist might consider the following:

- With other colleagues, incorporate a business venture in human resources, specializing in the recruitment, training, and development of pharmaceutical manpower, including an ACPE-accredited CE program for young pharmacists and such services as CPR and diabetes care certification.
- Create a trade venture in pharmaceutical products, advertising and promoting USA-made drugs, pharmaceutical raw materials, and pharmacy equipment to possible overseas clients and customers.
- Invest in a pharmacy consultancy business, targeting foreign governments for the training and development of their local pharmaceutical manpower, including immunization certification overseas.
- Cooperate with a group of interested colleagues in the business of pharmacognosy — the study and identification of medicinal plants — including the farming, sale, and packaging of herbal supplements.
- Embrace the challenge of serving the public in such western states as Idaho, Arizona, Wyoming, and New Mexico, which need pharmacists but to which few are willing to relocate.
- Remember the origin of the Pharmacists Mutual companies? Float a "1,000 pharmacists' corporation" challenge, inviting "1,000 concerned pharmacists" in the United States to start their own PBM or auto-insurance company targeting pharmacists.
- Establish a "Pharmacists' Business School," targeting only pharmacists globally for a unique training in pharmaceutical business management, drug manufacturing, internet pharmacy, pharmacy warehousing, and overseas business investments network.
- Promote a global volunteer services initiative for pharmacists, attracting interested pharmacists who are willing to volunteer their annual vacations for a week of professional services abroad.
- Create increasing numbers of independent pharmacy cooperatives for joint economic advancement in retail pharmacy business.

These are some suggestions an optimist might offer. Although some could cause a few pharmacists to cringe as they consider their bank balances and credit-card statements, they clearly show that pharmacists need not restrict the practice of their professional skills to the four walls of one particular location. DT

Oluwole Williams *practices pharmacy in the Philadelpha, Penn. area. Contact him at* pharmwillie@yahoo.co.uk.

Voices

Alive and kicking

Re: "Is fee for service dead?" [Mike Schuh, Dispensed as Written, December 2014]: Kudos, Michael, for identifying the fact that, for the most part, the profession has jumped on the MTM bandwagon way too soon and has done so in an environment without a lot of extra discretionary funds to make the experience financially worthwhile.

Mark Burger's posted response [see below] probably applies in just a few locations in this country. He's fortunate to have a pharmacy located in a community whose per capita household income is 50% higher than the national average, where there are extra dollars available to cover a novel pharmacy product. (Try cash-only compounding or MTM in inner Detroit and see how long you last.) In most large cities, locations where one or two individuals might succeed with an MTM practice are few and far between. The real shame is that the chains are now including MTM activities as part of their "productivity monitoring." This will only reduce the quality of these interventions by setting a target number/day vs. intervening when it really matters.

Anonymous

POSTED AT *WWW.DRUGTOPICS.COM*

All consults, all the time

"As pharmacists, we have no ability to bring money in." Really? I can make my annual salary and more without dispensing at all.

I charge cash for my consults (if you want to call them MTM, go right ahead). I don't care what some third party is willing to pay me. My patients are willing to pay cash.

Why? Because I get results, not "Band-Aids-over-bullet-holes," which is how most pharmacists practice MTM.

People want to be healed/cured — they don't want their medication changed, substituted, or given at another time of day, in another dose, or in a different form (e.g., omeprazole instead of lanzoprazole). They don't want to take medicine. They want to be told/taught how to heal the core issues.

When you:

- Get them off their medications (or reduce the quantity of what they take);
- See and correct the hypomagnesemia, for example, caused by the diuretic given for a one-time hypertensive measurement in the doctor's office;
- See that they are depressed because they have low 1,25-dihydroxyvitamin D levels and their doctor thinks 50,000 IU Q week of D2 is the answer when daily D3 dosing is appropriate;
- Notice that they are anemic because they can't absorb iron, B12, B6, or folate due to the PPI they are on;
- Explain all this to them and fix all the problems brought on by a system that treats them like a number (N=? in a study quoted as evidence), you will get results and you will get paid for it.

Try it. They'll like it.

Quit teaching pharmacists that no one will pay them for what they know. Just tell pharmacists to quit "knowing" what the doctors, epidemiologists, FDA, CDC, BC/BS, UHS, Caremark, Charter, and Express Scripts "know."

Shake off the shackles. Bill patients for helping them live better, with a better quality of life.

Mark Burger

POSTED AT WWW.DRUGTOPICS.COM

Community pharmacy forever

Re: "Is community pharmacy a dying profession?" [Truman Lastinger, DT Blog, Dec. 10, 2014]:

It is true that the pharmacy profession must change with the times and that the pharmacy model followed by Truman Lastinger and my father for decades is probably unreasonable now, but as long as people need/demand help and advice, pharmacists will be there for them. People still want someone there to provide advice on self-help OTCs or the new heart medication that the physician was too busy to tell them about, not to mention "How the heck do you use this newfangled lancet device, anyway?"

With more and more healthcare being pushed to the outpatient level because of cost-containment, there will be a demand for midlevel healthcare providers such as PAs, NPs, RPhs, etc. I find myself doing cholesterol tests on patients, providing vaccinations to keep them healthy, "furnishing" prescriptions to patients traveling overseas, and writing lab orders to monitor patients' white cell levels, all in the interests of making sure they stay as healthy as possible.

Is it a long way from the old-fashioned corner-store pharmacy with the soda fountain? Yes and no. The soda fountain is no longer there, but the "care" in pharmaceutical care is still there. As long people are in the community, there will be a community pharmacist to help them.

Jeffrey A. Wong, PharmD

SAN FRANCISCO, CALIF.

Continued on pg. 13

VIEW FROM THE ZOO David Stanley, RPh

What's blocking healthcare delivery in the pharmacy?

"But my doctor wants me to be on this for the rest of my life, why aren't there any refills?" It's a question all of us have heard, and if I were accepting nominations for the most cringe-inducing questions from patients, I'm sure that one would be in the top three.

You know what happens next. Often it's another recital of how prescriptions expire after a year, followed by a fax, an e-refill request, or a phone call to a doctor's office for an authorization; "spotting" the patient a few pills to get by on until we hear an answer; and all too often seeing the patient return before that answer comes, because we're dealing with that doctor who claims never to get our faxes no matter how many times the fax machine says they went through just fine.

First question

I'm not running a cringe-inducing-question contest with this article, though. I'm actually asking a question: In a world where insurance plans now fight for Star Ratings and Medicare now watches like a hawk for preventable patient readmissions to hospitals, why do we have a system that puts up barriers to patients trying to obtain their routine maintenance medications?

The most common answer you'll probably hear to this question cites the necessity for the patient to make periodic physician appointments, many times for an annual physical.

In a world of evidence-based medicine, though, it should be pointed out that there is no strong evidence that an annual physical leads to better healthcare outcomes.

This opinion is shared by Allan Goroll, a professor of medicine at Harvard Medical School, in an online article in the January, 2010, issue of the American College of Physicians publication for internists.

He does go on to say, "However, there is substantial evidence that checking for and treating cardiovascular risk factors, preventable or curable cancers, STDs, depression and substance abuse are all evidence-based, high-value activities."

Second question

This brings us to my second question. Is there any pharmacist out there who thinks that instead of being the point person for overcoming needless barriers to care, we couldn't better spend our time being the initial contact for these "high-value" activities?

Instead of "No, we still haven't heard from Dr. Nofaxback," imagine if your patients heard this:

"I see it's been a few months since we've done a blood pressure reading for you, Mr. Smith. Why don't you sit down here and we'll get your numbers while you're waiting for your Norvasc fill.

"And how did those nicotine patches work out for you? If they're not doing the job, there are a couple different options we could go with.

"I also see that you're due for your first colonoscopy; did you know that our computers link directly with your gastroenterologist now? When we're done here, my technician can make an appointment with her for you, if you'd like."

Throw in a little conversation about the general state of the patient's health and the fact that no one is in a better position to know about a propensity for substance abuse than a person's pharmacist, and you have now replaced a significant barrier to medication adherence with something valuable to the patient's health, opened the way for the doctor to spend more of her ever-more-limited time concentrating on diagnosing and solving problems, and found an actual opportunity for the pharmacist to sit down in the course of a 12-hour day.

A win-win-win — blocked

That brings us to the main reason this scenario is not taking place. The technology to accomplish this exists, and the pharmacists' skill set of is there, but the chances of the "Big Three" pharmacy chains setting up an environment where you have the time to pull this off are about zero.

The reason you don't sit down now for 12 hours is because your company isn't running a healthcare facility, it's running a prescription mill.

In other words, if you're looking for the biggest barrier to necessary reforms in daily pharmacy practice, you don't have to look any further than to the corporations that run the pharmacies.

That thought should make you cringe more than any question you'll hear from a customer today. DT

David Stanley *is a pharmacy owner, blogger, and professional writer in northern California. Contact him at drugmonkeyrph@gmail.com.*

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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.

ASHP continues to focus on provider status

The American Society of Health-System Pharmacists (ASHP) has been working hard for its membership, which now has topped 40,000, and according to ASHP President Christene Jolowsky, MS, RPh, FASHP, those efforts are paying off.

At the opening session of ASHP's 2014 midyear meeting in Anaheim, Calif., Jolowsky outlined how big wins by pharmacy-friendly congressional candidates in this year's mid-term elections improve pharmacist's chances to achieve provider status.

"As of today, we have reached a critical milestone of 123 congressional co-sponsors of the provider status legislation, H.R. 4190, with bipartisan support. This shows that our efforts and your efforts to educate Congress about the critical role that pharmacists play in patient care is working," she said.

Under H.R. 4190, Medicare beneficiaries will have access to pharmacist-provided ambulatory-based patient-care services under Medicare Part B. If H.R. 4190 is enacted, if these services are provided to beneficiaries living in medically underserved communities, they will be reimbursed under Medicare Part B. Reimbursement for pharmacy services would be approximately 85% of the physician fee schedule.

ASHP-PAC contributions

During the 2013-2014 election period, ASHP-PAC, the association's political action committee, supported candidates who favored efforts to expand the role of pharmacists to include patient care. Contributions from ASHP-PAC also supported legislators serving on the committees for Energy and Commerce and Ways and Means in the House of Representatives, and on the committees for Finance and Health, Education, Labor and Pensions in the Senate. All of the candidates that ASHP-PAC supported were reelected during the mid-term elections.

— Julia Talsma, Content Channel Director

Bipartisan co-sponsors of H.R. 4190 now number 123, "a critical milestone."

OTC WATCH

Pharmacists have role to play in preventing acetaminophen overdoses

Consumers are more aware about acetaminophen overdosing, but there is still much more that pharmacists and other healthcare professionals can do to educate them, said Leiana Oswald, PharmD, assistant professor, College of Pharmacy, Roseman University of Health Sciences, Henderson, Nev., during a Wolters Kluwer Clinical Drug Information webinar she conducted.

"Education is one of the first lines of defense in preventing overdoses. Consumer misperception can lead to abuse," she said. Consumers may believe products containing acetaminophen are safe because they are sold over-the-counter (OTC); they may use two or more acetaminophen products at a time; or they may take the next dose too soon.

Pharmacists need to watch out for other patients too. "We should consider reducing the dose of acetaminophen in liver-compromised patients or alcoholic patients. It is very difficult for the body to get rid of the … toxic chemical," Oswald said.

Educational messages

While there are no FDA-recommended dosing adjustments for alcoholics or liver-compromised patients, education would help prevent some of the 56,000 annual emergency room visits resulting from acetaminophen overdoses. "More than 14,000 of those cases were unintentional. We want to see those numbers drop to zero," Oswald said.

To that end, the Acetaminophen Awareness Coalition, a group of healthcare providers and consumers created in 2009 in response to an FDA advisory committee recommendation, continues to educate patients and consumers about acetaminophen safety through the "Know Your Dose" campaign.

"They have been distributing educational messages at physicians' offices, at retail pharmacy counters, and at the point of healthcare decisions, including relevant ads on healthcare websites and Internet platforms," Oswald said. Pharmacists can download the charts, brochures, and other information for patients at *www.KnowYourDose.org*. For example, Walmart distributes educational materials in its OTC pharmacy departments.

FDA will publish a proposed rule on acetaminophen dosing in 2015, but Oswald cautions healthcare providers not to wait to instruct patients on correct dosing. "It's only a proposed rule; it won't change immediate access to acetaminophen. The time between a proposed rule and a final rule can be months to years."

More retail pharmacies can help curb unintentional overdoses by spelling out "acetaminophen" on labels, instead of abbreviating it as APAP, Oswald said. "Seventy-five percent of retail chains spell out the word; we would like to see 100%."

— Christine Blank, Contributing Editor

Voices

Continued from pg. 9

Big Brother, Big Pharma, Big ... Watson?

In addition to all the points Truman has made in his article, consider the possibility that Big Pharma may one day surpass PBMs and deploy its own automated mail-order directly to the consumer, possibly from offshore fulfillment centers, if they can effect buy-in from the FDA.

Then there are the advances in computer science. What if IBM's Watson [cognitive information-processing technology] were applied to designing drug therapy? Suppose that for a small fee, Watson will evaluate all of a patient's data, design a drug regimen for optimum outcome, and forward the prescriptions (with the physician's electronic signature, of course) to the appropriate fulfillment center for next-day home delivery?

What's more, for a small fee, Watson could also review changes in a patient's health from the patient's smart wristband and contact the physician with an offer of appropriate alternatives to current therapy.

Naturally, somewhere in a cubicle, there will be a pharmacist to answer patients' questions — in between remotely verifying the accuracy of a robot that never makes mistakes — at a fulfillment center in India or China.

After seeing all the changes in my practice over the last 30 years, I don't believe that these scenarios are that far-fetched.

And Truman might be wrong about those coopers. Perhaps, in the next 30 years, being a cooper who makes oak barrels for premium American bourbon will become a far more lucrative trade than pharmacy.

Anonymous

POSTED AT *WWW.DRUGTOPICS.COM*

Clinical pharmacists in the ED? You betcha

Re: "Hospital puts pharmacists in ED to reduce med errors" [Dec. 1, 2014; *www.drugtopics.com*]:

Dr. Svenson's statement, that smaller hospitals could not afford to have a pharmacist sitting around, would apply to all hospitals. Clinical pharmacists should be engaged in patient care, not taking up space in the ED.

I piloted a clinical pharmacist-based ED service in a small 100-bed hospital with a 22-bed ED and proved that it is cost-effective to have the pharmacist in the ED. It is true that the volume is an issue to justify the cost of the pharmacist, but different models can be used to optimize the pharmacist's time and ED coverage provided.

My pilot program included staffing assignments for the pharmacist to assist with inpatient care, with a focus on critical care. For the safety of the patients, ED-trained pharmacists should be available to all EDs across the nation. According to the size of the facility and the volume, the model should be scaled and adapted to be as cost-effective as possible for each facility.

Todd White

POSTED AT *WWW.DRUGTOPICS.COM*

Clarification: *The online article "The pharmacists' role in preventing acetaminophen overdoses" [Drug Topics, Dec. 19, 2014], was updated Dec. 29 to clarify the timing of the proposed rule on adult acetaminophen; the labels referred to in the last paragraph, which are prescription labels; and Dr. Oswald's quote in the fifth paragraph.*

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Up front » In Depth

Julia Talsma, Content Channel Director

STOMPP to test adherence packaging, MTM model in community setting

Poor medication adherence is a $300 billion problem that has resulted in increased emergency room visits, medication-related hospitalizations, and approximately 125,000 deaths annually in the United States. An ambitious new clinical study known as STOMPP is testing whether a hybrid pharmacy practice model using adherence packaging and/or medication therapy management (MTM) will have a positive impact on medication adherence. Community pharmacists will be part of the solution.

STOMPP (Study the Effect of a Hybrid Pharmacy Practice Model on Medication Adherence), which started enrolling patients last September, will assess clinical, humanistic (quality of life), and economic outcomes of up to 300 patients with metabolic syndrome and type 2 diabetes.


Sharrel Pinto

The study is being conducted within an integrated delivery network that includes a physician's practice, an endocrinology practice group, and a multi-site pharmacy, said lead investigator Sharrel Pinto, BS Pharm, DMM, MS, PhD.

"In this randomized control trial, we will compare this adherence pharmacy model [adherence medication packaging and MTM services] to other current practice models [pill bottles; pill bottles with MTM services] in terms of the impact on medication adherence. We are excited about this research and will present our interim findings later this year at the American Pharmacists Association meeting in San Diego," said Pinto, division head and associate professor, Health Outcomes and Socioeconomic Sciences, and director, Center for Pharmaceutical Care and Outcomes Research, University of Toledo College of Pharmacy and Pharmaceutical Sciences, Toledo, Ohio.

An adherence pharmacy

Pinto recently published a white paper that provides guidance for pharmacists who want to develop and implement an adherence pharmacy. This pharmacy model delivers pharmacy services, including MTM, medication synchronization, and adherence packaging through scheduled appointments.

MTM in the adherence pharmacy embraces a comprehensive medication review, a personal medication record, and a medication action plan. The pharmacist can identify any potential or existing medication problems, refer the patient to a healthcare provider, and continue to follow the patient on chronic medications, said Pinto in her report, titled "Developing and implementing an adherence pharmacy."

Complex medication regimens require patients to remember when to take each dose; if they are taking multiple medications, some may have to be taken at different times during the day. As a result, patients can forget to take their medications, forget to take them at specific times, or take too much or too little.

"What we want to do is make sure our patients know what it is they are taking, how they are taking it, and what to do if they miss a dose. The pharmacist can play a significant role in working with patients in order to simplify that regimen," Pinto told *Drug Topics*.

Adherence medication packaging is not a new concept, having been used successfully in countries with universal health insurance such as Canada and Europe. It has been shown to increase medication adherence and treatment outcomes in the elderly. According to a 2008 U.S. study published in the *Journal of the American Pharmacists Association*, patients refill their prescriptions on time more often and have improved health outcomes when they use daily-dose blister packaging.

"The big factor for the move toward adherence packaging [in the U.S.] is the new emphasis on healthcare reform, outcomes-based care, and improvement in quality of care for patients," said Pinto. "We are starting to see independents and chains look at adherence packaging in a much different light than they have in the past."

Blister packs

The RxMAP adherence packaging system used in the STOMPP study is a customized calendar-style blister card that organizes oral solid tablets and capsules, including prescription medications, over-the-counter drugs, and vitamins/minerals. It also includes labels and instructions for as-needed medications that cannot be placed within the blister packaging. Each blister package can contain a 28-day supply of medication.

Because each blister package contains most of the patient's medication, it is important to enroll patients in a medication synchronization program to ensure that all the patient's medications

are filled at the same time, Pinto wrote in the white paper.

"Once patients are enrolled at the [adherence pharmacy] and educated on the process, then the filling of their medication in the adherence packaging may begin," Pinto said.

Follow-up

To avoid any gaps in the patient's care, refill reminders should be sent to the physician and the patient. The pharmacist or staff needs to call the patient a few days before the refill to ask about which medications are to be continued and included in the adherence packaging. If there are medication changes after the blister package has been dispensed to the patient, a procedure needs to be in place to reconcile the changes and correct the blister packaging.

For patients who have difficulty getting to the pharmacy, Pinto suggested providing a delivery or mail service. This offers a dual benefit — it keeps the patient within your healthcare network or pharmacy and keeps patients adherent to their medications, Pinto said.

"Adherence packaging is a great resource, yet it will take some hard data or meaningful experiences for patients and payers to come to the realization themselves," she said. "We are collecting evidence right now about the adherence packaging — to see what impact it has economically and from the pharmacy standpoint, how does that vary?"

A road map

For pharmacists who are interested in pursuing the adherence pharmacy model, Pinto suggested that they conduct a SWOT analysis, evaluating their strengths, weaknesses, opportunities, and threats — in other words, their readiness.

It is important to develop a roadmap, including an action plan that tracks who is doing what and when, she said.

Pharmacists need to evaluate their staff's acceptance of this model and level of expertise. All staff members must be trained in MTM, certified to perform MTM, and have experience with MTM.

"Once everyone is on board and trained in MTM, you can start talking to companies that offer adherence packaging solutions. You need to decide if you can invest in the machine [to fill the blister packaging] or if you are going to do it manually," she said. "A SWOT analysis will help you create the next phases before you actually roll out the adherence pharmacy model."

Reimbursement for MTM

Pharmacies are familiar with the reimbursement possibilities for MTM with Medicare Part D. However, employer groups, especially those that are self-insured, are open to the idea of MTM because many have had experience with disease management companies previously. These groups are able to understand the value of what pharmacists can offer in terms of MTM services, Pinto said.

"I have been fortunate in working with employer groups over that last 10 years," she said. "Working with employer groups opens up a whole window of opportunity. I know we are fighting for provider status and trying to get that reimbursement, but I feel that we have not even scratched the surface in this whole other area with employers [where 80% of Americans get their insurance]."

In 2005, Pinto began providing MTM services to employees in Lucas County, Ohio. She set up the program and demonstrated from their own data that there was a return on investment. At first physicians challenged this model, because they didn't understand the role played by pharmacists and considered these services a threat instead of a resource.

"We pharmacists need to educate folks that we really are a resource that is underutilized. We can really help and provide these services, especially as we move toward outcomes-based reimbursement," she said.

"I know we are fighting for provider status and trying to get that reimbursement, but I feel that we have not even scratched the surface in this whole other area with employers."

"We can make the biggest impact by helping patients released from the hospital. This will help with some of the reimbursement challenges that healthcare systems are still facing," Pinto said.

The STOMPP study will help to quantify the impact of medication adherence, she said.

The study is supported by Omnicell, a supplier of automation and business analytics software for medication and supply management.

Omnicell also owns MTS Medication Technologies brand, including the medication adherence packaging solutions used in this study. DT

Up front » In Depth

Julia Talsma, Content Channel Director

Specialty pharmacy benefits HCV patients, health system

Implementation of an on-site specialty pharmacy by the University of Illinois Hospital Health Sciences System, Chicago, offers a streamlined process for excellent and cost-effective care for patients with hepatitis C virus, said Michelle T. Martin, PharmD, BCPS, BCACP, a presenter at the ASHP Midyear 2014 meeting in Anaheim, Calif.

Before 2012, clinicians at the University of Illinois system had to work with nurses and other providers in their outpatient clinics to obtain specialty pharmacy medication approvals, with most of the prescriptions going to external pharmacies not associated with the health system. Securing medication approval was time-consuming and could delay the initiation of treatment. There also were limitations once prior authorizations were obtained.

"Our prior authorizations for HCV medications are often limited to an eight-week time frame," said Martin, a clinical pharmacist and clinical assistant professor, ambulatory pharmacy, Department of Pharmacy Practice, University of Illinois at Chicago. "So if the patient doesn't start immediately, the patient may be unable to get all the medication refills in before another prior authorization is needed."

As a clinical pharmacist, Martin had to spend most of her time before 2012 working with a technician in the dispensing pharmacy who assisted with prior authorizations for the in-network patients. Martin also coordinated out-of-network prior authorizations by herself for more than 70 patients. At that time, patients were being treated with protease inhibitors and additional agents for treatments lasting 24 to 48 weeks.

"There was an enormous amount of paperwork when we were doing all the prior authorizations for in-network and out-of-network patients," Martin said.

Better care

Implementation of the on-site specialty pharmacy in 2012 streamlined the process, with the specialty pharmacy handling all the prior authorizations for medication approval. On the clinic side, Martin no longer had to be concerned with the avalanche of prior-authorization paperwork.

That changed in 2014, after simeprevir and sofosbuvir were approved. Treatment referrals for hepatitis C patients increased, and the paperwork became too much for the on-site specialty pharmacy to manage.

The health system's specialty pharmacy decided it could only handle prior authorizations for the in-network patients whose medications it would fill. Martin again was needed to assist with prior authorizations for out-of-network patients. She decided to take advantage of the talents of experienced pharmacy technicians and third-year pharmacy students, and turned to them for help with the benefit verification and prior-authorization process for in-network and out-of-network patients.

"What sets our specialty pharmacy apart from other specialty pharmacies is the we have access to the electronic medical record [EMR] system. So our specialty pharmacy is always communicating with providers — physician assistants, nurse practitioners, physicians, as well as the clinical pharmacist — making this a seamless process," Martin said.

How the process works

When Martin receives a referral from a physician designating the start of treatment for a patient with hepatitis C, she evaluates the patient's chart and treatment for appropriateness and dosing. She forwards a note to the specialty pharmacy, asking for an evaluation of the patient for benefit verification, and then receives a response from the specialty pharmacy — all accomplished through the EMR.

If the patient doesn't have pharmacy benefits or needs assistance with high copays, she refers the patient to the health system's medication assistance program.

Often the patient's insurance company denies initial requests for medication; Martin will write letters of medical necessity and send them back to the specialty pharmacy through the EMR system. She also helps out-of-network patients. Pharmacy students assist with prior authorizations. She gets doctor signatures and letters of medical necessity.

"Our specialty pharmacy is always communicating with providers — physician assistants, nurse practitioners, physicians, as well as the clinical pharmacist — making this a seamless process."

With additional "free time" she gains through the assistance of her students, Martin can work one-on-one with patients at treatment initiation and follow-up. She also works closely with the clinicians on appropriate medication prescribing.

In 2014, she has been able to help approximately 350 patients with hepatitis C, with the aid of pharmacy technicians and pharmacy students in the clinic and specialty pharmacy. "We have fewer insurance issues, as the process is more streamlined. We are able to care for more patients and start more patients on treatment, because we have a pharmacist in the clinic able to do patient care as opposed to mostly paperwork," she said. DT

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Serious, life-threatening, or fatal respiratory depression may occur with use of HYSINGLA ER. Monitor for respiratory depression, especially during initiation of HYSINGLA ER or following a dose increase. Instruct patients to swallow HYSINGLA ER tablets whole; crushing, chewing, or dissolving HYSINGLA ER tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of HYSINGLA ER with all cytochrome P450 CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving HYSINGLA ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.11), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

Please read Brief Summary of Full Prescribing Information on the following pages, including Boxed Warning.

PURDUE

A8971-AVAIL-A 11/2014

Hysingla™ ER

(Hydrocodone Bitartrate) II

EXTENDED-RELEASE TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details please see the Full Prescribing Information and Medication Guide.)

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

Addiction, Abuse, and Misuse

HYSINGLA™ ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing HYSINGLA ER, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of HYSINGLA ER. Monitor for respiratory depression, especially during initiation of HYSINGLA ER or following a dose increase. Instruct patients to swallow HYSINGLA ER tablets whole; crushing, chewing, or dissolving HYSINGLA ER tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of HYSINGLA ER with all cytochrome P450 CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving HYSINGLA ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.11), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

4 CONTRAINDICATIONS

HYSINGLA ER is contraindicated in patients with: • Significant respiratory depression • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Known or suspected paralytic ileus and gastrointestinal obstruction • Hypersensitivity to any component of HYSINGLA ER or the active ingredient, hydrocodone bitartrate

5 WARNINGS AND PRECAUTIONS 5.1 Addiction, Abuse, and Misuse HYSINGLA ER contains hydrocodone, a Schedule II controlled substance. As an opioid, HYSINGLA ER exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9.1)]*. As extended-release products such as HYSINGLA ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydrocodone present. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed HYSINGLA ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing HYSINGLA ER, and monitor all patients receiving HYSINGLA ER for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of HYSINGLA ER for the proper management of pain in any given patient. Abuse or misuse of HYSINGLA ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the hydrocodone and can result in overdose and death *[see Drug Abuse and Dependence (9.1), and Overdosage (10)]*. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing HYSINGLA ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product. **5.2 Life-Threatening Respiratory Depression** Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10.2)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. While serious, life-threatening, or fatal respi-

$_2$ retention) may be markedly

$_2$ retention, such as those with evidence of

Hypotensive Effect HYSINGLA ER may cause severe hypotension includ-

Obstruction, Dysphagia, and Choking In the clinical studies with spe-

Inhibitors and Inducers Since the CYP3A4 isoenzyme plays a major role

in hydrocodone plasma concentrations. The clinical results with CYP3A4

tinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent

Machinery HYSINGLA ER may impair the mental and physical abilities

needed to perform potentially hazardous activities such as driving a car or operating machinery. Peak blood levels of hydrocodone may occur 14 – 16

tolerant to the effects of HYSINGLA ER and know how they will react to the medication *[see Clinical Pharmacology (12.3)]*. **5.13 Interaction with Mixed Agonist/Antagonist Opioid Analgesics** Avoid the use of mixed

5.14 QTc Interval Prolongation QTc prolongation has been observed with HYSINGLA ER following daily doses of 160 mg *[see Clinical Pharmacology (12.2)]*. This

ER should be avoided in patients with congenital long QT syndrome. In patients who develop QTc prolongation, consider reducing the dose by 33 – 50%, or changing to an alternate analgesic.

6 ADVERSE REACTIONS The following serious adverse reactions are described elsewhere in the labeling: • Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]* • Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]* • Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]* • Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]* • Hypotensive Effects *[see Warnings and Precautions (5.8)]* • Gastrointestinal Effects *[see Warnings and Precautions (5.9, 5.10)]* **6.1 Clinical Trial Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. A total of 1,827 patients were treated with HYSINGLA ER in controlled and open-label chronic pain clinical

opioid-naïve and opioid-experienced patients with persistent moderate to

Table 2: Adverse Reactions Reported in ≥2% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period: Opioid-Naïve and Opioid-Experienced Patients

	Open-label Titration Period	Double-blind Treatment Period	
MedDRA Preferred Term	**(N=905) (%)**	**Placebo (N=292) (%)**	**HYSINGLA ER (N=296) (%)**
Nausea	16	5	8
Constipation	9	2	3
Vomiting	7	3	6
Dizziness	7	2	3
Headache	7	2	2
Somnolence	5	1	1
Fatigue	4	1	1
Pruritus	3	<1	0
Tinnitus	2	1	2
Insomnia	2	2	3
Decreased appetite	1	1	2
Influenza	1	1	3

The adverse reactions seen in controlled and open-label chronic pain studies are presented below in the following manner: most common (≥5%), common (≥1% to <5%), and less common (<1%).

The most common adverse reactions (≥5%) reported by patients treated with HYSINGLA ER in the chronic pain clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, somnolence.

The common (≥1% to <5%) adverse events reported by patients treated

with HYSINGLA ER in the chronic pain clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class were:

Gastrointestinal disorders	abdominal pain, abdominal pain upper, diarrhea, dry mouth, dyspepsia, gastro-esophageal reflux disease
General disorders and administration site conditions	chest pain, chills, edema peripheral, pain, pyrexia

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.

CAUTION
DEA FORM REQUIRED

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

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)

Up front
In Depth

Julia Talsma, Content Channel Director

Protect your pharmacy from data breaches

The data breach that occurred in late 2013 when cybercriminals stole 40 million credit and debit card numbers from 70 million customers has now cost Target Corp. more than $200 million. In addition, Target's brand has been severely compromised, resulting in the resignation of Target's CEO and CIO.

Unfortunately, many retailers large and small are vulnerable to data breaches, and thousands of smaller businesses are being breached, according to Chad Leedy, director of retail compliance, ANXeBusiness Corp. He spoke about what pharmacies can do to protect themselves from data breaches involving patient information and credit and debit card information during the National Community Pharmacists Association meeting in October last year.

The costs of a data breach

A data breach costs, on average, a total about $80,000 per pharmacy location. Once a data breach is detected, a forensic audit is necessary, at a price tag of between $20,000 and $30,000.

Then determination is made as to how far out of compliance the pharmacy was and how many credit cards were comprised and will have to be replaced — at a cost between $20 and $50 per card from the bank.

On top of that, there will be fines and fees and the expense of getting the pharmacy back into compliance. During that time, the pharmacy cannot accept any payments made with credit cards.

"If your pharmacy had to pay $80,000 and couldn't take credit cards for two to three months, how devastating would that be to your business? You might have to go out of business or declare bankruptcy," Leedy said. "Unfortunately, one in six small businesses will suffer a credit card breach in the next 24 months."

PCI compliance

For pharmacies and other retailers that store, process, or transmit credit/debit card data, PCI compliance is mandatory. All businesses must comply with the Payment Card Industry Data Security Standard (PCI-DSS), a set of more than 300 requirements that businesses using point-of-sale (POS) systems need to meet annually.

According to the PCI Security Standards Council, the PCI-DSS is a framework for payment-card data security that includes prevention, detection, and response to data breaches. The council has lists of qualified security assessors (QSAs) and approved scanning vendors (ASVs) to help businesses with compliance at *www.pcisecuritystandards.org/security_standards/*.

When you check the qualifications of PCI vendors, find one that is a QSA or ASV, Leedy said. "A QSA is the highest level of credentials that you can get with the PCI Security Standards Council. Make sure the vendor understands the pharmacy business, so it is aware of your unique challenges," he said.

Six goals for PCI compliance

PCI lists six objectives that businesses need to follow to secure sensitive data.

Firewall. Your firewall needs to be secure and fully managed by a security company. Make sure that the default passwords are changed and regularly updated. A structure needs to be in place to change passwords on a regular basis.

Encrypted data. You need to protect sensitive data, such as credit card and patient information, and ensure that it is encrypted across all open public networks. Contact your information technology professionals for their expertise.

Maintenance. Every business must maintain its system with antivirus software, and systems and applications need to be updated regularly. This includes Microsoft patches and patches for many different pharmacy applications.

Access limitations. Be sure to have strong access-control measures in place. Restrict access to a need-to-know basis. Do not allow employees to share access to the system. Make sure that remote access from outside the pharmacy is secure.

"Never use a free version of a remote-access tool. It should have two-factor authentication, which is usually something you know, like a password, and something you have, like your cell phone number," Leedy said.

Internal and external testing. Track and monitor access to your system and test network security internally and externally. An outside company will have to test your network externally.

Security policy. Develop and implement a security policy that includes PCI compliance. Your employees need to read it and acknowledge their awareness. DT

VIDEO

Chad Leedy, director of retail compliance, ANXeBusiness Corp., discusses ways to protect data security in the pharmacy. To view the video, go to **http://drugtopics.modernmedicine.com/drug-topics/news/video-protecting-your-pharmacy-against-data-breaches.**

Up front
» In Depth

Jill Sederstrom

U.S. pharmacists share insights about Ebola treatment

With few patients and no approved medications for the treatment of Ebola virus in the United States, caring for those who develop the disease may seem like uncharted territory to many. Pharmacists who have already worked with these patients can help provide a road map for others in the profession.

During a session at ASHP's 2014 midyear meeting in Anaheim, Calif., pharmacists who treated patients with Ebola virus disease in hospitals across the United States shared their clinical insights, nutritional considerations, and experiences working with investigational medications.

Impact in the United States

While most confirmed cases of Ebola virus have been in West Africa, the United States also has played a role in the 2014 Ebola outbreak by conducting trials, caring for patients with the disease in America, and sending officers of the U.S. Public Health Service Commissioned Corps to lend a hand in Liberia.

According to Robert DeChristoforo, RPh, MS, FASHP, chief of the National Institutes of Health (NIH) Clinical Center Pharmacy, the NIH is currently conducting two Ebola vaccine trials at its campus in Maryland. The first will assess the safety and immunogenicity of the NIH/GSK cAd3-EBO vaccine, while the second will seek to establish the maximum safe and tolerated dose of a two-dose prime boost IM VSV EBOV vaccine.

The United States also has begun to see cases of patients infected with the Ebola virus disease within its own borders, and healthcare teams across the country are preparing to treat this complicated and potentially deadly disease.

Clinical presentation

Clinical pharmacists can play a valuable role throughout the treatment of patients with Ebola virus disease. They can determine drug distribution, serve as coordinators of pharmaceutical care, and participate in daily patient meetings, although since pharmacists are not typically numbered among the personnel essential to the patient room, they may need to communicate by means of such alternative methods as short-wave radio or walkie-talkie.


Andrew Faust

Andrew Faust, PharmD, BCPS, is a critical care pharmacy specialist at the Texas Health Presbyterian Hospital, where two of the first Ebola cases to arise in the United States — both nurses at the hospital —were treated.

Experts agree that early detection of Ebola virus disease is critical to providing the best patient outcome; however, said Faust, the difficulty with the early stage of the disease is that it looks like many other viral illnesses. Early disease symptoms that occur between days one and four include fever, myalgias, malaise, and cramping.

"Really, what you need to do with these people is draw labs, and the hallmark labs here are going to be leukopenia, thrombocytopenia, and transaminitis," he said. "If you see those in conjunction with the travel history and it all seems to fit, you need to start thinking 'Ebola virus.'"

Faust recommends consideration of alternative infectious diseases, such as malaria or bacterial gastroenteritis, and the use of empiric antibiotics, if needed, until EVD is confirmed.

Fluid loss

The acute phase, which is said to begin about day five, consists of severe gastrointestinal symptoms, hypotension, coagulopathies, electrolyte derangements, and renal failure.

"The amount of GI output in these patients is profound — I mean eight to 10 liters of diarrhea a day. Even as an ICU clinical specialist, having seen people who are really, really sick, I've never seen diarrhea like that before," Faust said.

Supportive care is an essential part of caring for these patients.

To compensate for the large volume of diarrhea patients can discharge, fluid resuscitation is particularly important. Faust said that when teams at Texas Health Presbyterian Hospital were treating patients, they tried to ensure that the amount of fluid going in matched the amount of fluid going out.

"Your rates on fluids may exceed things like 300 or 400 cc an hour, especially if your patients have GI loss of diarrhea and vomiting at the same time," he said.

There's no established best choice for fluid, but based upon what's known about sepsis and septic shock, said Faust, crystalloids may be preferred over colloids.

"What we found was that when our patients developed liver failure or hypoalbuminema, we ended up using a combination of IV albumin and crystalloid," he said.

Anticipate problems

As the Ebola virus runs its course, all electrolytes may be affected, creating the need for electrolyte management. It is best to anticipate problems early, Faust said, such as the need for saline if the

Continued on pg. 20 »

U.S. pharmacists share insights about Ebola treatment

Continued from pg. 19

patient is vomiting a lot or of bicarbonate if there is frequent diarrhea.

One of the biggest challenges with electrolyte management and provision of other types of treatment is that the healthcare team may not have the luxury of frequently running patient labs. According to Faust, most hospitals do not have biosafety level 4 facilities equipped for the safe handling of such virulent pathogens. Thus, labs should be preferentially run on point-of-care devices in the patient's room; however, not all lab tests are available on such platforms.

Finally, those patients who reach the late stage of Ebola disease may experience immunosuppression, rapid deterioration with multiple organ failure, anuria, respiratory failure, or hemorrhage.

Limited data are available concerning critical care practices for Ebola patients; however, Faust believes, the most important aspect of any care plan is to plan ahead and be prepared for whatever may happen.

Nutritional considerations

Early aggressive nutrition support may also be beneficial for patients with Ebola virus disease. Most patients experience significant gastrointestinal symptoms as well as cytokine surges and releases of reactive oxygen species associated with the disease.


Nisha Dave

According to Nisha Dave, PharmD, BCNSP, a nutrition support clinical specialist at Emory University, it is important to monitor a patient's nutrition intake and tolerance very carefully.

"If diarrhea is present, oral rehydration salts or solutions should be considered and used early on in the disease process," she said. "Once the GI symptoms progress, however, the use of parenteral nutrition as well as enteral nutrition should be considered and started, earlier rather than later."

Micronutrient supplements, such as vitamin A, vitamin B complex, or vitamin C, could also be used in an effort to replace nutritional losses and boost a patient's immunity.

Investigational drugs

Investigational drugs can play an important role in the treatment of Ebola virus disease, but owing to their investigational status, they aren't always easy to acquire, and obtaining them may require some additional preparation.


Jonathan Beck

Jonathan Beck, PharmD, pharmacist coordinator of the Investigational Drug Service at Nebraska Medicine, the teaching hospital for the University of Nebraska Medical Center, said that once a hospital is notified of an incoming Ebola patient, one of the first places to start actually is with a drug manufacturer.

"They are at the point now where they have all gone through this procedure several times," Beck said. "They have protocols. They have policies. They know shipping, they know how to get things across international borders, and they have INDs that can help," he said, referring to Investigational New Drug applications.

Hospitals can apply for an IND as well, or for an exemption from the FDA to allow the transport of investigational medications; however, the application process is lengthy and time-consuming to complete.

An eIND bypasses the IND application and allows the FDA to authorize the use of an experimental drug in an emergency situation; however, Beck said, another option is contacting the manufacturer who may already have INDs available.

"So what you are doing is basically you are becoming a site in their protocol, so you are following their protocol, you're working with them, you're using the IND, and from that point forward it saves you a lot of time and you can work on all the other documentation," he said, adding that drug plans will also have to be approved by a hospital's institutional review board.

There are several investigational products that can be used in the treatment of Ebola.

- TKM-Ebola is a small-interfering RNA using lipid nanoparticles that has been tolerable for healthy volunteers at a dose of 0.3 mg/kg through an IV. Doses over 0.5 mg/kg have been linked to some adverse events, primarily cytokine release syndrome.
- Brincidofovir is a DNA polymerase inhibitor that is currently being evaluated in a phase 2 trial to determine its safety and activity in Ebola virus disease patients. It has a recommended 200-mg loading dose followed by 100-mg twice-weekly doses for a total of five doses.
- Another investigational drug option is ZMapp, a blend of three chimeric monoclonal antibodies that is given through an IV, preferably in three doses. However, the drug is often in very low supply.

"It's frozen; it takes a long time to thaw," Beck said. "It takes anywhere from an hour and a half, they say, even up to four hours, to thaw the medication, so this brings about a problem when you don't really know what's going on in the room and you don't know where the staff is at. So you really have to guess and be prepared ahead of time."

Beck said that all three patients treated at Nebraska Medicine were also given convalescent plasma from a survivor of the Ebola virus.

"What I do like about the plasma is that the patient who survived more than likely had the same strain of virus as the patient we were treating, so these antibodies should be pretty specific for that type of protein, and hopefully it could catch these patients at an early time, where they could still respond with their immune system and they could fight the virus." DT

Jill Sederstrom *is a freelance writer based in Kansas City.*

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2015 SALARY SURVEY

Jill Sederstrom

INCOMES HOLD STEADY

Satisfaction among pharmacists remains high, thanks in part to favorable compensation and benefits, and low unemployment

While the healthcare industry is rapidly evolving, one thing remains the same: Most pharmacists are happy in their profession. Pharmacists responding to *Drug Topics*' 2015 salary survey continue to report high levels of satisfaction, in part because of the low unemployment, infrequent overtime, and high salaries that are characteristic of the profession.

But the field isn't immune to the changing healthcare landscape, and as more Americans obtain healthcare coverage and pharmacists assume greater responsibilities in providing patient care, pharmacists are also finding that workload and stress levels are also on the rise.

Marvin Moore

"We're still holding onto the traditional roles of filling prescriptions and handing those for patients, and counseling and all that goes into that, but on top of that, more and more pharmacists are providing immunizations and taking blood pressures and healthcare screenings. And then, you know, we've got these MTM [medication therapy management] opportunities that we are trying to fit into the day as well," said Marvin Moore, PharmD, president and owner of The Medicine Shoppe in Two Rivers, Wisconsin.

This year's salary survey polled in mid-November pharmacists working across the country in independent, hospital, chain, retail, mail-order, and payer environments to gauge trends in satisfaction, salaries, workloads, and stress among those in the field. There were 1,987 respondents.

Overall, nearly three-quarters of survey participants (73.2%) reported being either satisfied, very satisfied, or extremely satisfied with their jobs.

Unemployment rates also continue to remain low, with 85.4% of respondents reporting full-time employment this year. Only 1.2% of those who responded were either unemployed or a temporary employee.

Significant overtime is also not a factor for most pharmacists. According to the results, slightly more than half of the respondents — 52.3% —work between 40 and 44 hours a week, with just 8.1% reporting 50 or more work hours each week.

Financial earnings

The financial picture for pharmacists remains relatively positive. Slightly more than half of respondents (52.9%) say their earnings each year are based on an hourly wage, and that hourly

IMAGE: ISTOCK / GETTY IMAGES PLUS

TABLE 1

Pharmacists' earnings based on hourly wage, 2014

Hourly wage	Respondents	Percentage
$71 and higher	58	5.6%
$61 to $70	385	37.0%
$56 to $60	274	26.4%
$51 to $55	184	17.7%
$46 to $50	77	7.4%
$41 to $45	30	2.9%
$40 or less	32	3.1%

Source: Drug Topics' *2015 salary survey, deployed in mid-November 2014. Total respondents, 1,987 pharmacists.*

wage appears to be on the rise. While in 2013 only about a third of hourly employees reported making more than $61 an hour, this year that figure has grown to 42.6% (**Table 1**). An additional 44.1% of hourly employees report making between $51 and $60 each hour.

Compensation may also be on the rise for salaried employees. In 2013, 12% reported earning $141,000 or more each year. This year, that number has grown to 14.4% (**Table 2**). A significantly greater percentage (46.2%) of salaried employees, however, report earning between $116,000 and $140,000 each year, with an additional 18.6% of salaried pharmacists making somewhere between $101,000 and $115,000.

Among the respondents, 45.5% believe their salaries are average compared to those of other pharmacists in their region who work in the same practice settings.

Some pharmacists were able to boost their take-home pay in 2014 through additional commissions, profit-sharing, or bonuses. This was the case for 46.9% of the respondents who received additional income last year. Of those who reported the extra earnings, 53.3% reported that the additional compensation was $3,999 or less (**Table 3**).

Additional income wasn't the only thing increasing pharmacist's overall income in 2014. Last year, 61.9% of pharmacists reported receiving a raise. The raises have remained modest for most, however, with 65.2% of those who received a pay increase reporting raises of 2% or less.

Moore believes that the likelihood of large raises for pharmacists is a thing of the past — at least for now, as members of the profession adapt to new roles and responsibilities, and get a better sense of where future revenue streams will come from.

"We're going to see the salaries remain pretty steady. Perhaps down the road that will change, but I think right now we're seeing less revenue for dispensing and more revenue for MTM, and until that all flushes out and we know what the future looks like, I think it's going to be kind of just wait and see," said Moore, a *Drug Topics* editorial advisory board member.

TABLE 2

Pharmacists' earnings based on salary, 2014

Annual salary	Respondents	Percentage
Over $150, 000	135	6.8%
$141,000 to $150,000	151	7.6%
$131,000 to $140,000	298	15.0%
$121,000 to $130,000	411	20.7%
$116,000 to $120,000	208	10.5%
$111,000 to $115,000	132	6.6%
$106,000 to $110,000	115	5.8%
$101,000 to $105,000	124	6.2%
$91,000 to $100,000	137	6.9%
$81,000 to $90,000	63	3.2%
$71,000 to $80,000	38	1.9%
$70,000 or less	175	8.8%

Source: Drug Topics' *2015 salary survey, deployed in mid-November 2014. Total respondents, 1,987 pharmacists.*

Nearly 60% of pharmacists, however, say that they expect a raise in 2015, although most believe it will once again be 2% or less.

As far as employee benefits, approximately 70% or more of the survey respondents are receiving health insurance, dental and vision coverage, life insurance, paid vacation and sick days, and a 401k retirement plan (**Table 4**). Almost half said they receive discounts on store merchandise and more than 25% are offered continuing education reimbursements and profit sharing.

Job satisfaction

Survey results suggest that most pharmacists are content with their jobs. They report high satisfaction levels and have no plans to switch jobs in the immediate future.

In this year's survey, 35% of pharmacists describe themselves as satisfied with their current positions, while 24.5% are very satisfied and another 13.7% would classify themselves as extremely satisfied. Only about a quarter are somewhat dissatisfied or extremely dissatisfied with their positions.


Nancy Nesser

"I think most people are pretty happy around here with their job," said Nancy Nesser, PharmD, JD, director of pharmacy for the Oklahoma Healthcare Authority. "We tend not to get paid the same as a dispensing pharmacist, but it's gotten better."

TABLE 3

Pharmacists' additional income*, 2014

Additional income amount	Respondents	Percentage
$11,000 or more	163	17.6%
$10,000 to $10,999	34	3.7%
$9,000 to $9,999	20	2.2%
$8,000 to $8,999	28	3.0%
$7,000 to $7,999	19	2.1%
$6,000 to $6,999	38	4.1%
$5,000 to $5,999	78	8.4%
$4,000 to $4,999	53	5.7%
$3,000 to $3,999	88	9.5%
$2,000 to $2,999	136	14.7%
$1,000 to $1,999	144	15.5%
Less than $1,000	126	13.6%

*Additional income includes commission, bonus, and profit-sharing.

Source: Drug Topics' *2015 salary survey, deployed in mid-November 2014. Total respondents, 1,987 pharmacists.*

Nesser has been with the state's Medicaid program for 13 years. As the pharmacy director, she's in charge of the pharmacy benefit and decides on restrictions and coverage for the state's Medicaid program. While the job can be challenging, she said, the advantage is that she is able to work fairly standard office hours, with no obligations to work nights, holidays, or weekends.

Moore said that his satisfaction on the job can be attributed to the expanding role he's been able to take on as a pharmacist in Wisconsin, where pharmacists can get paid for providing MTM services through the Wisconsin Pharmacy Quality Collaborative.

"Those things are exciting to me, and I think other pharmacists are seeing that we're being more integrated into the healthcare team and being relied upon for our skills and knowledge a little bit more. Hopefully, overall, pharmacists are excited about those sorts of things and looking forward to the future and getting even more involved with patient care," he said.

But not all pharmacists are finding happiness in their current surroundings. As one veteran hospital pharmacist told *Drug Topics*, he's not overly optimistic about the years ahead.

"I don't really see pay raises going up. I kind of see an overabundance of pharmacists, which is going to suppress the pay scale. And then there's what's going on with politics at the federal level. I know healthcare does not like change, so typically when that happens, I am used to seeing hiring freezes, no expansions, no this and no that," he said.

Regardless of their satisfaction levels, most pharmacists aren't planning to make a job change in the year ahead. While 73.4% of respondents said they do not plan to leave their present circumstances this year, David Stanley, RPh, a regular columnist for *Drug Topics*, pointed out that it is also important to note that more than one-fourth of pharmacists do plan to leave their positions.


David Stanley

"If you're at a busy pharmacy with four pharmacists, one of them is looking to get out of there. I suspect that ratio is even higher among retail pharmacists working for the big chains," he said.

Stanley himself bought an independent drugstore in 2013 after 21 years spent practicing in major chains.

"I love my current position," he said. "Being my own boss means I have the tools to practice my profession that I was never given while working for the chains, mainly adequate staffing, reference materials — even a speedy Internet connection can make a big difference."

Those who do plan to make a job change listed professional advancement, income, job security, and geographic location as some of the reasons that they plan to leave their current positions.

Growing workload

While job satisfaction remains high for most, most pharmacists say they've seen an increase in their workload during the last year. According to the survey, 71.7% say their workload has increased in 2014, while 23.4% say that it has remained about the same. Only 3.6% saw a decrease in their workload.

"Our prescription count and sales are up consistently by double digits over last year," said Stanley. "Some of that is due to implementation of an automatic refill program, but the single biggest factor driving growth is the beginning of Obamacare. I have a lot of regular customers getting prescriptions now who lacked coverage and couldn't afford it before the ACA."

Moore said that in the midst of tighter margins for filling prescriptions and increased responsibilities, more pharmacy owners are trying to find ways to become more efficient, instead of hiring more staff and raising the pharmacy's expenses.

"It' a little tough to do that sometimes, but I think that's what we are all trying to figure out," he said.

Even those who aren't in the business of dispensing are seeing an increase in their daily workload.

Continued on pg. 29

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- **94%** relative reduction in febrile neutropenia (17% placebo vs 1% Neulasta; $P < .001$)[1,2]
- **93%** relative reduction in febrile neutropenia–related hospitalization (14% placebo vs 1% Neulasta; $P < .001$)[1,2]
- **80%** relative reduction in febrile neutropenia–related IV anti-infective use (10% placebo vs 2% Neulasta; $P < .001$)[1,2]

Phase 3 study in patients with breast cancer receiving 100 mg/m^2 docetaxel for up to 4 cycles given placebo (n = 465) or Neulasta (n = 463); primary endpoint: incidence of febrile neutropenia.[1]

Febrile neutropenia = absolute neutrophil count (ANC) < 0.5 × 10^9/L and temperature ≥ 38.2°C.

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Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Important Safety Information

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta.

Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta for ARDS. Discontinue Neulasta in patients with ARDS.

Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta in patients with serious allergic reactions.

Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

The granulocyte colony-stimulating factor (G-CSF) receptor, through which pegfilgrastim and filgrastim act, has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

Bone pain and pain in extremity occurred at a higher incidence in Neulasta-treated patients as compared with placebo-treated patients.

Please see brief summary of Neulasta Prescribing Information on the adjacent page.

References: 1. Vogel C, et al. *J Clin Oncol.* 2005;23:1178-1184. **2.** Neulasta (pegfilgrastim) Prescribing Information. Thousand Oaks, CA: Amgen; 2011.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Neulasta® (pegfilgrastim) injection, for subcutaneous use

INDICATIONS AND USAGE

Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

CONTRAINDICATIONS

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

WARNINGS AND PRECAUTIONS

Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta, for ARDS. Discontinue Neulasta in patients with ARDS.

Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta in patients with serious allergic reactions. Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

Use in Patients With Sickle Cell Disorders

Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte-colony stimulating factor (G-CSF) receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the Brief Summary:

- Splenic Rupture [*See Warnings and Precautions*]
- Acute Respiratory Distress Syndrome [*See Warnings and Precautions*]
- Serious Allergic Reactions [*See Warnings and Precautions*]
- Use in Patients with Sickle Cell Disorders [*See Warnings and Precautions*]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*See Warnings and Precautions*]

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo controlled clinical trials are bone pain and pain in extremity.

Clinical Trials Experience

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

Neulasta clinical trials safety data are based upon 932 patients receiving Neulasta in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n = 56) received Neulasta after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 1 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m^2 every 21 days. (Study 3). A total of 928 patients were randomized to receive either 6 mg Neulasta (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American or other.

Bone pain and pain in extremity occurred at a higher incidence in Neulasta-treated patients as compared with placebo-treated patients.

Table 1. Adverse Reactions With ≥ 5% Higher Incidence in Neulasta Patients Compared to Placebo in Study 3

System Organ Class Preferred Term	Placebo (N = 461)	Neulasta 6 mg SC on Day 2 (N = 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in less than 1% of 932 patients with nonmyeloid malignancies receiving Neulasta. No complications attributable to leukocytosis were reported in clinical studies.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Neulasta with the incidence of antibodies to other products may be misleading.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Neulasta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) reported frequency of the reaction, or (3) strength of causal relationship to Neulasta.

Gastro-intestinal disorders: Splenic rupture [see *Warnings and Precautions*]

Blood and lymphatic system disorder: Sickle cell crisis [see *Warnings and Precautions*]

Hypersensitivity reactions: Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema and flushing [see *Warnings and Precautions*]

Respiratory, thoracic, and mediastinal disorder: ARDS [see *Warnings and Precautions*]

General disorders and administration site conditions: Injection site reactions

Skin and subcutaneous tissue disorders: Sweet's syndrome, Cutaneous vasculitis

DRUG INTERACTIONS

No formal drug interaction studies between Neulasta and other drugs have been performed. Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes. Consider these findings when interpreting bone-imaging results.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Pegfilgrastim was embryotoxic and increased pregnancy loss in pregnant rabbits that received cumulative doses approximately 4 times the recommended human dose (based on body surface area). Signs of maternal toxicity occurred at these doses. Neulasta should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In animal reproduction studies, when pregnant rabbits received pegfilgrastim at cumulative doses approximately 4 times the recommended human dose (based on body surface area), increased embryolethality and spontaneous abortions occurred. Signs of maternal toxicity (reductions in body weight gain/food consumption) and decreased fetal weights occurred at maternal doses approximately equivalent to the recommended human dose (based on body surface area). There were no structural anomalies observed in rabbit offspring at any dose tested. No evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area).

Women who become pregnant during Neulasta treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

Nursing Mothers

It is not known whether pegfilgrastim is secreted in human milk. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates. Caution should be exercised when administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Neulasta in pediatric patients have not been established. The adverse reaction profile and pharmacokinetics of pegfilgrastim were studied in 37 pediatric patients with sarcoma. The mean (± standard deviation [SD]) systemic exposure (AUC_{0-inf}) of pegfilgrastim after subcutaneous administration at 100 mcg/kg was 22.0 (± 13.1) mcg·hr/mL in the 6 to 11 years age group (n = 10), 29.3 (± 23.2) mcg·hr/mL in the 12 to 21 years age group (n = 13), and 47.9 (± 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, n = 11). The terminal elimination half-lives of the corresponding age groups were 20.2 (± 11.3) hours, 21.2 (± 16.0) hours, and 30.1 (± 38.2) hours, respectively. The most common adverse reaction was bone pain.

Geriatric Use

Of the 932 patients with cancer who received Neulasta in clinical studies, 139 (15%) were age 65 and over, and 18 (2%) were age 75 and over. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

Renal Impairment

In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim. Therefore, pegfilgrastim dose adjustment in patients with renal dysfunction is not necessary.

DOSAGE AND ADMINISTRATION

The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle in adults. Do not administer Neulasta between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Neulasta if discoloration or particulates are observed.

NOTE: The needle cover on the single-use prefilled syringe contains dry natural rubber (latex); persons with latex allergies should not administer this product.

This product, its production, and/or its use may be covered by one or more US Patents, including US Patent Nos. 5,824,784; 5,582,823; 5,580,755, as well as other patents or patents pending.

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Incomes hold steady

Continued from pg. 24

"For us it's driven by different things. There are a lot of new drugs coming out and that impacts our workload, because we have to evaluate all the new drugs and then set coverage," Nesser said.

Emotional impact

With reports of an increasing workload for most pharmacists, it isn't surprising to find that stress levels are also on the rise. Among respondents, 64.5% believe that, over the past year, their stress levels have increased, primarily because of increased work volume, inadequate staffing, and increased paperwork.

Moore said he thinks one factor in rising stress levels involves the additional responsibilities and services pharmacists across the country are now performing, such as MTM services. He hopes that as pharmacies revamp their workflow process to accommodate these new types of services over the next few years, stress levels will also decrease for those behind the counter.

But regardless of how the demands of the job change in the years ahead, Stanley said, pharmacists need to find ways to manage stress and prevent it from affecting their health.

"You have to make an active effort to fight being dragged down by the working environment in most modern pharmacies," he said.

One important aspect of that, he said, is leaving work-related stress at work.

"Develop an identity unrelated to your work, where you can go to decompress — a hobby, volunteer work, even just giving yourself an hour of solitude each day," he said. "Anything that will let you get away from the problems of your work life."

Future prospects

The profession of pharmacy is evolving. One place where that is most evident is in the classroom, where a new generation of pharmacists prepares to step behind the counter.

Nesser, who teaches a pharmacy law class, said that she thinks new graduates will enter an industry full of opportunity and potential.

"I think that they will end up actually being more of a true healthcare practitioner and less of a dispenser," she said. "The students are getting a totally different kind of education now than we were getting in the '80s and even in the '90s."

Stanley believes that the industry's future success and ability to become a more valuable partner in healthcare will depend on whether pharmacy can find a way to provide services at a lower price point than others in the healthcare industry are able to do.

"You can easily imagine a future where a patient comes in and has his blood pressure checked at the pharmacy when he is due for a prescription renewal, or when a pharmacist can issue an order for a thyroid level to be e-mailed to the store and then issue a levothyroxine renewal, and if there are any problems, have the ability to schedule an appointment for the patient with the appropriate doctor through a direct connection to the physician's office computer," he said. "This would save the health system money by working these services into regular pharmacy visits that are already happening, while saving the time of the physician to diagnose and solve problems."

While some may be apprehensive about the changes ahead, Moore said, he is looking forward to the next decade.

"I think it's an exciting time to be a pharmacist. I think our role is evolving — not that we won't hold onto some of the traditional roles. But I think it's exciting to become more involved with the healthcare team and have collaboration with other practitioners," he said. DT

TABLE 4

Benefits employers offer, 2014

Benefit	Respondents	Percentage
Paid vacation	1,772	89.2%
Health insurance	1,723	86.7%
Paid holidays	1,627	81.9%
Dental insurance	1,570	79.0%
Vision plan	1,474	74.2%
Life insurance	1,419	71.4%
401k plan	1,396	70.3%
Paid sick days	1,379	69.4%
Discount on store merchandise	990	49.8%
Continuing education reimbursement	525	26.4%
Profit sharing	519	26.1%
Flex hours	215	10.8%
Other*	210	10.6%
Student loan repayment	40	2.0%
Job sharing	33	1.7%

*Other income derived from other retirement plans (401a, 403b, state-run retirement, pension), employee stock purchase plan and stock options, incentive bonus, association membership fees, wellness membership, tuition reduction and/or reimbursement, short- and long-term disability insurance.

Source: Drug Topics' *2015 salary survey, deployed in mid-November 2014. Total respondents, 1,987 pharmacists.*

Jill Sederstrom *is a freelance writer in Kansas City.*

NEW DRUG REVIEW Kathryn Wheeler, PharmD, BCPS

FDA approves apremilast, first-in-class treatment option for plaque psoriasis

In September, FDA approved apremilast (Otezla; Celgene) for treatment of moderate-to-severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy. Apremilast was first approved by FDA for treatment of adults with active psoriatic arthritis in March 2014. The first of a new class of drug therapy for these conditions, apremilast is a phosphodiesterase 4 (PDE4) inhibitor. It reduces the inflammatory processes associated with these conditions, resulting in symptom improvement. For patients with moderate-to-severe plaque psoriasis, apremilast offers a new oral option for treatment.

Efficacy

Apremilast was approved for treatment of moderate-to-severe plaque psoriasis on the basis of two randomized, double-blind, placebo-controlled trials (ESTEEM 1 and 2). Participants were at least 18 years of age with moderate-to-severe plaque psoriasis and were candidates for phototherapy or systemic therapy.

In both studies, participants were randomized to receive either apremilast 30 mg twice daily or placebo for 16 weeks. The primary endpoint in both studies was the proportion of participants achieving a 75% reduction in the Psoriasis Area and Severity Index (PASI-75). At week 16, 5% of participants taking placebo achieved PASI-75 in each trial compared to 33% (ESTEEM-1) and 28% (ESTEEM-2) of participants taking apremilast. The static Physician Global Assessment (sPGA) scores of "clear" or "almost clear" were assessed as a secondary endpoint.

Both studies demonstrated greater achievement of significantly improved sPGA scores with apremilast use at 16 weeks compared to placebo (21.7% vs. 3.9% in ESTEEM-1; 20.4% vs. 4.4% in ESTEEM-2). Study findings were deemed significant and clinically meaningful improvements in plaque psoriasis. While apremilast provides a therapeutic option for treatment of psoriasis, its efficacy has not been studied in comparison with other approved treatment options.

Safety

Apremilast was well tolerated in clinical trials. The most common adverse effects observed in the ESTEEM trials include diarrhea, nausea, headache, and upper respiratory infections. Nausea generally resolved within one month of use. The discontinuation rates resulting from adverse reaction for participants taking apremilast was 6.1% compared to 4.1% of participants taking placebo in studies.

In trials, apremilast is associated with an increase in depressed mood in some patients. A careful consideration of the risks and benefits of apremilast therapy should be performed before initiation of treatment in patients with a history of depression or suicidal thoughts or behaviors. Patients and caregivers should be advised to contact their healthcare provider immediately should changes in mood, worsening depression, or suicidal thoughts occur in patients taking apremilast.

The first of a new class of drug therapy for these conditions, apremilast is a phosphodiesterase 4 (PDE4) inhibitor. It reduces the inflammatory processes associated with these conditions, resulting in symptom improvement.

Significant weight reduction has also been associated with apremilast use. Discontinuation of apremilast should be considered with any unexplained or clinically significant weight loss. Patients taking apremilast should be advised to monitor their weight regularly.

Dosage

Apremilast should be initiated with a 10-mg morning dose and titrated up over six days to 30 mg twice daily. The drug is available in a two-week starter blister pack to simplify the dosing schedule for the patient. Tablets should not be crushed or split. A maximum daily dose of 30 mg should be used for patients with severe renal impairment (creatinine clearance <30 mL/min). Coadministration of apremilast with strong CYP450 inducers may result in reduced apremilast efficacy and should therefore be avoided. Apremilast may be taken without regard to food. DT

Kathryn Wheeler *is associate clinical professor, Pharmacy Practice, University of Connecticut, School of Pharmacy, Storrs, Conn.*

ANTICOAGULATION THERAPIES Anna D. Garrett, PharmD, BCPS

NSAIDs increase bleeding risk in patients taking anticoagulants

Patients with atrial fibrillation (AF) receiving antithrombotic treatment are at increased risk for bleeding if they also take a nonsteroidal anti-inflammatory drug (NSAID), even for a short period, a new nationwide Danish study has found.

The data suggest that a serious bleeding event occurs in up to one in 400 to 500 patients with AF exposed to an NSAID for two weeks, and that the risk is elevated for patients taking selective cyclooxygenase (COX)-2 inhibitors or nonselective NSAIDs.

The analysis included 150,900 patients, median age 75 years, who were hospitalized with a first-time diagnosis of AF between 1997 and 2011. During a median follow-up of 6.2 years, 35.6% of patients were prescribed an NSAID.

Study participants had a mean HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score of 1.5 and a mean CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, sex) score of 2.8. Approximately 70% were being treated with an antiplatelet or oral anticoagulant.

The study showed that serious bleeding events, including intracranial and gastrointestinal bleeding, occurred in 11.4% of the patients; thromboembolic events occurred in 13.0%. The absolute risk for serious bleeding with 14 days of continuous NSAID exposure was 3.5 events per 1,000 patients vs. 1.5 events per 1,000 patients without NSAID exposure for an absolute risk difference of 1.9 events per 1,000 patients. In patients treated with oral anticoagulant therapy, the absolute risk difference was 2.5 events per 1,000 patients.

The study showed that the risk for serious bleeding with NSAID treatment was doubled compared with no NSAID treatment. The risk for thromboembolism was also increased.

Source: Lamberts M, Lip GYH, Hansen ML, et al. Relation of non-steroidal anti-inflammatory drugs to serious bleeding and thromboembolism risk in patients with atrial fibrillation receiving anti-thrombotic therapy: A nationwide cohort study. Ann Intern Med. *2014;161:690–698.*

Reversal agent for apixaban shows promise

Results from the Phase 3 ANNEXA-A (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors – Apixaban) studies showed that the drug produced rapid and nearly complete reversal (approximately 94%) of the anticoagulant effect of Eliquis (apixaban) in healthy volunteers ages 50 to 75.

The trial included 33 subjects, with 24 randomized to andexanet alfa and nine to placebo. In the study, reversal was achieved two to five minutes after completion of a bolus dose of andexanet alfa. The reversal of anti-Factor Xa activity correlated with a significant reduction in the level of free, unbound Eliquis in the plasma, consistent with the mechanism of action of andexanet alfa. Additionally, andexanet alfa restored thrombin generation to what were baseline normal levels before initiation of Eliquis therapy.

The drug is an FDA-designated breakthrough therapy because there is currently no approved reversal agent for target-specific anticoagulants.

Source: Positive results for factor Xa inhibitor antidote: ANNEXA-A. www.medscape.com/viewarticle/832648. *Accessed Nov. 26, 2014.*

Dementia risk increases with dual anti-stroke therapy in atrial fibrillation

A new study investigating the long-term use of warfarin in conjunction with antiplatelet therapy using aspirin or clopidogrel may result in an increased risk of dementia in patients with atrial fibrillation.

The study, presented at the American Heart Association's (AHA) Scientific Sessions 2014, followed 1,031 AF patients for up to 10 years. None of the participants had a previous history of stroke or dementia.

The researchers found that patients with an INR>3.0 on at least 25% of their monitoring tests were more than twice as likely to be diagnosed with dementia than patients who had an elevated INR less than 10% of the time.

The increase in dementia risk was higher than that observed in a previous study examining warfarin use only. These previous findings led to the conclusion that brain injury caused by both micro bleeds and clots plays a key role in the development of dementia among AF patients. The results of this study appear to support this theory as well.

Source: Medical News Today. Dementia risks rise with overuse of anti-stroke dual-drug combo. www.medicalnewstoday.com/articles/285471.php. *Accessed Nov. 26, 2014.* DT

Anna D. Garrett *is a clinical pharmacist and president of Dr. Anna Garrett (www.drannagarrett.com). Her mission is to help women in midlife maximize their mojo! Contact her at info@drannagarrett.com.*

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It may be necessary to update your pharmacy and/or patient medication management systems.

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Indications

TREANDA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first-line therapies other than chlorambucil has not been established.

TREANDA is indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

Important Safety Information

Contraindication: TREANDA is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine.

Myelosuppression: TREANDA caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies. Three patients (2%) died from myelosuppression-related adverse reactions. If myelosuppression occurs, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle.

Infections: Infection, including pneumonia, sepsis, septic shock, and death have occurred. Patients with myelosuppression following treatment with TREANDA are more susceptible to infections.

Important Safety Information (continued)

Anaphylaxis and Infusion Reactions: Infusion reactions to TREANDA® have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus, and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe (Grade 3-4) reactions. Ask patients about symptoms suggestive of infusion reactions after their first cycle of therapy. Consider measures to prevent severe reactions, including antihistamines, antipyretics, and corticosteroids in subsequent cycles in patients who have experienced Grade 1 or 2 infusion reactions.

Tumor Lysis Syndrome: Tumor lysis syndrome associated with TREANDA treatment has occurred. The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death. Preventive measures include vigorous hydration and close monitoring of blood chemistry, particularly potassium and uric acid levels. There may be an increased risk of severe skin toxicity when TREANDA and allopurinol are administered concomitantly.

Skin Reactions: Skin reactions have been reported with TREANDA treatment and include rash, toxic skin reactions, and bullous exanthema. In a study of TREANDA (90 mg/m^2) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab. Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. Where skin reactions occur, they may be progressive and increase in severity with further treatment. Monitor patients with skin reactions closely. If skin reactions are severe or progressive, withhold or discontinue TREANDA.

Other Malignancies: There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with TREANDA, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma. The association with TREANDA therapy has not been determined.

Extravasation Injury: TREANDA extravasations have been reported in postmarketing resulting in hospitalizations from erythema, marked swelling, and pain. Ensure good venous access prior to starting TREANDA infusion and monitor the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of TREANDA.

Embryo-fetal Toxicity: TREANDA can cause fetal harm when administered to a pregnant woman. Women should be advised to avoid becoming pregnant while using TREANDA.

Most Common Adverse Reactions: The most common non-hematologic adverse reactions for CLL (frequency ≥15%) are pyrexia, nausea, and vomiting. The most common non-hematologic adverse reactions for NHL (frequency ≥15%) are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. The most common hematologic abnormalities for both indications (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia.

Please see accompanying brief summary of Full Prescribing Information on the following pages.

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TEVA Oncology

LIQUID FORMULATION
TREANDA™
(bendamustine HCl)
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TREANDA™
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Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

TREANDA® is indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established.

1.2 Non-Hodgkin Lymphoma (NHL)

TREANDA is indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions for CLL

Recommended Dosage:

The recommended dose is 100 mg/m^2 administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles.

Dose Delays, Dose Modifications and Reinitiation of Therapy for CLL:

TREANDA administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ≤ Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L], TREANDA can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. *[See Warnings and Precautions (5.1)]*

Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m^2 on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle.

Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

2.2 Dosing Instructions for NHL

Recommended Dosage:

The recommended dose is 120 mg/m^2 administered intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Dose Delays, Dose Modifications and Reinitiation of Therapy for NHL:

TREANDA administration should be delayed in the event of a Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ≤ Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L], TREANDA can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. *[See Warnings and Precautions (5.1)]*

Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.

2.3 Preparation for Intravenous Administration

Each vial of TREANDA Injection is intended for single use only. Aseptically withdraw the volume needed for the required dose from the 90 mg/mL solution.

Immediately transfer the solution to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2 - 0.7 mg/mL. The admixture should be a clear colorless to yellow solution. Use either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined above. No other diluents have been shown to be compatible.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Any unused solution should be discarded according to institutional procedures for antineoplastics.

2.4 Admixture Stability

TREANDA Injection contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration. Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored under refrigerated conditions at 2°-8°C (36°-46°F) or for 2 hours when stored at room temperature 15°-30°C (59°-86°F) and room light. Administration of TREANDA must be completed within this period.

3 DOSAGE FORMS AND STRENGTHS

TREANDA Injection is supplied in single-use vials containing either 45 mg/0.5 mL or 180 mg/2 mL of bendamustine HCl.

4 CONTRAINDICATIONS

TREANDA is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine. *[See Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

TREANDA caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies (see Table 4). Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV).

In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be ≥ 1 x 10^9/L and the platelet count should be ≥ 75 x 10^9/L. *[See Dosage and Administration (2.1) and (2.2)]*

5.2 Infections

Infection, including pneumonia, sepsis, septic shock, and death have occurred in adult and pediatric patients in clinical trials and in postmarketing reports. Patients with myelosuppression following treatment with TREANDA are more susceptible to infections. Advise patients with myelosuppression following TREANDA treatment to contact a physician if they have symptoms or signs of infection.

5.3 Anaphylaxis and Infusion Reactions

Infusion reactions to TREANDA have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Ask patients about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experience Grade 3 or worse allergic-type reactions should not be rechallenged. Consider measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids in subsequent cycles in patients who have experienced Grade 1 or 2 infusion reactions. Discontinue TREANDA for patients with Grade 4 infusion reactions. Consider discontinuation for Grade 3 infusions reactions as clinically appropriate considering individual benefits, risks, and supportive care.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome associated with TREANDA treatment has occurred in patients in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death. Preventive measures include vigorous hydration and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of TREANDA therapy. However, there may be an increased risk of severe skin toxicity when TREANDA and allopurinol are administered concomitantly *[see Warnings and Precautions (5.5)]*.

5.5 Skin Reactions

Skin reactions have been reported with TREANDA treatment in clinical trials and postmarketing safety reports, including rash, toxic skin reactions and bullous exanthema. Some events occurred when TREANDA was given in combination with other anticancer agents.

In a study of TREANDA (90 mg/m^2) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert). Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to TREANDA cannot be determined.

Where skin reactions occur, they may be progressive and increase in severity with further treatment. Monitor patients with skin reactions closely. If skin reactions are severe or progressive, withhold or discontinue TREANDA.

5.6 Other Malignancies

There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with TREANDA, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. The association with TREANDA therapy has not been determined.

5.7 Extravasation Injury

TREANDA extravasations have been reported in post marketing resulting in hospitalizations from erythema, marked swelling, and pain. Assure good venous access prior to starting TREANDA infusion and monitor the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of TREANDA.

5.8 Embryo-fetal Toxicity

TREANDA can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of bendamustine in mice and rats administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations, and decreased fetal body weights.

6 ADVERSE REACTIONS

The following serious adverse reactions have been associated with TREANDA in clinical trials and are discussed in greater detail in other sections of the label *[See Warnings and Precautions]*: Myelosuppression *(5.1)*; Infections *(5.2)*; Anaphylaxis and Infusion Reactions *(5.3)*; Tumor Lysis Syndrome *(5.4)*; Skin Reactions *(5.5)*; Other Malignancies *(5.6)*; Extravasation injury *(5.7)*. The data described below reflect exposure to TREANDA in 329 patients who participated in an actively-controlled trial (N=153) for the treatment of CLL and two single-arm studies (N=176) for the treatment of indolent B-cell NHL. 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.

6.1 Clinical Trials Experience in CLL

The data described below reflect exposure to TREANDA in 153 patients with CLL studied in an active-controlled, randomized trial. The population was 45-77 years of age, 63% male, 100% white, and were treatment naïve. All patients started the study at a dose of 100 mg/m^2 intravenously over 30 minutes on Days 1 and 2 every 28 days.

Adverse reactions were reported according to NCI CTC v.2.0. Non-hematologic adverse reactions (any grade) in the TREANDA group that occurred with a frequency greater than 15% were pyrexia (24%), nausea (20%), and vomiting (16%).

Other adverse reactions seen frequently in one or more studies included asthenia, fatigue, malaise, and weakness; dry mouth; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis.

Worsening hypertension was reported in 4 patients treated with TREANDA in the CLL trial and in none treated with chlorambucil. Three of these 4 adverse reactions were described as a hypertensive crisis and were managed with oral medications and resolved.

The most frequent adverse reactions leading to study withdrawal for patients receiving TREANDA were hypersensitivity (2%) and pyrexia (1%).

Table 1 contains the treatment emergent adverse reactions, regardless of attribution, that were reported in ≥ 5% of patients in either treatment group in the randomized CLL clinical study.

Table 1: Non-Hematologic Adverse Reactions Occurring in Randomized CLL Clinical Study in at Least 5% of Patients

	Number (%) of patients			
	TREANDA (N=153)		Chlorambucil (N=143)	
System organ class Preferred term	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Total number of patients with at least 1 adverse reaction	**121 (79)**	**52 (34)**	**96 (67)**	**25 (17)**
Gastrointestinal disorders				
Nausea	31 (20)	1 (<1)	21 (15)	1 (<1)
Vomiting	24 (16)	1 (<1)	9 (6)	0
Diarrhea	14 (9)	2 (1)	5 (3)	0
General disorders and administration site conditions				
Pyrexia	36 (24)	6 (4)	8 (6)	2 (1)
Fatigue	14 (9)	2 (1)	8 (6)	0
Asthenia	13 (8)	0	6 (4)	0
Chills	9 (6)	0	1 (<1)	0
Immune system disorders				
Hypersensitivity	7 (5)	2 (1)	3 (2)	0
Infections and infestations				
Nasopharyngitis	10 (7)	0	12 (8)	0
Infection	9 (6)	3 (2)	1 (<1)	1 (<1)
Herpes simplex	5 (3)	0	7 (5)	0
Investigations				
Weight decreased	11 (7)	0	5 (3)	0
Metabolism and nutrition disorders				
Hyperuricemia	11 (7)	3 (2)	2 (1)	0
Respiratory, thoracic and mediastinal disorders				
Cough	6 (4)	1 (<1)	7 (5)	1 (<1)
Skin and subcutaneous tissue disorders				
Rash	12 (8)	4 (3)	7 (5)	3 (2)
Pruritus	8 (5)	0	2 (1)	0

The Grade 3 and 4 hematology laboratory test values by treatment group in the randomized CLL clinical study are described in Table 2. These findings confirm the myelosuppressive effects seen in patients treated with TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

TREANDA® (bendamustine hydrochloride) Injection

Table 2: Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA or Chlorambucil in the Randomized CLL Clinical Study

	TREANDA N=150		Chlorambucil N=141	
Laboratory Abnormality	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Hemoglobin Decreased	134 (89)	20 (13)	115 (82)	12 (9)
Platelets Decreased	116 (77)	16 (11)	110 (78)	14 (10)
Leukocytes Decreased	92 (61)	42 (28)	26 (18)	4 (3)
Lymphocytes Decreased	102 (68)	70 (47)	27 (19)	6 (4)
Neutrophils Decreased	113 (75)	65 (43)	86 (61)	30 (21)

In the CLL trial, 34% of patients had bilirubin elevations, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of Grade 3 or 4 were limited to 1% and 3% of patients, respectively. Patients treated with TREANDA may also have changes in their creatinine levels. If abnormalities are detected, monitoring of these parameters should be continued to ensure that further deterioration does not occur.

6.2 Clinical Trials Experience in NHL

The data described below reflect exposure to TREANDA in 176 patients with indolent B-cell NHL treated in two single-arm studies. The population was 31-84 years of age, 60% male, and 40% female. The race distribution was 89% White, 7% Black, 3% Hispanic, 1% other, and <1% Asian. These patients received TREANDA at a dose of 120 mg/m^2 intravenously on Days 1 and 2 for up to eight 21-day cycles.

The adverse reactions occurring in at least 5% of the NHL patients, regardless of severity, are shown in Table 3. The most common non-hematologic adverse reactions (≥ 30%) were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%) and pyrexia (34%). The most common non-hematologic Grade 3 or 4 adverse reactions (≥ 5%) were fatigue (11%), febrile neutropenia (6%), and pneumonia, hypokalemia and dehydration, each reported in 5% of patients.

Table 3: Non-Hematologic Adverse Reactions Occurring in at Least 5% of NHL Patients Treated with TREANDA by System Organ Class and Preferred Term (N=176)

	Number (%) of patients*	
System organ class Preferred term	**All Grades**	**Grade 3/4**
Total number of patients with at least 1 adverse reaction	176 (100)	94 (53)
Cardiac disorders		
Tachycardia	13 (7)	0
Gastrointestinal disorders		
Nausea	132 (75)	7 (4)
Vomiting	71 (40)	5 (3)
Diarrhea	65 (37)	6 (3)
Constipation	51 (29)	1 (<1)
Stomatitis	27 (15)	1 (<1)
Abdominal pain	22 (13)	2 (1)
Dyspepsia	20 (11)	0
Gastroesophageal reflux disease	18 (10)	0
Dry mouth	15 (9)	1 (<1)
Abdominal pain upper	8 (5)	0
Abdominal distension	8 (5)	0
General disorders and administration site conditions		
Fatigue	101 (57)	19 (11)
Pyrexia	59 (34)	3 (2)
Chills	24 (14)	0
Edema peripheral	23 (13)	1 (<1)
Asthenia	19 (11)	4 (2)
Chest pain	11 (6)	1 (<1)
Infusion site pain	11 (6)	0
Pain	10 (6)	0
Catheter site pain	8 (5)	0
Infections and infestations		
Herpes zoster	18 (10)	5 (3)
Upper respiratory tract infection	18 (10)	0
Urinary tract infection	17 (10)	4 (2)
Sinusitis	15 (9)	0
Pneumonia	14 (8)	9 (5)
Febrile neutropenia	11 (6)	11 (6)
Oral candidiasis	11 (6)	2 (1)
Nasopharyngitis	11 (6)	0

	Number (%) of patients*	
System organ class Preferred term	**All Grades**	**Grade 3/4**
Investigations		
Weight decreased	31 (18)	3 (2)
Metabolism and nutrition disorders		
Anorexia	40 (23)	3 (2)
Dehydration	24 (14)	8 (5)
Decreased appetite	22 (13)	1 (<1)
Hypokalemia	15 (9)	9 (5)
Musculoskeletal and connective tissue disorders		
Back pain	25 (14)	5 (3)
Arthralgia	11 (6)	0
Pain in extremity	8 (5)	2 (1)
Bone pain	8 (5)	0
Nervous system disorders		
Headache	36 (21)	0
Dizziness	25 (14)	0
Dysgeusia	13 (7)	0
Psychiatric disorders		
Insomnia	23 (13)	0
Anxiety	14 (8)	1 (<1)
Depression	10 (6)	0
Respiratory, thoracic and mediastinal disorders		
Cough	38 (22)	1 (<1)
Dyspnea	28 (16)	3 (2)
Pharyngolaryngeal pain	14 (8)	1 (<1)
Wheezing	8 (5)	0
Nasal congestion	8 (5)	0
Skin and subcutaneous tissue disorders		
Rash	28 (16)	1 (<1)
Pruritus	11 (6)	0
Dry skin	9 (5)	0
Night sweats	9 (5)	0
Hyperhidrosis	8 (5)	0
Vascular disorders		
Hypotension	10 (6)	2 (1)

*Patients may have reported more than 1 adverse reaction.

NOTE: Patients counted only once in each preferred term category and once in each system organ class category.

Hematologic toxicities, based on laboratory values and CTC grade, in NHL patients treated in both single arm studies combined are described in Table 4. Clinically important chemistry laboratory values that were new or worsened from baseline and occurred in >1% of patients at Grade 3 or 4, in NHL patients treated in both single arm studies combined were hyperglycemia (3%), elevated creatinine (2%), hyponatremia (2%), and hypocalcemia (2%).

Table 4: Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA in the NHL Studies

	Percent of patients	
Hematology variable	**All Grades**	**Grades 3/4**
Lymphocytes Decreased	99	94
Leukocytes Decreased	94	56
Hemoglobin Decreased	88	11
Neutrophils Decreased	86	60
Platelets Decreased	86	25

In both studies, serious adverse reactions, regardless of causality, were reported in 37% of patients receiving TREANDA. The most common serious adverse reactions occurring in ≥ 5% of patients were febrile neutropenia and pneumonia. Other important serious adverse reactions reported in clinical trials and/or postmarketing experience were acute renal failure, cardiac failure, hypersensitivity, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome.

TREANDA® (bendamustine hydrochloride) Injection

Serious drug-related adverse reactions reported in clinical trials included myelosuppression, infection, pneumonia, tumor lysis syndrome and infusion reactions *[see Warnings and Precautions (5)]*. Adverse reactions occurring less frequently but possibly related to TREANDA treatment were hemolysis, dysgeusia/taste disorder, atypical pneumonia, sepsis, herpes zoster, erythema, dermatitis, and skin necrosis.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TREANDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: anaphylaxis; and injection or infusion site reactions including phlebitis, pruritus, irritation, pain, and swelling; pneumocystis jiroveci pneumonia and pneumonitis.

Skin reactions including SJS and TEN have occurred when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. *[See Warnings and Precautions (5.5)]*

10 OVERDOSAGE

The intravenous LD_{50} of bendamustine HCl is 240 mg/m^2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

Across all clinical experience, the reported maximum single dose received was 280 mg/m^2. Three of four patients treated at this dose showed ECG changes considered dose-limiting at 7 and 21 days post-dosing. These changes included QT prolongation (one patient), sinus tachycardia (one patient), ST and T wave deviations (two patients), and left anterior fascicular block (one patient). Cardiac enzymes and ejection fractions remained normal in all patients.

No specific antidote for TREANDA overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of solutions prepared from TREANDA Injection. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If a solution of TREANDA contacts the skin, wash the skin immediately and thoroughly with soap and water. If TREANDA contacts the mucous membranes, flush thoroughly with water.

TREANDA is a cytotoxic drug. Follow special handling and disposal procedures[1].

16.2 How Supplied

TREANDA (bendamustine hydrochloride) Injection is supplied as a 90 mg/mL clear colorless to yellow solution as follows:

NDC 63459-395-02: 45 mg/0.5 mL of solution in an amber single-use vial

NDC 63459-396-02: 180 mg/2 mL of solution in an amber single-use vial

Vials are supplied in individual cartons.

16.3 Storage

TREANDA Injection must be stored refrigerated between 2°-8°C (36°-46°F). Retain in original package until time of use to protect from light.

Distributed By:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

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TRE-40202

This brief summary is based on TRE-009 TREANDA full Prescribing Information.

Valerie DeBenedette

Diabetes and depression

The interrelationship between depression and diabetes is only now being studied and understood. It can almost seem like a chicken-and-egg question. Which comes first? Do symptoms of depression predate those of diabetes, or are the very early stages of diabetes causing depression?

The situation becomes even more complicated when you consider the adverse effects that some antidepressant medications have on body weight and blood glucose levels. Treating depression with medications has been associated with pre-diabetes and diabetes.

Tracing the connection

Numerous papers published over the last several months have examined the interplay between diabetes and depression.

Depression is seen twice as often in people with type 2 diabetes as it is in the general population, but no similar increased incidence is seen in type 1, said Paula M. Trief, PhD, senior associate dean for faculty affairs and faculty development, and professor in the Departments of Psychiatry and Medicine at the State University of New York Upstate Medical University in Syracuse.


Paula Trief

"People who have diabetes and depression have poorer diabetes-related outcomes," she said. "They have poorer glycemic control, more complications, higher mortality, and higher costs."

Trief was lead author on a study that screened more than 6,000 patients with type 1 diabetes and found that between 4.6% and 10.3% had signs of major depression. Those who were found to be depressed tended to have worse clinical outcomes; they were more likely to exercise less often, to miss insulin doses, and to experience more complications.[1]

A significant public health problem

This past August, the National Institute of Diabetes and Digestive and Kidney Diseases, in collaboration with the National Institute of Mental Health and the Dialogue on Diabetes and Depression, published a report on the subject.

"Shared biological and behavioral mechanisms, such as hypothalamic-pituitary-adrenal axis activation, inflammation, autonomic dysfunction, sleep disturbance, inactive lifestyle, poor dietary habits, and environmental and cultural risk factors, are important to consider in understanding the link between depression and diabetes," the report stated. The report called the association between diabetes and depression or depressive symptoms a major public health problem.[2]

Symptoms and likelihood

Data from the Black Women's Health Study, a large prospective study, found that both depressive symptoms and the use of antidepressant medications were associated with a later diagnosis of diabetes. The data was collected from 1999 through 2011 on almost 36,000 women who did not have a diagnosis of diabetes to begin with. The association between depressive symptoms and later diabetes was stronger with women with higher numbers of depressive symptoms.[3]

Research using data from the South London Diabetes Study found an association between depressive symptoms and systemic inflammation in people who were newly diagnosed with type 2 diabetes. The study, which was based on nearly 1,800 patients, concluded that increased inflammation might be involved in the pathogenesis of depressive symptoms in type 2 diabetes.[4]

A prospective study from 2011 used data from the Women's Health Initiative on postmenopausal women. It found that women who had symptoms of depression and who took antidepressants had a greater risk of developing diabetes later on. This study followed nearly 162,000 women for an average of 7.6 years.[5]


Charlene Williams

"Pharmacists and other healthcare providers are aware of this growing body of evidence that has established a connection between diabetes and depression," said Charlene R. Williams, PharmD, BCACP, CDE, Western Experiential Education Coordinator and clinical assistant professor

Continued on pg. 34

Diabetes and depression

Continued from pg. 33

at the University of North Carolina's Eshelman School of Pharmacy in Asheville. Williams helps place pharmacy students for their advanced practice experience in western North Carolina.

Search for the cause

Even with many new findings about diabetes and depression coming out, it is hard to know what causes the interplay between diabetes and depression. The two conditions are connected, but one may not necessarily predate the other. "The association between diabetes and depression appears to be bidirectional," Williams said.


Marjorie Cypress

"Part of the issue is what comes first? People who have diabetes and have high blood sugar levels — their symptoms are fatigue and a feeling of not wanting to do anything, and lack of enjoyment because they just don't feel good," said Marjorie Cypress, PhD, CDE, a nurse practitioner in a group practice in Albuquerque, N.M., and 2014 president of healthcare and education for the American Diabetes Association in Washington, D.C.

Stress and depression can raise levels of cortisol in the body, Cypress noted. Elevated cortisol levels can increase a person's desire for foods with a lot of calories and sweet foods. "This alters the metabolism and promotes the accumulation of visceral fat," she said.

Depression also makes people want to be less physically active, which also leads to added body weight and elevated blood sugar levels, she added.

Some antidepressants may be associated with diabetes, because treatment of the depression has caused patients to gain weight, Cypress said. "Did we start this person on antidepressants and then they developed diabetes, or were they already at high risk?"

Depression is more prevalent in people with type 2 diabetes than it is in the general public, and more common in people with other chronic illnesses, such as stroke and heart disease, said Trief. The rate of depression in people with diabetes has not been compared to the rate of depression seen with other chronic diseases.

"There is a connection between depression and diabetes, but whether it is unique to diabetes or is connected in other types of chronic illness, we don't know," she said.

Diabetes distress

Diabetes is a complex and progressive condition. It requires considerable intensive self-care and many life changes. Receiving a diagnosis of diabetes, especially in adulthood, can add significant stress and disruption to everyday life, Cypress pointed out.

Some people in the diabetes community have started to talk about "diabetes distress," said Cypress. "Maybe what we are calling depression is the distress of having diabetes."

"I sometimes talk to people about it as being a loss, the loss of their self-concept of being a healthy person," she said.

Helping patients cope with their disease can help their distress, Williams said. "Interventions that assist patients with self-care management may improve depressive symptoms. Early intervention may prevent more severe depressive symptoms from emerging later."

Diabetes and antidepressants

Choosing the right medications for depression for a patient with diabetes can be tricky. "The hope is that an effective treatment for depression will help improve some of the other triggers for diabetes," Williams said. "In many cases, patients will become more active and their nutritional habits will improve when their depression is improved."

Several medications used to treat depression can have an adverse effect on metabolism, either by affecting blood glucose levels or by contributing to weight gain, which in turn can increase insulin resistance.

Several medications used to treat depression can affect metabolism adversely, either by affecting blood glucose levels or by contributing to weight gain.

Pharmacists are familiar with the adverse effect profiles of these drugs, which puts them in an excellent position to educate patients about possible risks, as well as to work collaboratively with other providers to optimize medication regimens, Williams said.

Antidepressants that may adversely affect body weight or blood glucose levels include atypical antipsychotic drugs, which increasingly are being used as adjunctive therapy in treating depression, Williams said. Ariprazole and ziprasidone may have less of an adverse effect.

Tricyclic antidepressants are also associated with weight gain and hyperglycemia, she added.

Monoamine oxidase (MAO) inhibitors are not used as commonly for depression as they once were, but they can cause weight gain, she noted.

Selective serotonin reuptake inhibitors (SSRIs) are thought to improve glycemic control, but there is little data on their long-term use, Williams said.

"Some evidence suggests that longer duration of treatment and higher doses of antidepressants could be linked to worsened glycemic control," she said, adding that she usually avoids recommending paroxetine and mirtazapine because of weight-gain issues.

However, even drugs that have a lower risk of causing weight gain or glycemic issues — the drugs that are thought of as better choices for people with diabetes — may still cause problems.

"I have seen a few patients who have been prescribed one of those drugs, who say they have gained 20 to 30 pounds," Cypress said.

Other treatments

Medications are not the only choice to consider when dealing with diabetes and depression comorbidity, especially in the area where depression and diabetes distress overlap. Patients with diabetes distress who are showing symptoms of depression can be helped with educational and support programs.

A recent study divided a group of type 2 diabetes patients showing high rates of depressive symptoms into three groups that received different interventions for a year.

One group was enrolled in an online diabetes self-management program; a second group, enrolled in the same program, received individualized assistance to help them solve problems related to their diabetes; and the third group was given personalized information about their health risks and sent educational materials by mail.

All patients also received personal phone calls during the study. All three intervention strategies significantly reduced distress levels and symptoms of depression.[6]

Screening tools

The American Diabetes Association recommends that all patients with diabetes be screened for depression regularly. Screening for depression is not onerous and is something that pharmacists can do in the course of counseling a patient with diabetes.

Several versions of the Patient Health Questionnaire can be used in a pharmacy setting and quickly administered.

The PHQ 9 has just nine questions. There is also the even briefer PHQ 2, which asks only the first two questions on the PHQ 9: "Are you bothered by having little interest or pleasure in doing things? Are you feeling down, depressed, or hopeless?"

Screening for depression is not onerous and is something that pharmacists can do in the course of counseling a patient with diabetes.

"In my practice, we try to screen patients for depression once a year," Williams said. Screening is performed more often if patients seem to be having a problem, such as losing control of their condition after a period of successful self-management, she said.

"Both the PHQ 9 and the PHQ 2 are relatively simple to administer in a variety of settings," Williams said. "Patients whose results suggest depressive symptoms should be referred to their primary care provider."

A system of collaborative care for a patient, one that involves all the patient's healthcare providers, can improve both depression symptoms and glycemic control, she added.

Tools such as the PHQ 9 and PHQ 2 screen for symptoms of depression. Some of these symptoms may reflect diabetes distress rather than a co-morbid psychiatric disorder.

There is also the PAID, the Problem Areas in Diabetes Scale, which is a measure of emotional function in diabetes, such as how well the patient is adjusting to a wide range of diabetes management situations, said Cypress.

PAID is a larger questionnaire, which may mean that PHQ 9 or PHQ 2 would be easier to use in a primary care situation, she said.

Further research on diabetes and depression may clarify the relationship between the two conditions. However, it is wise for pharmacists to keep that relationship in mind when counseling and assisting their patients with diabetes. DT

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Valerie DeBenedette *is a medical news writer in Putnam County, N.Y.*

LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

HRSA withdraws proposed 340B rule

Agency to issue guidance in 2015

In April 2014, the Health Resources and Services Administration (HRSA) submitted a proposed rule on the 340B drug-pricing program to the executive branch office that oversees federal rulemaking.

Observers predicted that the rule would address issues identified in a report issued by the U.S. Department of Health and Human Services (HHS) Inspector General that cited inconsistencies in how contract pharmacies determine whether a prescription is 340B-eligible when they dispense the drug on behalf of a covered entity.

The rule was also expected to discuss monitoring of contract pharmacy arrangements by covered entities. In addition, experts anticipated that the rule would clarify HRSA's "patient" definition to ensure covered entities dispensed 340B drugs only to eligible patients.

In November 2014, HRSA withdrew the proposed 340B rule from the regulatory review process. The rule is one of only three HHS rules withdrawn in 2014. Although HRSA withdrew the rule, the agency could resubmit a new version for consideration at a future date. This scenario is unlikely, given ongoing litigation and the midterm shift in control of Congress.

The PhRMA challenge

The agency's decision to withdraw the 340B rule is related to a May 2014 judicial decision on the first-ever HRSA rule. That federal court case tested the limits of HRSA's rulemaking authority.

In *Pharmaceutical Research and Manufacturers of America (PhRMA) v. HHS*, the court found that Congress gave HRSA the authority to issue 340B rules on three subjects: civil monetary penalties, the calculation of the 340B discount price offered to covered entities, and an administrative dispute-resolution process.

PhRMA argued that HRSA lacked the authority to issue a rule excluding orphan-drug purchases by certain covered entities from 340B discounts when the drugs were purchased for use as an orphan drug, but not when the drugs were purchased for non-orphan-indicated uses.

The court found that HRSA had exceeded its rulemaking authority by issuing a rule on orphan-drug purchases and invalidated the rule.

After the decision, HRSA reissued the orphan-drug exclusion rule as an interpretive rule without the force of law, which instructs the public on the agency's interpretation of its own statute. HRSA noted that the court had let the agency's interpretation of the statute stand.

PhRMA disagreed, arguing that the agency's use-based interpretation was contrary to the statute, and filed a second suit against HRSA's interpretive rule. That suit is pending.

HRSA concedes

By withdrawing the proposed 340B rule after the *PhRMA* decision, HRSA is essentially conceding that it requires new rulemaking authority from Congress to issue future rules on many 340B issues. Indeed, HRSA announced it would propose legally binding rules only in the three subject areas identified by the court as those for which HRSA had explicit rulemaking authority.

The incoming Republican-led Congress is unlikely to grant HRSA broad additional rulemaking powers, however. Republican leadership has questioned whether the 340B program is helping low-income patients and has cited the HHS Inspector General report as evidence that HRSA needs to provide greater oversight.

Where things stand

HRSA's withdrawal of the rule does not render the agency powerless to provide direction on ambiguities in the 340B program. HRSA has stated that it will use guidance in 2015 to address "key policy issues."

The court found that HRSA had exceeded its rulemaking authority.

While agency guidance does not have legal effect, create legal rights or obligations, or bind HRSA or private parties, guidance does demonstrate an agency's current approach to an issue.

Until HRSA issues guidance, covered entities and contract pharmacies will continue to address the complexities of the 340B program in different ways. DT

This article is not intended as legal advice and should not be used as such. When legal questions arise, pharmacists should consult with attorneys familiar with the relevant drug and pharmacy laws.

Ned Milenkovich *is vice-chair of the Illinois State Board of Pharmacy. Contact him at 312-656-4153 or at nedmilenkovich@yahoo.com.*

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OTC

Cough-and-cold fighters in the pharmacy

JULIANNE STEIN, CONTENT CHANNEL MANAGER

What is it about colds that makes you feel so much sicker than you actually are? You know that cold in your head or chest is only temporary. It isn't going to dog you for the rest of your life or heaven forfend be the death of you. It's just a cold: a minor ailment that makes you cough until you're blue in the face, sneeze until your brains rattle, and ache as if you've been pounded with mallets — not to mention the way it gunks up your head until you're gasping for air, fills your throat with razor blades, and sets fire to your chest.

Oh, yeah. Only a cold.

But wait! You have options. Before things get that far, you and your patients might consider exploring the symptom relief offered by the following products.

Three new products from Robitussin are designed to ameliorate colds and their related miseries. **Lemon-flavored Medi-Soothers** lozenges with liquid centers feature the same combination of dextromethorphan and menthol used in Robitussin's liquid formulas to suppress coughs and ease throat pain. Adults and children over 12 can take two lozenges every four hours. They are not for children under 12 years of age or patients taking Rx MAOIs. **(www.robitussin.com)**

For cold sufferers who want to keep up a steady fight against coughing and congestion, Robitussin offers its two-bottle **Maximum Strength Day/Night Pack**. The daytime formula combines dextrometh-orphan with the expectorant guaifenesin to suppress coughs and ease chest congestion. The nighttime formula combines the cough suppressant with an antihistamine to relieve itchy throat, runny nose, watery eyes, and sneezing. These products are not for MAOI users and should not be used to sedate a child. **(www.robitussin.com)**

A product designed especially for children is Robitussin's **Children's Cough and Chest Congestion DM**. Intended for children over the age of six, the grape-flavored liquid is formulated to relieve coughs and thin mucus and chest congestion. Children under six and MAOI users should not use. **(www.robitussin.com)**

Also formulated specially for children is **Zim's Advanced Vapor Rub**, a non-greasy "100% natural" cough suppressant and topical analgesic containing menthol, arnica extract, aloe vera, camphor, coconut oil, white beeswax, and eucalyptus. Product literature indicates that the ointment targets "those seeking natural alternatives and parents not wanting to use harsh chemical products on children." The product is available in either a jar or a tube with a simple no-mess applicator, and was slated to commence distribution to independent and regional drugstores by the end of 2014. It is also available from the Zim's website. **(www.zimsusa.com)**

Infirst Healthcare has launched a new product line for children, leading off with three cough-and-cold remedies that are 10% cocoa, intended to improve medication compliance through enhanced flavor with greater appeal for children. **Dr. Cocoa for Children Long-Acting Cough Relief**, with dextromethorphan, relieves cough for up to eight hours in

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Cold-Eeze Cold Remedy Plus Multi-Symptom Relief Cold & Flu QuickMelts: The name says it all.

Virus Zero Air Purification System uses proprietary technology to zap 99.7% of airborne viruses, bacteria, and molds.

children four to 13 years of age. The non-drowsy formula can be used day or night. Intended for the same age group, **Dr. Cocoa for Children Daytime Cough + Cold Relief** combines dextromethorphan and phenylephrine to relieve cough, congestion, and stuffy nose without compromising children's alertness throughout the day. **Dr. Cocoa for Children Nighttime Cough + Cold Relief**, formulated with diphenhydramine and phenylephrine, relieves the symptoms of cough, congestion, and stuffy nose while enabling restful sleep. This product is intended for children between the ages of six and 13. All three Dr. Cocoa for Children products are dye-, alcohol-, and gluten-free. **(www.drcocoa.com)**

New for children from Matrixx Initiatives is **Zicam Kids' Soft Chew**, a grape-flavored homeopathic cold product designed to relieve scratchy throats and congested or runny noses of children six to 11 years of age. The zinc-based chewable can be administered at the first sign of symptoms and will not cause drowsiness. **(www.zicam.com)**

Matrixx has also launched **Zicam Cold Remedy Nasal Spray**, which, says the manufacturer, in addition to symptom relief "actually shortens the length of the cold" and is "clinically proven to reduce cold symptoms by up to 45% by the midpoint of a cold when taken as directed." The plant-based nasal spray is zinc-free; ingredients include menthol and eucalyptus. **(www.zicam.com)**

Another new homeopathic product is **Cold-Eeze Cold Remedy Plus Multi-Symptom Relief Cold and Flu QuickMelts** from ProPhase Labs. Formulated with zinc gluconate, elderberry, agueweed, peppermint, myrrah (the source of myrrh), and licorice, the tablets are said to diminish a cold's duration and help relieve symptoms such as sore throat, congestion, and cough. They have a honey-lemon flavor and dissolve rapidly in the mouth without water. **(www.coldeeze.com)**

New from Ricola, manufacturer of homeopathic cough drops, are lemon-flavored **Revitalizing Herb Drops**, which offer both cold and cough relief and an "energy boost" through the addition of B vitamins to the effervescent powder in the center of the lozenge. Other ingredients include ginseng, elder, horehound, hyssop, lemon balm, linden flowers, mallow, peppermint, sage, thyme, and wild thyme.

An entirely different approach to colds and coughs involves tackling them at their source. Two Massachusetts entrepreneurs have launched the **Virus Zero Air Purification System**, which uses "revolutionary" Samsung SPi technology to neutralize up to 99.7% of viruses, bacteria, and molds. The partners, who hold an exclusive U.S. license to market this technology, state that the product is the first of its kind in the U.S. market. It operates through continuous release of disinfecting ions that attack and neutralize not only airborne contaminants, "without noisy fans or ineffective filters," but also surfaces with which the ions come in contact. The process is described as quiet and energy-efficient, and units are expected to last five to 10 years. Three units are available: A portable unit that fits into a cupholder and would be effective in a car, a small office, hotel room, or bedroom; a larger unit for living rooms, kitchens, basements, and shared spaces; and **Virus Zero Pro**, for larger open spaces, offices, and other commercial applications. Product literature states that Virus Zero holds 42 patents globally and is certified worldwide for its ability to greatly reduce viruses like influenza, H1N1, and other germs or volatile organic compounds in the air. **(www.viruszero.com)** DT

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Goal: To empower pharmacists to engage patients with cardiovascular disease in the practices of self-management.

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- Discuss devices used for home blood pressure monitoring
- Describe the benefits of self-monitoring blood pressure
- Discuss the safety and efficacy of over-the-counter medications and dietary supplements for cardiovascular health
- Describe successful pharmacist medication therapy management services for cardiovascular health

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing education.

Pharmacists are eligible to participate in the knowledge-based activity, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the online system and your participation will be recorded with CPE Monitor within 72 hours of submission.

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MTM opportunities in caring for the patient with cardiovascular disease

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Abstract

Pharmacists are highly accessible and well trained to provide a multitude of services to patients with cardiovascular disease. One area in which pharmacists can demonstrate their expertise is in the selection of a home blood pressure monitoring device that best suits the patients' needs. As a drug information resource, pharmacists also need to stay abreast of new information and evidence regarding the use of over-the-counter products and dietary supplements in patients with cardiovascular disease. By collaborating with the patient and medical provider, pharmacists can positively affect heath outcomes through medication therapy management and can successfully engage patients in self-care.

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CPE SERIES: MTM CONSIDERATIONS FOR ADULT PATIENTS WITH CARDIOVASCULAR DISEASE

Welcome to the CPE series, Medication Therapy Management Considerations for Adults with Cardiovascular Disease, which was designed for pharmacists who take care of patients with CVD. Beginning in February 2014 and continuing through January 2015, pharmacists can earn up to 24 hours of CPE credit with 12 monthly knowledge-based activities from the University of Connecticut School of Pharmacy and *Drug Topics*.

This series concludes this month with an activity about medication therapy management opportunities in caring for the patient with CVD.

The series also offers an application-based activity in April 2015. The case studies in the activity will apply CVD management concepts to practice-relevant cases. Pharmacists will answer questions throughout the activity in an interactive web-based format and receive immediate feedback to their answers.

Introduction

Pharmacists are highly accessible healthcare professionals who have the ability to provide effective medication therapy management (MTM). Pharmacies are located in nearly every community, and patients visit pharmacies an average of once per month, more often than they visit any other healthcare facility.[1,2] Community pharmacists strive to enhance the patient experience through relationship building and collaboration with other medical providers to optimize patient care and health outcomes. To achieve these positive outcomes, patients must take an active role in the treatment and management of medical conditions by adhering to medical visits and engaging in self-care. Methods for patient-pharmacist collaboration in the practice of self-care for cardiovascular disease (CVD) will be discussed throughout this article.

Blood pressure self-monitoring

According to the American Heart Association (AHA), nearly 77.9 million (one in three) adults have hypertension; 48% of these cases are uncontrolled.[3] Medication selection and management are often based on one or two blood pressure (BP) measurements in a prescriber's office and often, unfortunately, do not take into account home BP readings, which can vary from in-office readings. Self-monitoring of BP enables patients to capture readings that reflect their baseline status, provide feedback on BP control, and determine medication effectiveness. Pharmacists can identify patients who would benefit from self-monitoring and assist them in selecting the device that best suits their needs. Additionally, pharmacists can educate patients on how to properly use and care for the device, as well as how to interpret the values provided by the device.

Home BP monitoring is beneficial for numerous patient populations. Specifically, the AHA recommends home monitoring for patients who are initiating treatment for hypertension to determine the effectiveness of the treatment; patients who require closer monitoring than can be provided in intermittent office visits (especially those with heart disease, diabetes, and/or kidney disease); pregnant women who are at risk for preeclampsia or pregnancy-induced hypertension; and patients with BP readings that are affected by doctor's visits, better known as "white coat hypertension." The AHA does not recommend home monitoring for patients with atrial fibrillation or other arrhythmias, as these devices may provide inaccurate readings in these patients.[4]

When assisting patients in choosing a device, pharmacists should browse the aisles alongside patients, as a number of devices with varying features are available. Pharmacists should ensure that the monitor has been tested, validated, and approved for use by the Association for the Advancement of Medical Instrumentation (AAMI), the British Hypertension Society (BHS), and the International Protocol for the Validation of Automated BP measuring devices. Validation by the AAMI confirms that the product is held to a high standard of production.[5] Pharmacists should determine whether the device is "clinically tested" or "clinically validated," as devices described as "clinically tested" have not been tested or evaluated against a set of defined criteria.[6] Pharmacists should also assess the BHS systolic and diastolic rating, as the values will reflect whether the device has been clinically validated by the BHS. Devices are graded on an A/B/C/D grading scale, with A being the best. A higher rating confirms that the product will accurately and effectively read BP.[5] Finally, pharmacists should determine whether the monitor is accommodating to an individual's needs (eg, elderly patient, pregnant patient, pediatric patient, hearing-impaired patient).[7]

Among the many commercially available home BP monitors is the aneroid monitor. The aneroid monitor is compact, easy to transport, and ranges in price from $15 to $40.[8] The aneroid monitor contains an inflatable cuff attached to a rubber bulb and mechanical manometer with a separate or attached stethoscope. Available cuff sizes include pediatric, small adult, standard adult, and large adult. Selecting the correct cuff size is essential, as using an incorrect cuff size results in inaccurate readings.[9] Considerations for determining the appropriate cuff size as well as important counseling points for self-monitoring are described in **Table 1**.[10-12]

To correctly use an aneroid monitor, the patient must know how to properly place both the cuff and diaphragm of the stethoscope over the brachial artery. Once in place, the rubber bulb must be squeezed at a rapid rate to inflate the cuff. This may pose a challenge to patients with arthritis

TABLE 1

DETERMINING APPROPRIATE CUFF SIZE AND PHARMACIST COUNSELING POINTS FOR HOME MONITORING OF BLOOD PRESSURE BY PATIENTS

Determining the appropriate cuff size for aneroid and automatic cuff-style bicep devices	Variables that can alter a blood pressure reading
■ The inflatable portion of the blood pressure cuff should cover approximately 80% of the circumference of the upper arm ■ The cuff should cover two-thirds of the distance from the patient's elbow to his or her shoulder ■ The measured circumference, at the midpoint between the shoulder and elbow, corresponds to the circumference size of available cuffs	■ Incorrect cuff size ■ Cigarette smoking, consumption of caffeinated beverage or alcohol, or exercise within 30 minutes of a reading ■ Arm, back, or feet unsupported ■ Elbow not supported; arm not at heart level ■ Posture: lying vs sitting down ■ Alternating arms to check and assess readings ■ Reading taken over clothing ■ Emotional state ■ Talking ■ Bladder distention

Source: Ref 10-12

or other dexterity impairments. The cuff should be inflated to 30 points above the last systolic reading and deflated at a rate slow enough to allow the patient to hear the systolic and diastolic BP. If patients do not receive proper training on these devices, the BP readings may be inaccurate. Furthermore, patients with hearing or visual impairments may have difficulty hearing the heart sounds and seeing the manometer, respectively.[9]

Another option for at-home BP monitoring, recommended by the AHA, is the automatic, cuff-style bicep monitor.[7] This device contains a main digital unit with an attached arm cuff. As with the aneroid monitor, the use of this device requires correct cuff size selection and placement. Available cuff sizes include pediatric, small adult, standard adult, and large adult (additional cost). Unlike the aneroid monitor, inflation and deflation with this device are performed with the push of a button. This option is beneficial for patients who are unable to correctly operate the aneroid monitor. As with the other available devices, a change in body position or an irregular heartbeat can influence the accuracy of readings. The digital unit shows the BP reading, heart rate, date, and time in a large, easy-to-read format.[9] Some devices also deliver audio readings in a multitude of languages for patients with vision impairment. Additionally, some devices record readings for up to two users with space for 30 to 90 readings per user; readings are retrievable through the memory button. Some also offer a programmable alarm to remind patients to check BP. In contrast to the aneroid monitor, the automatic monitor requires batteries for use; an AC adapter can be purchased separately. The automatic meter is not as compact and easy to transport as the aneroid monitor and can range in price from $30 to more than $100.[8]

Storage and care for aneroid monitors and automatic monitors are comparable. At home, they should be stored in a safe, dry location, away from extreme hot or cold temperatures, humidity, and direct sunlight. After use, patients should ensure that the tubes are not twisted or coiled and that there are no cracks or leaks. Users should not clean the cuff with abrasive cleaning products and should not submerge the cuff in water. Instead, the cuff can be cleaned with a moist cloth.[9] Additionally, home blood pressure monitors should be brought annually to medical visits to confirm correct calibration and patient use. If a home monitor is suspected to be inaccurate when compared to in-office equipment or determined to be malfunctioning, the monitor should be sent to the manufacturer for calibration.

Other available home BP monitoring devices include wrist and finger monitors. Both are compact and easy to transport and are options for those who may have difficulty determining the appropriate cuff size (although patients will still need to determine correct wrist or finger cuff size) or experience discomfort with bicep devices.[13] Analogous to the automatic monitor, each device has the ability to measure BP with the touch of a button. Additionally, both types of devices store BP readings, with some devices recording 30 to 90 readings each for up to two users. Wrist and finger monitors are battery operated, although an AC adapter can be purchased separately.[14] Wrist monitors range in price from $20 to more than $80, whereas finger monitors are more expensive, costing more than $100.[9,15] Wrist monitors should be stored in a dry location, out of extreme hot and cold temperatures, and inside the provided storage case. Storage and care for a finger monitor are similar to those for wrist and automatic BP monitors.[14,16]

The basic procedure for using a wrist monitor is as follows: The patient should

Pause&Ponder

What factors will you take into consideration when assisting a patient who is selecting a device to monitor blood pressure at home?

place the device on the inside of the wrist, with the positioning mark found outside the meter aligned with the center of the wrist. The cuff should be secured firmly around the wrist to prevent inaccurate readings. The same wrist should be used on a consistent basis, as BP may differ between the right and left wrist by up to 10 mmHg.[14] When the patient is ready to measure BP, he or she must sit upright, with the arm extended wrist-side up on table, resting the relaxed, unclenched wrist on the included storage case for the monitor. (Using the storage case as a resting point better aligns the wrist with heart level.) These monitors include a wrist height sensor function to validate that the patient's positioning is correct. If the device is at a height lower than the heart, the reading may be higher than the patient's true BP. Conversely, if the device is at a height higher than the heart, the reading may be lower than the patient's true BP.[14] For these reasons, the patient should bring the wrist monitor to medical visits to determine any discrepancy between wrist and arm readings and to discuss how to interpret at-home readings.[17]

Tests have shown that finger devices are extremely sensitive to body temperature and position, which increases the risk of these monitors yielding erroneous readings. Just as with the wrist monitor, patients using these devices should measure their BP using a standard BP cuff to determine any discrepancy between the devices and understand how to interpret at-home readings.[16]

While wrist and finger monitors are available options for home blood pressure monitoring, the AHA does not recommend their use because they yield less reliable readings.[7] Arteries in the wrist are not as deep as the brachial artery and consequently can cause higher and less accurate BP readings. Furthermore, limited literature defends the use of finger monitors.[16,17] If these devices are used, they must be held at heart level to improve accuracy.[17]

Over-the-counter products and dietary supplements for self-care

This section will discuss over-the-counter (OTC) products and dietary supplements that may be beneficial for patients with CVD. This section will also discuss products that may be of concern for patients with CVD and products that may lead to adverse CVD outcomes.

Aspirin

Patients often take OTC products and dietary supplements to promote health. Primary prevention includes measures taken to prevent the onset of a medical condition. Aspirin is commonly used as primary prevention for CVD. Several guidelines provide recommendations regarding aspirin's use for primary prevention. The U.S. Preventive Services Task Force (USPSTF) recommends that men aged 45 to 79 years take aspirin 81 mg daily because of aspirin's benefit in reducing the risk of myocardial infarction. The USPSTF also recommends that women aged 55 to 79 years take aspirin 81 mg daily because of aspirin's benefit in reducing the risk of ischemic stroke. Both of these recommendations are classified as "grade A," meaning that there is high certainty that the net benefit is substantial; however, this benefit needs to be weighed against the potential risk of increased gastrointestinal bleeding. For men younger than 45 years and women younger than 55 years, aspirin use is not recommended; this is a grade D recommendation, meaning that with moderate to high certainty there is no net benefit or that the harms outweigh the benefits. The USPSTF notes that there is insufficient evidence to assess the risks and benefits of aspirin use in older individuals (age >80 years). Of note, the USPSTF is currently reviewing its "Aspirin for the Prevention of Cardiovascular Disease: Preventive Medication" recommendations.[18]

The 2014 AHA/American Stroke Association's Guidelines for the Primary Prevention of Stroke recommend the use of aspirin for CVD prophylaxis in individuals with a 10-year risk of more than 10% (calculated using an online calculator at http://my.americanheart.org/cvriskcalculator) when potential benefits of this treatment outweigh the risks. Additionally, aspirin may be used to prevent a first stroke in "sufficiently high risk" women for whom the benefit outweighs the risks and in individuals with an estimated glomerular filtration rate of 30 to 45 mL/min/1.73 m^2. The guidelines also state that aspirin is not beneficial in stroke prevention for low-risk individuals or for individuals with diabetes and no other high-risk conditions.[19]

The 2009 guidelines from the American College of Chest Physicians recommend the use of low-dose aspirin (75-100 mg/d) in patients older than 50 years without symptomatic CVD,[20] whereas the AHA recommends the use of low-dose aspirin (75-160 mg/d) only in individuals with a 10-year risk of coronary heart disease ≥10% for primary CVD and stroke prevention.[21] Three other societies published a combined position paper on the primary prevention of cardiovascular (CV) events in individuals with diabetes mellitus.[22] These societies recommend the use of low-dose aspirin when the 10-year risk is >10%; eligible patients include men older than 50 years and women older than 60 years with at least one additional risk factor (smoking, hypertension, dyslipidemia, a family history of premature CVD, or albuminuria) who are not at high risk of bleeding. Aspirin use may be considered for those at intermediate risk (10-year risk of 5% to 10%), but aspirin should not be used in those at low risk of CVD.[22]

Despite numerous guidelines supporting the use of aspirin for primary prevention in certain individuals, the U.S. Food and Drug Administration (FDA) recently released a statement noting that available evidence does not support the use of aspirin for primary prevention of a heart attack or stroke, as the risk of bleeding with the use of aspirin may outweigh the potential benefits of treatment.[23] Given varying recommendations for aspirin's use, pharmacists should collaborate with the patient's medical provider to weigh the benefits and risks of using aspirin for primary CVD prevention.

Naproxen

Individuals with CVD may consult with a pharmacist for an OTC recommendation for pain relief. OTC nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) include aspirin, ibuprofen, and naproxen. Naproxen and ibuprofen are reversible inhibitors of cyclooxygenase-1 (COX-1)

and cyclooxygenase-2 (COX-2), whereas aspirin is an irreversible inhibitor of COX-1 and COX-2. Available evidence does not suggest an increased risk of serious CV events with short-term use of low-dose OTC NSAIDs; however, in 2005, the FDA stated that the labeling for all OTC NSAIDs must include specific information about potential gastrointestinal and CV risks. Aspirin was exempt from this request, as it has been shown to reduce the risk of CV events in certain populations.[24]

Given the results of several head-to-head trials indicating that naproxen is not associated with an increased CV risk compared to other nonselective NSAIDs and COX-2 selective inhibitors, naproxen may be considered the preferred NSAID for use in individuals with high CV risk.[25,26] Additionally, a meta-analysis found that high-dose naproxen is associated with no excess risk of major vascular or major coronary events compared to other NSAIDS.[27] Despite these findings, an FDA advisory committee voted in 2014 that naproxen's label should not be changed to suggest a lower CV risk than the risk seen with other NSAIDs. Results of the ongoing Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION) study, set to conclude in September 2015, may provide further insight into the risks associated with NSAIDs in individuals with either osteoarthritis or rheumatoid arthritis who have or are at high risk of CVD.[28]

Pharmacists can educate patients using OTC NSAIDs about associated side effects, including increased BP, edema, and potential gastrointestinal bleeding. Additionally, pharmacists can assist patients in weighing the risks and benefits associated with NSAID use and can recommend an alternative product, as appropriate. When helping patients to select a NSAID, pharmacists should advise patients to use the lowest possible dose for the shortest possible period of time. For patients with hypertension using NSAIDs, pharmacists should recommend BP monitoring and should discuss the potential for NSAIDs to reduce the BP-lowering effects of antihypertensive therapy.[29,30]

Calcium and vitamin D

Recent evidence has raised concerns regarding the use of calcium and vitamin D supplementation in patients at high CVD risk. A secondary analysis of a calcium supplementation study suggested a potential increased risk of CV events in women older than 55 years who were taking calcium citrate (400 mg in the morning and 600 mg in the evening) without vitamin D for at least five years compared to women who were taking placebo.[31] The composite endpoint of myocardial infarction, stroke, and sudden death in the intervention group was 76 events compared to 54 events in the control group (RR = 1.21; 95% CI, 0.84-1.74; P = 0.32). This study was limited by its population of mainly older Caucasian women, its high dropout rate, and its variability in cardiac risk factors. In a systematic review of four randomized trials focused on calcium supplementation, reported CV events in women receiving calcium supplementation with or without vitamin D was increased, but this difference was not statistically significant.[32]

A meta-analysis that did not use CV outcomes as primary endpoints found that calcium supplementation (average daily dose, 1000 mg) increased the risk of myocardial infarction at the patient level and at the trial level; however, no association was found between supplementation and stroke risk or occurrence of a CV event (composite of myocardial infarction, stroke, or sudden death).[33] The authors concluded that calcium supplementation of more than 500 mg per day, without vitamin D supplementation, is associated with a ~30% increased risk of myocardial infarction. This meta-analysis was later updated to include data from women in the Women's Health Initiative Calcium/Vitamin D Supplementation Study who were not taking calcium at randomization. The updated analysis demonstrated that the number needed to treat with calcium with or without vitamin D for five years to cause one myocardial infarction was 240, whereas the number needed to treat to prevent one fracture was 302. This analysis suggests that the risks of calcium supplementation with or without vitamin D outweigh the potential benefits.[34]

In light of these conflicting study results, the USPSTF has stated that current evidence is insufficient to assess the benefits and risks of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men.[35]

Pharmacists should remain abreast of the emerging evidence and should be able to discuss study results with patients who may inquire about the benefits and potential CV risks associated with calcium and vitamin D supplementation. Pharmacists should always encourage patients to obtain calcium and vitamin D through dietary sources.

Omega-3 fatty acids

Alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are all considered omega-3 (or n-3) fatty acids. Given their derivation from plants or marine life, these oils must be consumed through foods or dietary supplements.[36] Vegetable oils (particularly soybean and canola oils) and flaxseed are rich in ALA, whereas fish contain EPA and DHA.[36] The AHA recommends dietary consumption of omega-3 fatty acids for healthy individuals and for those with or at high risk for CVD, suggesting that individuals should consume at least two servings of fatty fish (3.5 ounces cooked or three-fourths of a cup flaked) per week. Examples of fatty fish include salmon, mackerel, herring, trout, sardines, and albacore tuna.[37]

Pause&Ponder

How might you respond to a patient's inquiry about the use of aspirin for primary prevention of cardiovascular disease?

For individuals with coronary heart disease, the AHA encourages the consumption of 1 g of EPA and DHA per day for secondary prevention to reduce cardiac and all-cause mortality (**Table 2**).[36] In the GISSI-Prevention Study, this dose led to a reduction in the combined endpoint of death, nonfatal myocardial infarction, and nonfatal stroke.[36] Following post hoc analysis of this trial, which suggested the benefit was concentrated in the congestive heart failure population, the American College of Cardiology Foundation/AHA guidelines recommend omega-3 polyunsaturated fatty acids as adjunctive therapy in patients with New York Heart Association (NYHA) class II to IV symptoms and heart failure with reduced or preserved ejection fraction, unless contraindicated, to reduce mortality and hospitalizations.[38]

For individuals unable to consume the suggested daily amount, pharmacists can recommend a supplement or collaborate with a patient's medical provider to obtain a prescription omega-3 fatty acid product. When recommending OTC supplements, pharmacists should read the label to determine the content of EPA and DHA in each capsule. Dietary supplement labeling cannot recommend or suggest daily intake of EPA and DHA in excess of 2 g.[39] Pharmacists should remind patients about the lack of regulation of OTC supplements. Furthermore, pharmacists should suggest the consumption of foods high in EPA, DHA, and ALA.

Available prescription products that contain DHA and/or EPA are Epanova, Lovaza, Omtryg, and Vascepa (**Table 3**).[40-43] All of these products should be used with caution in patients with known sensitivities or allergies to fish and/or shellfish. Furthermore, while patients are taking these products, periodic monitoring of alanine aminotransferase, aspartate aminotransferase, and low-density lipoprotein cholesterol should occur. Pharmacists should counsel patients to swallow the capsules whole and to not break open, crush, chew, or dissolve the capsules. Patients should not double the dose if the previous dose was missed. All products should be used in conjunction with a heart-healthy diet. Pharmacists should also educate patients about potential inhibition of platelet aggregation, prolonged bleeding time, and increased risk of hemorrhagic stroke when doses greater than 3 g per day of omega-3 fatty acid products are used.[36,44]

Of note, the 2013 American College of Cardiology/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Disease in Adults state that no data support the routine use of nonstatin drugs combined with statins to further reduce atherosclerotic cardiovascular disease events. Additionally, the guidelines state that no studies have assessed atherosclerotic cardiovascular disease event outcomes in statin-intolerant patients. The use of omega-3 fatty acids is not recommended unless an individual has triglyceride levels of at least 500 mg/dL.[45]

Lastly, prospective trials investigating the use of polyunsaturated fatty acids for the prevention of recurrent atrial fibrillation (AFib) generally have found no difference with its use. Therefore, use of polyunsaturated fatty acids is not recommended for the prevention of AFib recurrence in patients with AFib, unless another indication warrants use.[46]

TABLE **2**

TYPE AND QUANTITY OF FISH REQUIRED TO MEET CONSUMPTION RECOMMENDATIONS

Type of fish	Amount needed to provide 1 g of EPA and DHA (in ounces)
Tuna, white, canned in water, drained	4
Salmon, Atlantic, wild	2 to 3.5
Trout, rainbow, farmed	3
Mackerel	2 to 8.5
Herring, Atlantic	2

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid

Source: Ref 36

Antioxidants

Cardiovascular disease is a broad term that includes coronary artery disease (CAD). CAD manifests as arterial atherosclerosis and results in reduced blood flow due to narrowing of the arteries. The development of atherosclerosis increases the risk for sequelae, including myocardial infarction or cerebrovascular accident.[47] Given that proatherogenic and prothrombotic oxidative events are part of the atherosclerotic process, antioxidants such as vitamins C and E and beta-carotene were once thought to play a protective role. However, a meta-analysis and clinical trials have failed to demonstrate a benefit with antioxidants on CVD morbidity and mortality.[48] Thus, the AHA and other guidelines do not support the routine use of antioxidant supplements for the prevention and treatment of CVD.[49-51] The USPSTF concludes there is insufficient evidence to support the use of multivitamins for the prevention of CVD.[52] Lastly, the USPSTF recommends against the use of vitamin E and beta-carotene for the prevention of CVD.[52]

Other dietary supplements

Patients may also inquire about herbal supplements and their role in cardiovascular health. The February 2014 article in this *Drug Topics*-UConn CVD MTM series discusses some OTC products, including niacin, red yeast rice, soluble fiber, stanols, and sterols, that have been found to reduce cholesterol. The May 2014 article in this series discusses some OTC products, including garlic and ginseng, that reduce BP and other products, including licorice, yohimbine, and St. John's wort, that may increase BP. This previous article also addresses the side effects and potential drug interactions for these products.

Important considerations regarding dietary supplements

Results of the 1987, 1992, and 2000 National Health Interview Survey indicated increasing use of vitamin and mineral supplements among adults in the United States (23.2%, 23.7%, and 33.9%, respectively).[53] With this in mind, it is important for pharmacists to be familiar with the regulations and available evidence supporting or opposing the use of these products. Furthermore, pharmacists need to routinely inquire about patients' use of supplements.

Dietary supplements, as defined by the

TABLE 3

OVERVIEW OF AVAILABLE PRESCRIPTION OMEGA-3 FATTY ACID PRODUCTS

Product, year approved	Dosage form, strength	Suggested dose and frequency, instructions for use	Lipid-lowering effects	Common adverse reactions
Epanova (omega-3 carboxylic acids), 2014	Soft gelatin capsule, 1 g	2 or 4 g once daily	LDL-C ↑: 21% (2 g/d); 26% (4 g/d) HDL-C ↑: 7% (2 g/d); 5% (4 g/d) TG ↓: 25% (2 g/d); 45% (4 g/d)	Diarrhea, nausea, abdominal pain
Lovaza (omega-3-acid ethyl esters), 2004	Soft gelatin capsule, 1 g	4 g once daily OR 2 g twice daily	LDL-C ↑: 44.5% HDL-C ↑: 9.1% TG ↓: 45%	Eructation, dyspepsia, taste perversion
Omtryg (omega-3-acid ethyl esters A), 2014	Soft gelatin capsule, 1.2 g	4.8 g once daily OR 2.4 g twice daily Take with meals	LDL-C ↑: 20% HDL-C: No effect TG ↓: 25%	Eructation, dyspepsia, taste perversion
Vascepa (icosapent ethyl [ethyl ester of eicosapentaenoic acid]), 2012	Soft gelatin capsule, 1 g	2 g twice daily Take with food	LDL-C ↓: 5% HDL-C ↓: 4% TG ↓: 27%	Arthralgia

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride

Source: Ref 40-43

Dietary Supplement Health and Education Act of 1994 (DSHEA), are any products taken by mouth (formulated as a capsule, tablet, softgel, gelcap, powder, or liquid) that contain a "dietary ingredient" intended to supplement the diet. Dietary ingredients include vitamins; minerals; herbs or other botanicals; amino acids; other substances; and constituents, metabolites, concentrates, and extracts. Per DSHEA, a "new dietary ingredient" is a dietary ingredient that was not sold in the United States before October 15, 1994.[54]

Because dietary supplements are classified as foods rather than as drugs, the FDA does not need to approve supplements as safe and effective before manufacturing or distribution; rather, the FDA only needs to be notified of the intent to market a new dietary ingredient. Per DSHEA, it is the manufacturer's responsibility to ensure that a supplement is safe before its sale. However, once the product is marketed, the FDA can deem a supplement unsafe and take action to restrict its use or remove it from the market.[54] Furthermore, manufacturers must follow current good manufacturing practices to ensure that products meet quality standards and are consistently processed, labeled, and packaged.[54] Per FDA regulations, certain information must appear on the label of a dietary supplement, including a descriptive name of the product, a statement noting that the product is a supplement, the name and address of the manufacturer or distributor, a list of all ingredients, and the net contents of the product. A "supplemental facts" panel must be included to identify each dietary ingredient in the product.[54]

In advertisements for dietary supplements, only health claims, structure/function claims, and nutrient content claims are allowed. It is important for the pharmacist to be familiar with the different requirements for each claim and to educate patients about them.[55] Given the number of differences between prescription and dietary supplements, pharmacists must understand, explain, and, as appropriate, recommend available dietary supplements.

MTM: Pharmacists and cardiovascular health

Patients with CVD may greatly benefit from MTM given the high rate of morbidity and mortality associated with this disease. In fact, CVD is the leading cause of death worldwide and accounts for one-third of all deaths in the United States. As MTM becomes woven into the routine workflow of community pharmacies, comprehensive medication reviews by pharmacists will improve healthcare outcomes on both a widespread and individual basis.[56] The following are examples of ways that pharmacist interventions can improve health outcomes with respect to CVD.

A study, Project ImPACT: Hypertension, showed the benefits of a patient-centered care model in the community pharmacy setting.[57] During this six-month study, patients received four face-to-face visits with the pharmacist. Each visit focused on disease state education, awareness about triggers that cause an increase in BP, and medication adherence. If medication-related problems were discovered, the patient's physician was contacted to discuss changes in therapy. Between each visit, home BP readings were electronically transmitted via the patient's BP monitor to the community pharmacy computer, and the readings were discussed at the succeeding visit. The primary outcome was the percentage of patients achieving their BP goal. Of the patients not at goal at baseline (n = 62; total enrollment = 152), 21% had achieved their BP goal by the end of the study ($P< 0.001$). Statistically significant improvements from baseline in disease state knowledge were also seen ($P< 0.001$). This study showed that the combination of BP telecommunication, medication adherence, and disease state education was beneficial in lowering BP.[57]

In another study, pharmacists who engaged in an interdisciplinary team approach reported better BP control rates in their patients than those who engaged in standard practice.[1] At baseline, the pharmacist conducted a patient interview to assess the

medication regimen, suggest a goal BP, and provide recommendations to improve BP control. The pharmacist also educated all patients using written information from the National Heart, Lung, and Blood Institute (NHLBI) and taught them how to perform home BP monitoring.[1] Patients then met with pharmacists in medical office clinics at two, four, six, and eight months. Pharmacists were encouraged to initiate additional interviews through visits or telephone contact if a patient's BP remained uncontrolled. Based on these encounters, pharmacists provided feedback and suggestions to physicians. Of the 267 recommendations made to change a BP medication regimen (2.6 per patient), 256 were accepted by physicians (95.9%). Most of these recommendations involved increasing the dose, adding a drug, switching drug classes, decreasing a dose, or discontinuing a drug. Furthermore, pharmacists encouraged patients to engage in lifestyle modifications, such as increasing physical activity, adapting the Dietary Approaches to Stop Hypertension (DASH) diet, and losing weight. At the end of the study, BP was controlled in 90% of patients in the intervention group and 53% in the control group ($P< 0.001$).[1] The dynamic role of the pharmacist in this trial serves as the prototype for how a patient's hypertension should be managed.

Project ImPACT: Hyperlipidemia was an observational study that took place across 26 community pharmacies.[58] The main objectives of this study were to improve patient compliance and persistence with lipid-lowering medications, improve cholesterol levels, and reach and maintain National Cholesterol Education Program lipid goals in patients with newly diagnosed or poorly controlled dyslipidemia. Patients had an initial visit with a pharmacist, followed by monthly visits for three months and then quarterly visits over a span of two years. At each visit, the pharmacist used the Cholestech LDX analyzer (which provides lipid results in five minutes after a fingerstick blood sample) to assess the patient's current lipid values. After reviewing the results, the pharmacist communicated with the patient's physician to recommend changes in therapy as needed. Of the 346 recommendations made over the study's duration, 265 (76.6%) were accepted by physicians and implemented in the patient's care plan. Over two years, the 143 patients who completed the study achieved statistically significant reductions in low-density lipoprotein cholesterol, triglycerides, and total cholesterol (all had $P< 0.001$), along with a statistically significant increase in high-density lipoprotein cholesterol ($P< 0.001$). By the end of the study, 62.5% of patients had achieved the targeted National Cholesterol Education Program lipid goal. Of those patients receiving medication in the study, 93.6% demonstrated medication persistence (remained on medication throughout the study and after study completion). Similarly, 90.1% demonstrated good medication compliance (refilled medication within five days of due date and missed five or fewer doses per month). These results provide support for collaboration among the community pharmacist, patient, and medical provider for the treatment of hyperlipidemia.

Project ImPACT: Hypertension showed the benefits of a patient-centered care model in the community pharmacy setting. During this six-month study patients received four face-to-face visits with the pharmacist.

A 2013 systematic review analyzed the clinical and economic effectiveness of pharmacist intervention in the secondary prevention of CVD and discussed ways by which pharmacists in the inpatient and outpatient settings can improve heart failure outcomes.[59] Five of eight available studies found that pharmacists had a significant effect in improving CVD mortality when they were included as part of the healthcare team. Among the studies evaluated, 20 of 23 (86.9%) and 13 of 20 (65%) demonstrated a statistically significant difference in BP and lipid risk factor control, respectively, when patients were under the care of a pharmacist. The assessments measured improvements through patient education, MTM, or both.[59] This review also analyzed the effect of pharmacist intervention on patient outcomes, including patient knowledge and understanding, satisfaction, adherence, and quality of life. Among the studies evaluated, 22 of 31 (71%) demonstrated statistically significant differences in patient outcomes when the pharmacist was part of the healthcare team. Not only did pharmacists improve CVD treatment, their involvement also resulted in healthcare cost reductions.[59] Pharmacists are well positioned to identify drug-related problems, which should decrease the number of hospital/emergency department visits and ultimately decrease overall healthcare costs.

Conclusion

Pharmacists in the community setting are well positioned to provide a multitude of services to patients with CVD. Their role in assisting patients with the selection of a product for self-monitoring BP is critical for patient engagement and improved health outcomes. Furthermore, pharmacists identify drug therapy problems, collaborate with medical providers to resolve identified problems, and provide one-on-one patient education, all with the goal of improving CVD outcomes. Engaging patients with CVD in MTM is essential to reduce overall morbidity and mortality and to improve patient satisfaction and quality of life.[59] •

The references are available online at *www.drugtopics.com/cpe*.

TEST QUESTIONS

1. According to the American Heart Association, how many adults have uncontrolled blood pressure?
- **a.** 30%
- **b.** 38%
- **c.** 48%
- **d.** 60%

2. Which of the following devices is recommended by the American Heart Association for at-home monitoring of blood pressure?
- **a.** Automatic finger monitor
- **b.** Automatic wrist monitor
- **c.** Aneroid monitor
- **d.** Automatic cuff-style bicep monitor

3. With a wrist monitor, if the arm is positioned below heart level, the resulting blood pressure reading will be:
- **a.** Higher than a patient's true blood pressure
- **b.** Lower than a patient's true blood pressure
- **c.** Representative of a patient's true blood pressure
- **d.** Undetectable

4. A patient approaches the pharmacy counter asking which blood pressure monitor would be most appropriate for her. The patient states that her hands are weak due to Parkinson's disease. What option would be most suitable for this patient and why?
- **a.** Aneroid monitor, because the blood pressure reading is generated with the push of a button and results are read aloud
- **b.** Finger monitor, because it is easy to use and recommended by the American Heart Association
- **c.** Limit blood pressure readings to the physician's office because of these impairments
- **d.** Automatic cuff-style bicep monitor, because the blood pressure reading is generated with the push of a button

5. According to the American Heart Association, all of the following patient populations should monitor their blood pressure at home, except:
- **a.** Patients who recently began taking blood pressure medications
- **b.** Patients with atrial fibrillation/arrhythmias
- **c.** Patients with "white coat hypertension"
- **d.** Patients with heart disease, diabetes, and/or kidney disease

6. Which of the following should be avoided when caring for an automatic cuff-style bicep monitor?
- **a.** Ensure tubes do not have leaks.
- **b.** Keep out of direct sunlight.
- **c.** Use abrasive cleaning products.
- **d.** Store at room temperature.

7. Which of the following variables does not alter a blood pressure reading?
- **a.** Talking
- **b.** Recent exercise
- **c.** Unsupported feet
- **d.** Arm at heart level

8. Which of the following over-the-counter products is recommended for use in a healthy patient to promote cardiovascular health?
- **a.** Vitamin E
- **b.** Beta-carotene
- **c.** Calcium
- **d.** Omega-3 fatty acids

9. Which of the following products contain only eicosapentaenoic acid (EPA)?
- **a.** Lovaza
- **b.** Epanova
- **c.** Omtryg
- **d.** Vascepa

10. Which of the following products is most potent in lowering triglyceride levels?
- **a.** Lovaza
- **b.** Epanova
- **c.** Omtryg
- **d.** Vascepa

11. Fatty fish contain which of the following omega-3 fatty acids?
- **a.** Eicosapentaenoic acid (EPA)
- **b.** Docosahexaenoic acid (DHA)
- **c.** Alpha-linoleic acid (ALA)
- **d.** Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)

12. A 62-year-old woman comes to the pharmacy to inquire about calcium and vitamin D supplementation. Based on available evidence regarding supplement use, which of the following is the best response?
- **a.** "Using calcium and vitamin D supplements will cause a heart attack!"
- **b.** "Calcium and vitamin D should be consumed through the diet."
- **c.** "Calcium and vitamin D supplements are safe to use."
- **d.** "Calcium and vitamin D supplements are not recommended for use."

13. Which of the following statements is true regarding the meta-analysis by Bolland et al published in 2010?
- **a.** In the patient-level data, there was a statistically significant increase in stroke with calcium supplementation.
- **b.** In the trial-level data, there was a statistically significant increase in myocardial infarction with calcium supplementation.
- **c.** In the trial-level data, there was a statistically significant increase in stroke with calcium supplementation.
- **d.** In the trial-level data, there was a statistically significant increase in the composite of myocardial infarction, stroke, or sudden death with calcium supplementation.

14. Dietary supplements are classified as:
- **a.** Foods
- **b.** Over-the-counter products
- **c.** New dietary ingredients
- **d.** None of the above

15. Which of the following is a side effect of nonsteroidal anti-inflammatory drugs?
- **a.** Increase in blood pressure
- **b.** Decrease in blood pressure
- **c.** Weight loss
- **d.** Increased urination

16. Which of the following is a recommendation of the U.S. Preventive Services Task Force?
- **a.** Aspirin use is recommended in men aged 44 to 79 years because of its benefit in reducing the risk of ischemic stroke.
- **b.** Aspirin use is recommended in men and women older than 80 years.
- **c.** Aspirin use is recommended in women aged 55 to 79 years because of its benefit in reducing the risk of ischemic stroke.
- **d.** Aspirin use is not recommended in men younger than 55 years or women younger than 45 years.

17. Cardiovascular disease accounts for _____ of all deaths in the United States.
- **a.** One-quarter
- **b.** One-third
- **c.** One-half
- **d.** Two-thirds

18. All of the following are ways a pharmacist can positively affect CVD outcomes except:
- **a.** Improve patient knowledge and understanding
- **b.** Improve patient quality of life
- **c.** Help patients achieve individualized blood pressure goals
- **d.** Increase healthcare costs

19. What was the primary outcome of the Project ImPACT: Hypertension study?
- **a.** Percentage of patients achieving targeted blood pressure goal
- **b.** Percentage of patients reducing systolic/diastolic blood pressure by 20/10 mmHg
- **c.** Percentage of patients setting and maintaining dietary goals
- **d.** Percentage of patients maintaining medication adherence at each scheduled visit

20. Which of the following was the outcome of the Project ImPACT: Hyperlipidemia study?
- **a.** Medication persistence
- **b.** Medication compliance
- **c.** Percentage of patients achieving targeted National Cholesterol Education Program lipid goals
- **d.** All of the above

RX & OTC

New products

RX CARE

New drugs

FDA was busy in December. Here are some of the approvals announced before the year ended.

• **Nivolumab** (Opdivo; Bristol-Myers Squibb), a new treatment for patients with unresectable or metastatic melanoma who no longer respond to other drugs. Nivolumab received breakthrough therapy designation, priority review, and orphan product designation. **(www.bms.com)**

• **Peramivir** (Rapivab; Biocryst Pharmaceuticals), to treat influenza in patients 18 years and older who have acute uncomplicated influenza and have shown symptoms of flu for no more than two days. Peramivir is the first neuraminidase inhibitor approved for intravenous administration and is administered as a single IV dose. **(www.biocryst.com)**

• **Ceftolozane/tazobactam** (Zerbaxa; Cubist Pharmaceuticals), indicated to treat adults with complicated urinary tract infections and complicated intra-abdominal infections caused by Gram-negative bacteria. **(www.cubist.com)**

• **Ombitasvir, paritaprevir, and ritonavir tablets co-packaged with dasabuvir tablets** (Viekira Pak; AbbVie), indicated to treat patients with chronic hepatitis C virus (HCV) genotype 1 infection, including those with cirrhosis. **(www.viekira.com)**

• **Blinatumomab** (Blincyto; Amgen) to treat patients with Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL), an uncommon form of ALL. The first anti-CD19 drug to receive FDA approval, blinatumomab was awarded breakthrough therapy designation, priority review, and orphan product designation. This product will cost $178,000 for two rounds of treatment at $89,000 each. **(www.blincytorems.com)**

New generics

Dr. Reddy's has launched **valganciclovir tablets USP 450 mg**, a therapeutic equivalent generic version of Genentech's Valcyte, indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) and to prevent CMV disease in kidney, heart, or kidney-pancreas transplant patients at high risk. Boxed warning notes hematologic toxicity, carcinogenicity, teratogenicity, and impairment of fertility. **(www.drreddys.com)**

Heritage Pharmaceuticals has launched **furosemide injection, USP [1]**, in 20 mg/2 mL, 40 mg/4 mL, and 100 mg/10 mL strengths. It is generic equivalent to Sanofi's diuretic drug Lasix. **(www.heritagepharma.com)**

Camber Pharmaceuticals has launched **montelukast sodium tablets [2]**, generic for Merck's Singulair, indicated to treat asthma, exercise-induced bronchoconstriction, and allergic rhinitis. **(www.camberpharma.com)**

Teva has announced the launch of **celexicob capsules [3]** in dosage strengths of 50 mg, 100 mg, 200 mg, and 400 mg. The product is the AB-rated bioequivalent to Pfizer's Celebrex capsules, indicated for arthritis, acute pain, and dysmenorrhea. **(www.tevapharm.com)**

Teva has also launched **amlodipine/valsartan/hydrochlorothiazide tablets**, the generic equivalent of Novartis' Exforge tablets, indicated for the treatment of hypertension. **(www.tevapharm.com)**

Also newly launched by Teva is **levalbuterol inhalation solution, USP (concentrate)**, the bioequivalent of Sunovion's Xopenex, indicated to treat or prevent bronchospasm in patients four years of age and older with reversible obstructive airway disease. **(www.tevapharm.com)**

OTC

Dr. Reddy's has acquired the **Habitrol** brand over-the-counter nicotine replacement therapy transdermal patch, from Novartis. Shipment will commence shortly. **(www.drreddys.com)** DT

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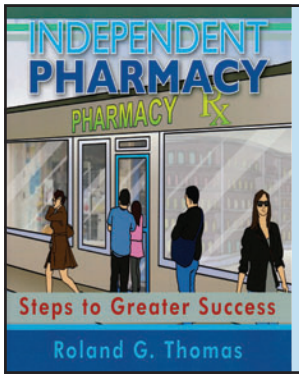

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VIEWPOINT Kelly Howard, BS Pharm, BCPS

2015: The #YearOfTheRPh

What with the lingering cloud of compounding scandals, rapidly shrinking reimbursements, and vital pharmacy legislation languishing in Congress, 2014 perhaps was not the best year for the profession of pharmacy. It certainly was not the best year for me professionally. Last year was, after all, the year I got fired from my job as a hospital pharmacist for "communicating threats."

No, that isn't a joke. If you've seen me play in my church's handbell choir, sponsored any of the marathons I've run for charity, or seen my name listed as the pharmacist in charge on the pharmacy license for the free clinic where I volunteer, you probably will want to know what I actually got fired for.

I think Tupac put it best when he said, "They say I'm violent. Because I refuse to be silent." Yes, I just quoted Tupac. 2014 was that kind of year.

When silence is not an option

In reality, my termination became inevitable when I refused to sign an attestation penned by the hospital's administration. It was a quasi-legal, murkily ethical document that I felt violated my professional code of ethics and restricted my abilities to care for my patients as required by my state's board of pharmacy.

You and every other reasonable pharmacist would have balked at signing it too. I was not quiet about my indignation over this form, so they called me violent.

Last year was also the year that I managed to land one of the best jobs I've ever had. I'm proud to say that I now work for a hospital that prizes character, compassion, and courage in its healthcare providers. My current manager will probably tell you, though, that silence is still not a technique I resort to very often.

I do not think pharmacists should routinely make a practice of keeping their heads down and their mouths shut, not when silence negatively affects patient care or marginalizes our profession.

If I could get into my Wayback Machine and do 2014 all over again, there isn't a lot I would end up doing differently. I would rather be falsely accused of being violent than rightly accused of being corrupt, lazy, incompetent, or anything else that characterizes a "bad pharmacist."

Yes, I have a huge black mark on my otherwise mostly spotless professional record, a blemish with which I'm completely at peace. I consider it to be a badge of honor earned in the defense of our rights as healthcare professionals.

Let this be the year

And this is my battle cry for change, right here and right now. Stand with me in refusing to be silent. Change may be hard, and giving up is easy. But look what you get — or don't get.

Let this be the year. Let 2015 be our year, the year that we finally show lawmakers, insurance companies, and the public at large our value. Let this be the year we finally get provider status. The year that equality finally makes it to the business of pharmacy and the Any Willing Provider law is rightfully applied to pharmacies.

Let this be the year a televised medical drama portrays a pharmacist as something other than a money-hungry, death-propagating drug dealer.

Let this be the year we stop lamenting our frustrations and do something about them. Something constructive, something profession-altering. Do one thing to advance our profession — e-mail your congressman, educate your patients about our struggles, write an editorial in your local newspaper. Do *something*.

If every pharmacist, all two million of us worldwide, were to do just one thing this year, imagine the impact we could have.

Just do it

So stop complaining and start doing. Do one thing for us this year, and don't be silent about it. Share it on social media, encourage your co-workers to act, shout it from the rooftops: 2015 is the #YearOfTheRPh. DT

Kelly Howard *lives and works in Southeastern North Carolina. Tweet her @PharmacistKelly and let her know what your "one thing" will be to make 2015 the #YearOfTheRPh.*

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