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Drug Topics®

VOL. 157 NO. 12

Voice of the Pharmacist | DrugTopics.com | December 2013

2014 BUSINESS OUTLOOK SURVEY

A TOUGHER YEAR AHEAD

ACA, shrinking margins, drug shortages pose challenges for hospital, community pharmacists

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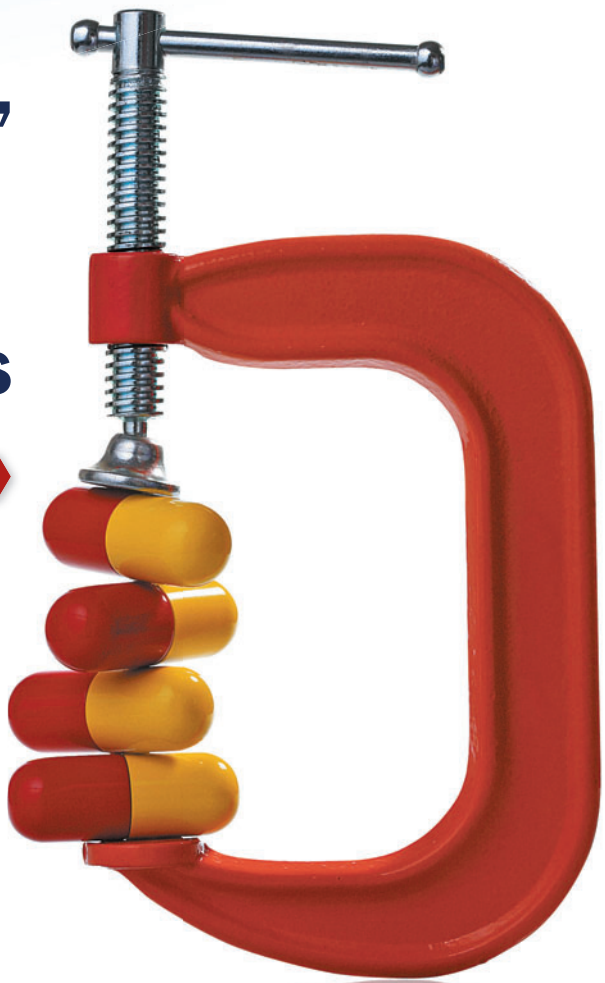

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Multiple Sclerosis, Part 2

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"Concomitant use of NSAIDs and aspirin: Is it ever a safe combination?"
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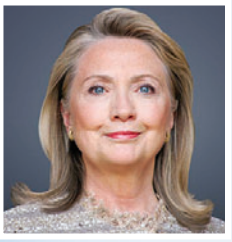

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DISPENSED AS WRITTEN Dave Ehlert, PharmD, MBA, FASHP

6 tips to boost pharmacy efficiency

Delivery of patient-centered care is a priority for clinicians and healthcare leaders alike. Making the switch from reimbursement based on a fee-for-service model to value-based care is changing everything.

Clinicians' workflow is being streamlined to enable them to focus on improving outcomes. This focus on efficiency is also applying itself to pharmacy, as pharmacists look for ways to maximize time spent on patient-care initiatives. From medication therapy management (MTM) to transition-of-care programs, the role of pharmacy has never been more critical. However, in a time of budget constraints and cost-containment measures, when staff cannot be added, this poses a management challenge for day-to-day pharmacy operations.

Evolving roles

To deliver high-quality patient-centered care, hospital and pharmacy leaders need to maximize the efficiency of their pharmacy operations in support of overall hospital initiatives and goals.

Pharmacy staff must be involved in supporting critical strategic mandates such as reduction of unnecessary readmissions and extension of the continuum of care. Specific areas of focus include integration of pharmacists into care transitions, improvement of post-discharge medication adherence, and provision of clinical pharmacy services in ambulatory care environments.

Pharmacists and technicians need to practice at the top of their licenses and/or certifications to provide the greatest possible value. Efficiency will not be optimized if pharmacists perform tasks that could be accomplished by technicians or if technicians spend time on work that could be automated.

Pharmacies need to adopt appropriate levels of automation so that staff can focus on the highest-priority clinical initiatives.

Best practices

Using proven tools and best practices, many hospital leaders and health-system pharmacy executives have worked with outside partners to help streamline pharmacy operations and redeploy staff. Here are six practices that can be implemented with minimal time, effort, and expense.

1. Use technologies to simplify drug-spend management. The creation of reports to analyze drug spend or track pharmacy initiatives is a time-consuming process. One study found that the process of creating a report that would yield meaningful information to analyze drug spend took 3.9 hours on average. Since hospital pharmacies in this study produced 11 reports per quarter on average, staff may spend more than 40 hours per quarter compiling and rearranging data to create meaningful reports.

Automated drug-spend analytics technology can produce these reports, requiring minimal staff time. Instead, pharmacy staff can use the time saved to analyze results and identify opportunities for savings.

2. Avoid reinventing the wheel. Pharmacy staff often spend significant time developing clinical initiatives or policies and procedures, as well as on other administrative tasks. For example, a thorough drug-class review prepared for a hospital's Pharmacy and Therapeutic Committee may require the creation of a complex document, which can take up to 200 hours.

However, by maintaining a robust, regularly updated repository of standardized documents that have been created and thoroughly reviewed by experienced pharmacists, pharmacy staff can modify preexisting documents instead of developing them from scratch. Examples of such standardized documents include drug-class reviews and interchanges, medication guidelines, competencies, and policies and procedures. Analysis shows that hospital pharmacies using such document repositories and averaging nine documents per quarter can save more than 550 hours.

3. Use analytics tools to optimize purchasing. As a result of meaningful-use requirements, most hospitals are adopting bar-code technologies that will scan medications at a patient's bedside. McKesson experts estimate that approximately 80% of oral solids are packaged in unit doses with bar-codes. The other 20% should be repackaged.

Increased use of bar-code scanning technology generates an immense amount of data about the drugs being purchased and administered. Analysis of this information for the valuable insights it can yield often does not occur, however, and when it does, it is extremely time-consuming, taking months of a technician's time. Sophisticated analytical tools can make recommendations to help a pharmacy optimize its practices for purchasing oral solids. These automated purchasing recommendations are produced efficiently and can help a health system streamline its drug purchases.

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6 tips to boost pharmacy efficiency

Continued from pg. 6

4. Use a perpetual inventory system along with automated systems. Hospitals often keep their drug inventory in various locations and use different systems to track this inventory. When such systems are not linked, the result is inefficient ordering and receiving processes.

Using a perpetual inventory system in concert with automation systems means that electronic orders are processed automatically, reducing order-creation time by up to 75%. Such systems can help reduce by 50% the time spent receiving and restocking drugs, help increase inventory turns by more than 40%, lead to a 30% reduction in inventory costs, and help a pharmacy maintain its formulary.

5. Optimize processes related to 340B. Management of drug purchases related to the 340B program is extremely complex. Historically, aspects of patient eligibility, drug purchasing, and inventory were handled manually. Software tools have helped pharmacies manage 340B patient eligibility, drug eligibility, and pharmacy replenishment, but often have not been integrated with a health system's drug-purchasing system.

New 340B systems integrate patient and drug eligibility for 340B with purchasing systems to give users greater visibility of their 340B accumulation data and availability of a supplier's inventory at the wholesaler's distribution center. This level of integration can help a health system better manage its purchasing of items in short supply in the market, as well as streamline the purchase of items requiring special management, such as controlled substances and drop-ship items.

6. Automate the NDC update process. It can be difficult and time-consuming to keep national drug code (NDC) information updated within pharmacy information systems. However, incorrect NDC data can adversely affect decision-making and billing, as well as nursing workflow and patient safety.

Solutions now exist to automate the NDC update process, so that the NDC data used throughout a health system are accurate and timely. Accurate NDCs can help reduce or eliminate NDC-related pricing errors, maximize bar-code scan rates, and improve overall workflow and efficiency.

The goal

Achievement of greater efficiency will allow pharmacists to spend more time on high-value-added activities, such as direct patient care and MTM across the continuum of care. These efforts support the entire health system in adapting to and succeeding in a value-based environment. DT

Dave Ehlert *is vice president, health systems product management, McKesson Health Systems. For information, contact McKesson at 800-571-2889 or healthsystems@mckesson.com.*

Voices

Singing her song


She works hard for the money

Re: "She works hard for the money" [JP at Large, November 2013]:

I'm one of those dinosaurs who managed to get my license in four years. I am now retired, after working 36 of the last 46 years.

The first blow to my confidence was the question asked at my first job interview: "What's your religion?" (They could ask questions like that back then.) I answered Roman Catholic, which didn't help. I was deemed unsuitable, since I might get married and of course pregnant.

My next application was to a three-store chain in a small town, where two-thirds of those looking for a fresh new RPh said, "A woman? No way."

Then I followed my new husband to another state and applied for a part-time position. I was hired. While my first paycheck was somewhat better than what a clerk made, it sure was less than the other part-timer (a man) was getting.

Eventually things got better. I led the way; other women were hired after I worked out OK, even working up to the delivery day for two of my kids.

I took 10 years off while living overseas and came back to a climate that was much more welcoming, although not for management opportunities in the corporate world, even after I had run a little neighborhood store, until my partner and I sold out.

By this time I had raised my kids and was ready to move forward. Lo and behold, the MBAs had arrived. Management was not to be left to mere pharmacists, male *or* female. Welcome to my world, fellas.

Now, of course, the big management (corporate) is handled by "civilian" MBA types, and even middle management is being done by nonprofessionals who are not bothered by thoughts of ethics and other such antiquated concerns.

But have you noticed? Respect for pharmacists is falling, the public's trust is waning, and lawsuit settlements are growing as those guys running the show ignore the rules. I feel so sorry for the new kids coming out of school with dreams of making a difference and stars in their eyes — which quickly seem to turn to dollar signs instead. The women may have been invited to the dance, but the same old guys are still piping the tune.

Diane Kreisher
CRAWFORDSVILLE, INDIANA

Seen at *DrugTopics.com*

Our article "Fired pharmacist sues WalMart over job policy" (November 1, http://bit.ly/firedpharm) *triggered some strong opinions. The following was excerpted from one post.*

First off, you are welcome to contact me. Please do if you need help. It can be very liberating to speak with another pharmacist about one's drug problem.

I am a pharmacist/pharmacy owner and recovering addict with more than 18 years clean time. I have been completely open about it and never been exposed to the kind of close-minded bigotry expressed by some of [the posted comments].

Alcoholism and drug addictions are *diseases.* Sufferers deserve the same concern and tolerance that we would grant any other patient. With proper treatment, the symptoms ameliorate or disappear.

We all know the symptoms. What we may not know are the changes that can and do occur with recovery. The key is proper treatment, which includes follow-up monitoring.

Pharmacists, of all professionals, should be cognizant of the truth about addiction. The reality is, it exists in our profession: One out of six! Unbeknownst to you, the best pharmacist you know may be an addict. We addicts are very adept at maintaining our public image, despite living in despair and self-loathing. You may be suffering yourself. If so, I beg you to seek help. Recovery is possible.

If you know, or suspect, that a colleague is suffering, be a friend and speak up, but speak with love and concern. You never know when you might need a helping hand.

Steven Streeper

We want to hear from you

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IN MY VIEW Bob Spera, RPh

The pharmacist's role in medication reconciliation

Gathering an accurate medication history for hospital patients is definitely a team effort shared by pharmacists, physicians, and nurses. To be successful, somebody has to take ownership of the process to monitor the medication reconciliation. The pharmacist must champion this process for it to work smoothly.

In the hospital

Hospitalists, attending physicians, medical residents, and interns all recognize how important it is to collect an accurate medication history and ensure precise medication reconciliation.

Hospitals should develop a clearly defined workflow for pharmacists and physicians to obtain and reconcile medication histories. Medication reconciliation, effectively conducted, will provide an accurate discharge medication list.

The electronic medical record system will maintain the medication histories; if patients are readmitted, this information will be readily available to the emergency department. However, the record must be reviewed and updated by clinicians.

In the community

The pharmacist in the community setting, whether it be in a chain store, an independent pharmacy, a big-box operation, a supermarket, or a hospital ambulatory care apothecary, will become involved in this process as well.

The hospital's clinical pharmacist may rely on the community pharmacist for an accurate and updated list of the medications currently prescribed to the patient. In most cases, the primary care physician has an accurate record of the patient's medications and will provide the patient with a printout, using the NextGen program. It is imperative for the patient to carry this list with him or her at all times — especially when being treated by a specialist or an emergency department clinician.

It is then up to the attending physician to determine which home medications the inpatient will continue taking while admitted, and which, if any, should be changed upon discharge.

Three types of meds

There are three major categories of medications that an inpatient can be prescribed during the admission process.

- The first group comprises the medications used to treat the symptoms that occasioned the admission. If a patient is admitted for bronchial pneumonia, he or she is usually given aggressive intravenous antibiotic therapy. If a patient presents with septic shock, therapy with vasopressors is usually initiated.
- The second group of medications includes those employed to prevent adverse events, such as heparin or enoxaparin used for prophylaxis against a DVT. Low-dose aspirin also falls into this category. Notice that heparin, norepinephrine, and vancomyin are not included in the patient's home medication reconciliation list.
- The third category of medications prescribed for the inpatient includes the home medications. This is the list of medications that the patient takes on a daily basis. It should be provided to the emergency department physician upon admission to the hospital.

The attending physician or hospitalist will then determine which of these medications should continue and which should be stopped while the patient is a hospital inpatient. If intravenous metoprolol is prescribed, the physician might want to discontinue the patient's PO carvedilol to prevent duplication of therapy. PO OxyContin and all combinations may be discontinued while the patient is being given IV morphine following a surgical procedure.

Teaching hospital

When pharmacists, retail or hospital, work in tandem with medical residents in a community teaching hospital, the collaboration should lead to a reduction in readmissions, emergency department visits, and hospital costs.

Complete and accurate medication reconciliation by the entire healthcare team will increase overall accuracy of the admission process. DT

Bob Spera *is a community pharmacist, a hospital pharmacist, and a writer for pharmacy trade journals. E-mail him at druggist37@verizon.net.*

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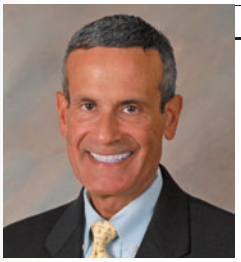

IN MY VIEW Jeffrey Fudin, BS, PharmD, DAAPM, FCCP

The hydrocodone question

A *Drug Topics* reader has asked: "What are your thoughts on making hydrocodone/APAP combinations CII?" At present, there is not much compelling, valid evidence upon which to base an answer.

No doubt FDA has based its move to make the schedule change on the many opioid deaths seen nationwide, which CDC has labeled an "epidemic."[1] There is more to the picture, however.

A murky subject

Many have said that the United States uses more hydrocodone than any other nation, but that is quite misleading.[2,3] Most other countries do not report prescription opioid use, so to say that more opioids are prescribed in the United States than in the rest of the world is unsubstantiated.

Prescribed indications are also a consideration.

European countries use dihydrocodeine more commonly than they do codeine, hydrocodone, or morphine.

In Canada, hydrocodone is generally used only in cough syrups or elixirs, not for pain treatment.

In Australia hydrocodone has largely been replaced by morphine.

Ignoring these factors skews the argument that the United States consumes the most hydrocodone worldwide and the claim that hydrocodone has been prescribed more than any other prescription drug in the United States. Unfortunately, many journalists have chosen to disregard these points in order to sell stories.

Mainstream media also are not shy about skewing the data, and politicians are not far behind, often avoiding objective evidence.

Practically in my own backyard, speaking on an extended-release formulation of hydrocodone, Senator Chuck Schumer said, "It's tremendously concerning that at the same time policymakers and law enforcement professionals are waging a war on the growing prescription drug crisis, new superdrugs could well be on their way, flooding the market … The FDA needs to grab the reins and slow down the stampede to introduce these powerful narcotics."[4]

Hydrocodone certainly is not a "superdrug." Hydromorphone is 10 times more potent, fentanyl is 100 times more potent, and remifentanil and sulfentanil supersede both of these in potency.

This is an example of media-driven political hyperbole. Hydrocodone is not a new drug; it has been on the market for over 40 years; and it certainly is not a "superdrug." Compared to hydrocodone, hydromorphone (Dilaudid) is 10 times more potent and fentanyl is 100 times more potent; and remifentanil and sufentanil supersede both of these in potency.[5]

Therapeutic need

The therapeutic reasons for including hydrocodone (and other opioids) in the standard formulary are to expand the armamentarium from which to choose for patients in legitimate need of opioid analgesic therapy.

While there are five different chemical classes of opioids[6], among the phenanthrenes alone there are very significant pharmacological and therapeutic differences. Examples of phenanthrene opioids include morphine, opium, diacetylmorphine (heroin), hydrocodone, naloxone, hydromorphone, oxycodone, oxymorphone, buprenorphine, nalbuphine, levorphanol, codeine, dextromethorphan, and others.

Each has its drawbacks and advantages. Codeine is very constipating and less potent than most. Oxycodone often causes agitation and inability to sleep. Morphine has a higher incidence of neurotoxicity and histamine reactions, etc.

Some of these drugs are pure mu agonists, others are partial agonists/antagonists, some are kappa, some cause NMDA receptor blockade, and others are uptaken variously by certain mu-receptor subtypes.

These differences all have a bearing on therapy choices, which is why several options are needed for specific pain types and select patients — and we have not yet even considered the metabolic differences resulting from

Continued on pg. 16

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The hydrocodone question

Continued from pg. 14

polymorphism, specific opioid selection to avoid drug interactions, and several other therapeutic factors. For politicians to simplify these issues is naïve at best.

More questions

While these considerations are not a direct response to the original query of whether or not hydrocodone should be included under Schedule II or Schedule III, in my mind there are other, more pressing questions, such as:

- How difficult should we make it to get these drugs?
- Should they be nonrefillable, regardless of schedule?
- Should all scheduled drugs be treated the same, since all have potential for abuse?
- If two drugs are mg-for-mg equipotent (e.g., hydrocodone and morphine), do they have the same abuse potential?
- How can we best monitor for diversion?
- Who is responsible for monitor ing these drugs along the supply chain?
- How can we encourage and engage contiguous states and federal facilities to share PMP (prescription monitoring program) data?
- What does it take to educate healthcare providers about important therapeutic distinctions among opioids and adjuvant analgesic options?
- How can we hold politicians accountable for promulgating fear among constituents, instead of supporting prescription take-back programs and calling for education for consumers and the prescribers/pharmacists who care for them?
- The poorest patients have the least medical coverage, the greatest access to abusable immediate-release formulations, and the least access to brand-name extended-release products and abuse-deterrent formulations. How can we convince third-party payers to cover such options as nutritional counseling, exercise (yoga, fitness centers, etc.), psychotherapy, and other alternatives to drugs?
- Most important, how do we ensure that our legitimate patients have access to the drugs they really need?

How difficult should we make it to get these drugs? Should they be nonrefillable, regardless of schedule? Should all scheduled drugs be treated the same? If two drugs are mg-for-mg equipotent, do they have the same abuse potential? How can we best monitor for diversion? Most important, how do we ensure that our legitimate patients have access to the drugs they really need?

New York State changed hydrocodone over to a Schedule II drug as of April 2013. Since that time, hydrocodone prescriptions for pain have diminished, codeine prescriptions for pain and cough products has remained the same, and prescriptions for oxycodone IR use have increased. I'm not sure whether these consequences are good, bad, or irrelevent; nor do I know whether trends will change or whether the example of New York's outcomes is an isolated one, compared to those of the rest of the country.

Answer TBA

I have often been asked whether or not hydrocodone should be rescheduled. To my mind, at least for now, we won't know whether there's a negative impact on legitimate pain patients or a positive impact on mitigating overdose risk until we have more data — *after* it is rescheduled. Perhaps the New York State PMP data will shed some light on possible outcomes. DT

References

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INVOKANA™ is the #1 branded therapy prescribed by endocrinologists when adding or switching non-insulin type 2 diabetes medications*

ENVISION NEW **POSSIBILITIES**

Invokana™
canagliflozin tablets

*Data on file. Based on NBRx data sourced from IMS NPA Market Dynamics Database, weekly data through 9/20/13.

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

INVOKANA™ is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

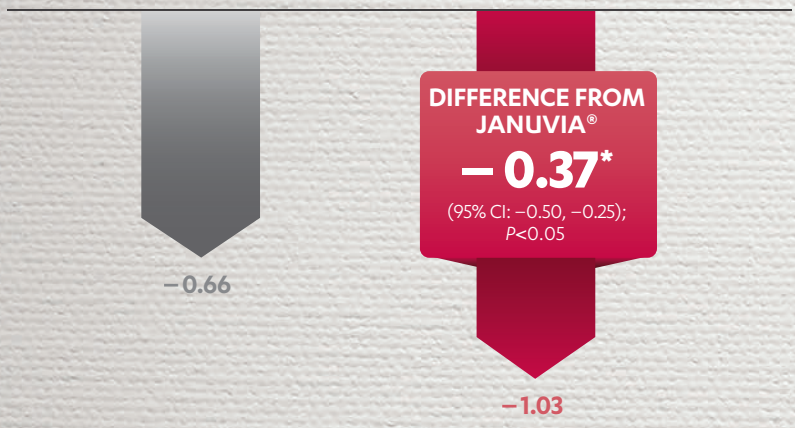
CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA™.
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

INVOKANA™ 300 mg demonstrated greater reductions in A1C vs Januvia® 100 mg at 52 weeks...

Adjusted Mean Change in A1C From Baseline (%): INVOKANA™ 300 mg vs Januvia® 100 mg, Each in Combination With Metformin + a Sulfonylurea[1]



Incidence of Hypoglycemia

With metformin + a sulfonylurea over 52 weeks: INVOKANA™ (canagliflozin) 300 mg: **43.2%**; Januvia® 100 mg: **40.7%**[1]

- Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue[1]

Convenient Once-Daily Oral Dosing[1]

- Recommended starting dose: INVOKANA™ 100 mg
- Dose can be increased to 300 mg in patients tolerating 100 mg who have an eGFR ≥60 mL/min/1.73 m^2 and require additional glycemic control

*INVOKANA™ + metformin is considered noninferior to Januvia® + metformin because the upper limit of the 95% confidence interval is less than the prespecified noninferiority margin of 0.3%.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS and PRECAUTIONS

- **Hypotension:** INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.
- **Impairment in Renal Function:** INVOKANA™ increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

COVERED FOR >**75%** OF COMMERCIALLY INSURED PATIENTS WITHOUT PRIOR AUTHORIZATION[3]

...as well as greater reductions in body weight† and systolic blood pressure (SBP)†

Change in Body Weight†

Significant reductions in body weight at 52 weeks, each in combination with metformin + a sulfonylurea (*P*<0.001)[1]

- Difference from Januvia®‡: 300 mg: **–2.8%**

Change in SBP†

Significant lowering of SBP at 52 weeks, each in combination with metformin + a sulfonylurea (*P*<0.001)[2]

- Difference from Januvia®‡: 300 mg: **–5.9 mm Hg**

INVOKANA™ is not indicated for weight loss or as antihypertensive treatment.

†Prespecified secondary endpoint.

‡Adjusted mean.

INVOKANA™ provides SGLT2 inhibition, reducing renal glucose reabsorption and increasing urinary glucose excretion.[1]

Adverse Reactions

In 4 pooled placebo-controlled trials, the most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.[1§]

References: 1. INVOKANA™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013. **2.** Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care*. 2013;36(9):2508-2515. **3.** Data on file. Janssen Pharmaceuticals, Inc., Titusville, NJ. Data as of 9/17/13.

SGLT2 = sodium glucose co-transporter-2.

§Included 1 monotherapy and 3 add-on combination trials with metformin, metformin + a sulfonylurea, or metformin + pioglitazone.

Learn more at **INVOKANAhcp.com/journal**

- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.
- **Genital Mycotic Infections:** INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.
- **Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

ENVISION NEW
POSSIBILITIES

Invokana™
canagliflozin tablets

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.
- **Digoxin:** There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

- **Pregnancy Category C:** There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at ≥0.5 times clinical exposure from a 300-mg dose.

  These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.
- **Pediatric Use:** Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.
- **Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in nine clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years of age. Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA™ 100 mg and -0.74% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).
- **Renal Impairment:** The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m^2); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

  The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.

Janssen Pharmaceuticals, Inc.

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»**Hepatic Impairment:** No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

OVERDOSAGE

»There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

ADVERSE REACTIONS

»The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritus, thirst, nausea, and constipation.

K02CAN13149

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

Invokana™
canagliflozin tablets

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14) in full Prescribing Information]*.

Limitation of Use: INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA *[see Warnings and Precautions]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function: INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA *[see Adverse Reactions]*. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hyperkalemia: INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia *[see Adverse Reactions]*.

Monitor serum potassium levels periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat per standard of care and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions]*. Monitor LDL-C and treat per standard of care after initiating INVOKANA.

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

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions]*
- Impairment in Renal Function *[see Warnings and Precautions]*
- Hyperkalemia *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions]*

Clinical Studies 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 the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to

INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Female genital mycotic infections†	3.2%	10.4%	11.4%
Urinary tract infections‡	4.0%	5.9%	4.3%
Increased urination§	0.8%	5.3%	4.6%
Male genital mycotic infections¶	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst#	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).

‡ Urinary tract infections includes the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials *[see Clinical Studies (14) in full Prescribing Information]* and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients received INVOKANA 100 mg (N=3092), INVOKANA 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.7% with comparator, 2.2% with INVOKANA 100 mg, and 2.0% with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg and 1.1% with INVOKANA 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.9, 2.7, and 0.9 per 1000 patient-years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) and age 75 years and older (Table 2) *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Use in Specific Populations]*.

Table 2: Proportion of Patients With at Least one Volume Depletion-Related Adverse Reactions (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

***** Includes placebo and active-comparator groups

† Patients could have more than 1of the listed risk factors

Impairment in Renal Function: INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

***** Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 3.4% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with INVOKANA 100 mg, and 9.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg *[see Warnings and Precautions]*.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents *[see Warnings and Precautions]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14) in full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies (continued)

In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Laboratory Tests: *Increases in Serum Potassium:* Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*. In this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions]*.

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including

UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

INVOKANA™ (canagliflozin) tablets

OVERDOSAGE

There were no reports of overdose during the clinical development program of INVOKANA (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Active ingredient made in Belgium

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from Mitsubishi Tanabe Pharma Corporation

10282400

K02CAN13080B

janssen

IN MY VIEW James "Goose" Rawlings, RPh

Tough week for pharmacy

I'm a hospital pharmacist in Central Indiana, and at my hospital, National Pharmacy Week is a big deal. It is observed during the last full week of October each year, and National Pharmacy Technician Day is also observed during that week. We have always made it a big event, but this year we decided to go all out.

We'll remember this one

I was a member of the committee to promote National Pharmacy Week. We had buttons for pharmacists and technicians to wear, recognizing the week. Sales representatives from various companies brought in breakfast and lunch. To involve the rest of the hospital, we had contests and giveaways the whole week. I even wrote an article for the hospital newsletter that was published on Wednesday of that week to promote our department and all the services we provide.

That is what made it so sad and ironic when our hospital picked that Wednesday to make cuts in the pharmacy department staff, layoffs that included both technicians and pharmacists. Friends we had worked with for years and who had racked up significant service time were gone in minutes.

One of the ones who left put up a Facebook post that said, "Happy Pharmacy Week."

My employer said all the right things: The employees involved left on good terms and are eligible for rehire. The staff reduction was made in reaction to declining census and an expected decrease in revenues resulting from implementation of the ACA. It was just a sign of the times, a necessary cutback to help us stay viable. Had to do it, no other choice.

I wish I could believe that.

A mushrooming liability

Here's what I think. Pharmacists are expensive. When you get rid of four or five, you save a lot on payroll. We do a lot of clinical work; theoretically we save our hospital money in medication costs and readmissions, but we don't get paid for any of it. We still are paid only to dispense.

We make a lot of saves every day. We save money, we save time on hospital stays, and we save lives. We make a difference, we're sure of it. And we're paying a big price.

The people we lost were casualties of the budget cuts because we still have not figured out how to get paid for what we know instead of for selling a product.

We can show you a bunch of figures and statistics on the good things that we do, but we produce no related revenue to pay the bills. It's a problem.

Since I started hearing that ACA is causing a shortage of primary care physicians (PCPs), I have said many times that there is not a shortage of doctors, there is a shortage of good doctors. We assist our physicians with medication orders all the time, and we document all that we do. We make a lot of saves every day. Our physicians and patients appreciate our efforts. We save money, we save time on hospital stays, and we save lives. We make a difference, we're sure of it. And we're paying a big price.

Something's gotta change

We need to have provider status and we need to be paid for it. It's just hard to prove value when you give it all away.

The person who figures all this out will be a rock star, more popular than Jimmy Buffett in Cincinnati. Somebody needs to get this worked out, for the students, for the young graduates with loans to pay, and for the older people like me who are still practicing.

Most important, they need to do it for my friends and for everyone else in this business who is currently out of a job or can't even find one to begin with.

And they need to do it pretty damn quick. DT

Jim "Goose" Rawlings *is a senior pharmacist in central Indiana. Contact him at redgoose54@gmail.com.*

VIEW FROM THE ZOO David Stanley, RPh

How do you hold two positions at once? Ask FDA

So FDA decides to tackle a huge problem, with the result that hydrocodone is soon to be a Schedule II controlled substance. Trying to make a dent in the seemingly never-ending increase in numbers of people who end up addicted to painkillers is a good thing.

However, coping with the burden of increased record-keeping and the unpleasant patient confrontations soon to be seen at every point of care, with people who won't understand why we can't fax their prescribers for more refills ... not so much.

I'm not particularly looking forward to the chaos that I suspect will result from this decision — the angry patients, the confused prescribers, the people truly in pain who will be inconvenienced or worse. But I've seen the statistics on addiction in this country, and I've looked into the faces of the addicted, so I'm well aware that very few of our attempts to stem the addiction epidemic have been working. I'm willing to give any idea a chance, if it might slow the tidal wave of opiate-related problems flooding this nation.

Or at least I was. Until I saw the complete plan.

Watch closely

First, let me recap exactly what happened. On October 24th, FDA recommended that all hydrocodone combination products — Vicodin, Lortab, Norco, and all the others — be moved from Schedule III to Schedule II. You know what that means. No refills. No faxes. No phone-ins. More red tape to order, store, dispense, and deliver the product.

If you're not familiar with what this decision means, you soon will be. Various hydrocodone products hold the No. 1, 3, and 5 positions in 2012's ranking of the top-selling prescription products in the United States, with a combined 129 million prescriptions written.

So get ready to explain to your patients what the FDA has done. A lot. Don't be so sure you'll be able to explain *why* they did it, though.

Watch how this went down: Even though we can all agree that narcotic addiction and its attendant social ills are a serious and growing problem in this country, and even though FDA said, in a press release announcing the decision, that it had "become increasingly concerned about the abuse and misuse of opioid products, which have sadly reached epidemic proportions in certain parts of the United States," FDA announced *the very next day* its approval of Zohydro, a pure hydrocodone product without the acetaminophen or aspirin that work to lower the amount of hydrocodone an abuser can take in a single dose.

Think of Zohydro as a little brother of the original OxyContin, the extended-release version of oxycodone that had to be reformulated to make it abuse-resistant after it all but launched the current wave of opiate-induced mayhem in this country. Zohydro has none of the safeguards of the new OxyContin, and it has no acetaminophen to put the brakes on anyone's potential narcotic bender.

Follow the bouncing bullet

What just happened? One day, FDA makes an effort to limit the damage that addicts can do to themselves, and the next, it gives them a cocked and loaded gun they can aim straight at their own temples.

You can see why I'm somewhat less than enthusiastic about the changes headed our way. If we had to cope with chaos in order for this country to take a shot at lessening a major public health problem, that would be one thing. But for every pharmacist, prescriber, caregiver, and pain sufferer in the United States to be inconvenienced while a repeat of the OxyContin disaster is simultaneously unfolding — that would be worse than accomplishing nothing.

Looking-glass logic

I learned long ago that stereotypes are wrong, but you'll have to excuse me; the image of the inept, bumbling government bureaucrat making nonsensical decisions based not on effective policy but on logic understandable only on the other side of the looking glass — well, that just got burned a little deeper into my mind.

We're all about to deal with a major, unpleasant, and — thanks to a little extra effort from FDA — most likely completely ineffective change in our professional practices.

Let's just hope FDA won't try to solve any more problems for a good long while. DT

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

Nearly 500 pharmacies endorse drug-dispensing bill

More than 480 pharmacies endorsed the Medicare Efficient Drug Dispensing Act (S.B. 1493) in a letter sent to its sponsor.

The bill, introduced by Sen. Ben Cardin (D-MD), seeks to preserve the $5.7 billion in budget savings estimated to result from the short-cycle dispensing policy enacted in 2010. The goals of the short-cycle policy are endangered by new reimbursement rules adopted by two of the largest prescription drug plan sponsors (PDPs), which control nearly two-thirds of the market, an announcement from Senior Care Pharmacy Alliance stated. The PDPs switched from paying pharmacies a flat, professional fee every time they fill an Rx to a professional fee tied to the number of days' supply of medication the pharmacy dispenses, SCPA said.

"This breadth of support demonstrates the negative impact this change has had on LTC pharmacies, and the need for Senator Cardin's bill. Pharmacies across the country had been aggressively investing in new technologies to increase efficiencies … but this change in policy has pharmacies holding off on those significant financial investments," said Larry Galluzzo, president of Skilled Care Pharmacy in Mason, Ohio.

Already, the average cost to dispense an LTC prescription is at least $13.70, and LTC pharmacies are being reimbursed between $4.50 and $5.00 per Rx on average, Galluzzo told *Drug Topics*.

"The costs — looking up medical records and stats, consulting, filling, and sorting it for different nursing homes — are there whether we fill a one-day supply or a 30-day supply. Our net profit is very slim as it is. If you take a percent or two off that, you are going to cut your profits by 25 to 35%," Galluzzo said.

"It is important that we achieve the savings that were projected from the short-cycle dispensing policy. My legislation would ensure that waste and unnecessary Medicare expenses are minimized in LTC facilities," Cardin said.

– Christine Blank, Contributing Editor

S.B. 1493 would preserve $5.7 billion in budget savings under the short-cycle dispensing policy.

TEST UPDATE

PTCB unveils redesigned certification exam for pharmacy technicians

Early in November, the Pharmacy Technician Certification Board (PTCB) introduced a retooled version of its Pharmacy Technician Certification Examination (PTCE). According to an official announcement, the updated exam measures the knowledge technicians need "to effectively support pharmacists and advance patient safety in today's pharmacies."

25,000 queried

PTCB based its changes to the exam on the findings of its latest "Job Analysis Study," which surveyed more than 25,000 pharmacy technicians in all 50 states. According to the official announcement, PTCB makes a regular practice of conducting this survey to keep current its understanding of changes in working conditions and job descriptions for pharmacy technicians. The changes in the certification exam were based on these latest findings.

"The PTCE is widely recognized and trusted to accurately reflect the current knowledge, skills, and abilities required for pharmacy technicians to effectively perform their duties, support pharmacists, and advance patient care," said PTCB Executive Director and CEO Everett B. McAllister, MPA, RPh, in a prepared statement. "The November updates in the PTCE are based on our latest study across community, hospital, and federal settings, with an increased focus on patient safety."

Changed and rearranged

According to PTCB, the updated examination places a greater emphasis on particular bodies of information, including medication safety and pharmacy information systems. The test was extensively recast, particularly through its arrangement around specific knowledge groupings and job function areas, each of which was broken down into even more particular subsections. The resulting examination has replaced three basic segments of the examination with nine. According to its official statement, no change was made to the 110-minute duration of the exam, the total of 90 multiple-choice questions, or the testing fee, which remains set at $129.

The exam will be offered at 237 Pearson Professional Centers across the country, as well as at military test centers. Pharmacy technicians can schedule their examinations, take a practice exam, and apply for certification, as well as find more information about PTCB and its services, at the PTCB website (*www.ptcb.org*). A guidebook for candidates, outlining certification guidelines and requirements, can be found at *http://www.ptcb.org/docs/get-certified/guidebook.*

– Julianne Stein, Content Channel Manager

This activity is supported by an unrestricted educational grant from the Western Pain Society.

Release Date: December 1, 2013
Expiration Date: December 1, 2014

LEARNING OBJECTIVE

- Cite risk factors for NSAID-induced renal failure
- List patient education pearls to prevent NSAID-related gastrointestinal and renal toxicity

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NSAIDs and Renal Toxicity in the Community Setting: A Practical Guide for Clinicians

Non-steroidal anti-inflammatory drugs (NSAIDs) are a diverse group of medications widely used for controlling pain and inflammation associated with musculoskeletal conditions.[1] NSAIDs have common analgesic, anti-inflammatory, and anti-pyretic properties. They represent approximately 60% of over-the-counter (OTC) analgesic agents (e.g., acetylsalicylic acid, ibuprofen, and naproxen) in the United States.[2,3] A recently published analysis of data from the National Ambulatory Medical Care Survey (NAMCS) representing 690 million individuals found that between 2000 and 2007, NSAIDs were prescribed for pain in 95% of patient visits.[4]

A recent multidisciplinary roundtable discussion among healthcare providers reinforced that, while NSAIDs act rapidly and are generally well tolerated, patients need to be informed about the range of adverse effects that can be associated with NSAID use, such as gastrointestinal (GI), cardiovascular, hepatic, and renal effects.[1,5]

Moderator: We're becoming more aware of adverse renal effects associated with NSAIDs. How do NSAIDs affect the kidneys?

John Devlin, PharmD: NSAIDs exert their analgesic and anti-inflammatory effects by inhibiting prostaglandin production through their ability to block the synthesis of the cyclo-oxygenase (COX)-2 products of arachidonic acid. At the same time, NSAIDs also inhibit COX-1 production that results in the reduced production of renal prostaglandin that has an important vasodilatory, protective effect in the renal vasculature.[5-8] While this effect is unlikely to be clinically significant in healthy patients with normal renal blood flow, it can result in renal impairment in patients with reduced renal blood flow (e.g., congestive heart failure) or in patients with preexisting renal vasoconstriction (e.g., hypertension).[5,7,9] A decrease in renal blood flow reduces the glomerular filtration rate (GFR) and leads to an increase in serum creatinine. Less commonly, NSAIDs can also exert an

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Two new clinically-focused, CME-certified case studies are now available online focusing on the use of NSAIDs in the primary care setting. To access these cases, please go to the initiative homepage at www.iche.edu/nsaids

Figure 1 NSAID-Related Renal Side Effects and Risk Factors for Renal Toxicity

Renal Side Effects[16,26]	Risk Factors
• Salt and water retention	• Age >60 years[16]
• Edema	• Heart failure[41]
• Kidney function	• ACE inhibitors, ARBs, loop diuretics, beta-blockers [23,32]
• Effectiveness of diuretic medication	• Underlying renal insufficiency (GFR <60mL per minute per 1.73m^2)[6]
• Urate excretion	• Intravascular volume depletion[16]
• Hyperkalemia	• Dehydration[33]
• Analgesic nephropathy	
• Chronic interstitial nephritis	
• Acute interstitial nephritis	
• Glomerulonephritis	

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acute toxic effect on the renal parenchyma that may result in interstitial nephritis that will also lead to a reduction in the glomerular filtration rate.[5,7]

Moderator: What are the most common NSAID-related renal complications you see in clinical practice?

C. Mel Wilcox, MD: NSAIDs are known to exert a range of adverse renal effects, including decreased renal perfusion, decreased GFR, edema, and increased blood pressure (Figure 1). These effects occur in approximately 1% to 5% of patients taking NSAIDs.[10,11] Most commonly, I see patients who are on an NSAID chronically. They might not be at high risk for toxicity—such as patients with hypertension or cardiovascular disease—but they might develop some peripheral edema, which is what brings them to my office. The prevalence of symptomatic edema associated with NSAID use is estimated at 3% to 5%,[11] and new onset or exacerbation can precipitate congestive cardiac failure, in which case NSAIDs should be avoided.[12]

The more drastic case would be an elderly patient with known congestive heart failure who is on an angiotensin-converting enzyme (ACE) inhibitor and develops potentially worsening heart failure. The anti-natriuretic and vasoconstrictive properties of NSAIDs can destabilize the blood pressure control exerted by ACE inhibitors and exacerbate heart failure.[13] In fact, a retrospective cohort study of 3,928 patients with hypertension who were prescribed acetaminophen or NSAIDs reported that, compared to patients taking acetaminophen, patients taking NSAIDs had a 2 mm Hg increase in systolic blood pressure. In a subgroup of patients taking ACE inhibitors and calcium-channel blockers, the systolic blood pressure increase among patients taking NSAIDs was 3 mm Hg.[13]

Moderator: What are some of the risk factors for developing renal toxicities among patients taking NSAIDs?

Wilcox: A patient with heart failure or a patient with cirrhosis first comes to mind.[5] In addition, the use of NSAIDs in patients with decreased renal perfusion may lead to hemodynamic decompensation and future renal complications.[2]

In conditions where blood volume is compromised, angiotensin II, norepinephrine, vasopressin, and sympathetic nerve activity all increase and raise renal vascular resistance.[7] American College of Cardiology/American Heart Association practice guidelines tell us to avoid NSAIDs when possible for patients with heart failure.[14] The evidence also suggests that we should avoid NSAIDs in patients with cirrhosis in order to prevent renal impairment.[5,15]

Moderator: Are there any concomitant medications that may put a patient at risk for renal problems if they're taking NSAIDs either on a short-term or long-term basis?

Devlin: Absolutely. Some of the most well-reported, longer-term medications that increase risk for NSAID-related renal toxicity are ACE inhibitors and angiotensin receptor blockers (ARBs),[5] which have anti-angiotensin II activity and can disrupt the kidney's ability to autoregulate GFR.[12,16] Studies have shown that the concurrent use of diuretics, ACE inhibitors, or ARBs taken with NSAIDs can increase the risk for kidney injury.[17-19]

Julia Pallentino, MSN, NP: I also see patients who are on antihypertensives plus loop diuretics, which increase the patient's risk for NSAID-induced renal toxicity.[16] It is wise to be cautious with these patients, since loop diuretics can adversely interact with NSAIDs to impair renal function.[2]

Devlin: There are other nephrotoxins that are used acutely in inpatient or outpatient settings that providers need to be mindful of. For example, a patient who had a computed tomography scan with contrast and was started on an NSAID would certainly increase his risk for contrast-induced nephropathy.[16] This is because NSAIDs inhibit the local vasodilatory effects of prostaglandins and render the kidney more vulnerable to nephrotoxic contrast agents.[20]

It's also been shown that patients who take chronic acetaminophen along with chronic NSAIDs are at a greater risk for chronic renal failure than patients on NSAIDs alone.[16,21]

"Providers should recommend NSAIDs with caution when combining them with agents that potentially decrease renal function, such as ACE inhibitors and beta blockers."

–C. Mel Wilcox, MD

Moderator: We talked about ACE inhibitors, ARBs, and diuretics as being anti-hypertensive agents that can pose potential risk for renal toxicity when used with NSAIDs. What are your thoughts about a patient who is taking an anti-hypertensive agent other than these three along with an NSAID?

Wilcox: My guess would be that they'd be slightly less at risk than they are from ACE inhibitors or ARBs. But if the patient is taking antihypertensives for long-standing hypertension, they still may be at risk for renal toxicity because they already have some renal insufficiency that may be subclinical.[7] Providers should recommend NSAIDs with caution when combining them with agents that potentially decrease renal function, such as ACE inhibitors and beta-blockers.[16]

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Devlin: As the blood pressure goals in the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines get tighter and tighter, patients—particularly the elderly—are increasingly being managed aggressively for hypertension and often need several medications to achieve adequate blood pressure control.[22] Some patients may be overtreated with antihypertensives, which could lead to decreased renal perfusion and confer risk for NSAID-associated renal toxicity.

A recent observational study using a large British primary care database (N=487,372) reported that adding an NSAID to dual antihypertensive therapy (diuretics with ACE inhibitors or ARBs) was associated with an increased rate of acute kidney injury (rate ratio: 1.31; 95% confidence interval [CI]: 1.12-1.53), especially in the first 30 days of use.[23]

Moderator: In general, does the duration and dose of NSAID treatment play a role in the risk of renal toxicity?

Devlin: In my experience in the hospital setting, if we have a patient with chronic kidney disease, particularly if they are intravascularly volume depleted from, say, diuretic administration, we can see relatively rapid reductions in creatinine clearance even with just a few doses of the NSAID. But I would say that nephrotoxicity is likely to be greatest with chronic NSAID users.

The main thing to look at is how long the patient is on the NSAID and the dose that they are taking (Figure 2). Although adverse events can potentially occur at any time during treatment, a higher dose poses a greater risk for renal toxicity than a lower dose,[18] and the risk for adverse events increases with the duration of treatment.[1,5] A nested, case-control study by Huerta and colleagues used a large primary-care database (N=386,916) to report that NSAID users had a relative risk (RR) for acute renal failure of 3.2 (95% CI: 1.8-5.8), which increased with both short- and long-term therapy, as well as with higher doses.[18] The risk ratio for renal insufficiencies in patients on short-term NSAID therapy (i.e., treatment duration of up to 1 year) was 2.6, and almost doubled as patients got closer to more than 1 year of continuous use (RR: 4.33). As doses increased from low-medium to high, the RR also increased from 2.51 to 3.38.

It's also important to look at the COX-1 specificity of NSAIDs. NSAIDs are ranked according to their anti-inflammatory potency, propensity to cause renal and GI toxicity, and relative selectivity for COX-1 and COX-2,[24] depending on the dose administered.[8] Both COX-1 and COX-2 NSAIDs reduce pain and inflammation in a time- and dose-dependent fashion,[9] but there's a huge variability in the COX-1 specificity between drugs like ketorolac vs. ibuprofen, or indomethacin vs. ibuprofen.[3,25] COX-2 inhibition is not an absolute property; it's a continuous variable.[9]

Wilcox: Dose and duration also depend on the individual patient and the patient's level of risk for renal toxicity. Although there is little difference in the mean efficacy of NSAIDs, patients vary in their responses to different NSAIDs.[26] Someone with a higher risk profile may be less likely to tolerate a higher dose for a short period or a smaller dose for a longer period. Is it an elderly patient with mild renal insufficiency or known heart failure? Would one ibuprofen be safe in that person? Perhaps. But most patients aren't just going to take one dose for a pain syndrome, back pain, or arthritis. They're probably going to take more than just one dose, which clearly would put them at a much higher risk.[5]

Pallentino: For patients with liver disease, I recommend NSAID use for a short duration of time, but certainly not very high doses for long periods.[27] Although the guidelines aren't completely clear, it's generally recommended that patients with chronic liver disease take lower than the usual recommended doses of OTC analgesics, including NSAIDs.[28]

Devlin: Many patients with pain are self-medicating. A lot of households have a bottle of ibuprofen or naproxen at home that is being used here and there on an as-needed basis. Data on national patterns of NSAID use show that 26% to 44% of individuals consume more than the recommended dosage.[29] In addition, chronic use of NSAIDs tends to increase with age.[3] Studies show that adults over the age of 65 are the largest users of OTC medications—20% to 30% of people >65 years of age take NSAIDs for pain relief on a given day.[29,30]

Concomitant medication use also increases with age. A recent community study found that approximately 75% of 357 people >55 years of age who used NSAIDs had more than one medical condition, including hypertension, chronic kidney disease (CKD), or cardiovascular disease.[31] In the same study, approximately 10% of the sample using NSAIDs were also taking ACE inhibitors, diuretics, and anti-hypertensive medications (11.2%, 10.7%, and 9.3%, respectively).[31]

These types of patients can be very hard to monitor. Even if you talk to a patient about the medications they take, they're very focused on their prescribed regimen—their heart-failure medications, diuretics, antihypertensives, or lipid-lowering agents—and they might not even mention that they pop an ibuprofen if they feel a little stiff in the morning or have a headache.

Moderator: What is the renal impact of NSAIDs on the patient who has no risk factors, who doesn't fit the bill for any of the situations discussed earlier?

Figure 2 COX Selectivity and Maximum Recommended Dosing of Commonly Used NSAIDs[3]

NSAID	COX-2 Selectivity	Maximum Daily Dose (mg/d)
Ibuprofen	Non-selective	1200-3200
Naproxen	Non-selective	500-1000
Ketoprofen	Non-selective	200-300
Celecoxib	Selective	200
Diclofenac	Non-selective	100-150

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Wilcox: Most healthy patients who self-medicate with NSAIDs for a limited time can tolerate these drugs without adverse effects, unless perhaps they increase their dose for pain relief and they get dehydrated for some reason.[2,7,25] But in general, NSAIDs are safe in those patients as long as they read the label and make sure they're not taking concomitant medications from the same class, since an increased total dose of NSAIDs is associated with a high risk of adverse reactions.[18,26]

Devlin: The only really dangerous thing that could happen to these patients is acute interstitial nephritis (AIN),[16] but the risk for AIN is very low relative to the huge number of healthy patients who take NSAIDs.

"Most healthy patients who self-medicate with NSAIDs for a limited time can tolerate these drugs without adverse effects, unless perhaps they increase their dose for pain relief and they get dehydrated for some reason." [2,7,26]

–C. Mel Wilcox, MD

Moderator: In general, is dehydration an issue among patients taking NSAIDs? How does it fit into the overall picture?

Wilcox: Yes. For many of the older patients that we see, although dehydration from exercise would be uncommon, dehydration from some other comorbidity can happen quite easily. A patient may have gastroenteritis,[5] get dehydrated, and have a little fever and then take NSAIDs for a couple of days. I've seen this on several occasions. Or someone with known renal insufficiency or known risk factors develops volume depletion from some other problem (e.g., loop diuretics pose a risk of volume depletion),[14] and then takes NSAIDs.

ACE inhibitors or ARBs can alter renal hemodynamics in patients who are volume depleted.[9] Research is ongoing to determine their role as "thirst blockers" by inhibiting the renin-angiotensin system implicated in thirst perception.[32]

Moderator: Let's say renal issues arise in a patient. Would NSAID-induced renal impairment be reversible?

Wilcox: The evidence indicates that acute NSAID-induced renal failure is commonly reversible within 24 hours of discontinuing NSAIDs,[7,33] but it depends on how big a hit the kidneys take. Reversibility might take longer if the patient has multiple kidney comorbidities, like the patient I mentioned with known heart failure and renal insufficiency who develops dehydration and acute tubular necrosis.

Devlin: It's really important to identify patients' baseline renal function when starting NSAID therapy. Although it's unclear whether monitoring improves morbidity or mortality, a recent review of consensus guidelines recommended that clinicians consider monitoring serum creatinine levels in patients taking NSAIDs who are at risk for renal failure, as well as in patients taking ACE inhibitors or ARBs.[5]

An analysis of NSAID use in a cross-section of 12,065 patients (using National Health and Nutrition Examination Survey data from 1999-2004) found that 2.5% to 5% of people with CKD reported using OTC NSAIDs in the previous 30 days, and 66% of patients with moderate to severe CKD had been using an NSAID for at least 1 year.[34] To put that in perspective, a Canadian cohort study of a community of 10,184 older adults reported that, over a 2.75-year period, patients with a baseline mean GFR between 60 to 89 mL/min/1.73m^2 using NSAIDs increased their risk of rapid kidney disease progression by 25% compared with non-NSAID users.[6] The National Kidney Foundation and other consensus guidelines recommend to avoid using NSAIDs in most patients with CKD.[34]

Moderator: What would you say to a patient with risk factors for renal impairment about the safe use of NSAIDs?

Devlin: I'd have a discussion about maybe choosing and maximizing the use of acetaminophen, though obviously not in a patient with end stage liver disease, and then evaluating the patient's pain level, especially if it's an arthritic-type picture where the pain is more chronic. Several clinical guidelines, including those from the American Geriatric Society, recommend acetaminophen as the first option of pain relief for arthritis in older adults,[35] with the caveat that clinicians should educate patients about the maximum safe dose of acetaminophen from all sources (<4 g/24 hours).[24] In elderly patients, patients with cardiac or renal failure, or those who are taking ACE inhibitors or ARBs, clinicians should monitor blood pressure and a serum creatinine concentration (to estimate GFR) 1 to 2 weeks after starting NSAID treatment.[5,12,18]

Pallentino: Patients with mild liver disease can usually tolerate lower doses of both NSAIDs and acetaminophen.[28] However, we should really save those for when they are really needed, caution patients not to use them on any kind of regular basis, and talk to them about the absolute maximum they can take.

Wilcox: I think one of the patient education pearls that I would emphasize is the importance of avoiding OTC NSAIDs if you know you're at risk for renal toxicity. Studies show that patients may be unaware of the risks and of adverse effects associated with NSAIDs.[36] A study summarizing results from two national consumer surveys (9,062 respondents) showed that, among respondents using OTC NSAIDs, 60% were unaware that NSAIDs posed any risks for side effects, and 49% were unconcerned about risk potential.[29]

Pallentino: Many patients, especially older adults, may feel that it is unimportant to disclose information about using NSAIDs. One study reported that only 58% of patients told their physicians about any OTC use, and physicians asked about OTC use in only 37% of patient encounters.[37]

When you ask patients, "Are you taking this?" they will say, "Oh, you mean that's a medicine, too?," especially with regard to OTC agents. Since I treat patients with cirrhosis, I tell them that I want to know everything they're taking, including supplements and anything they're buying at the health food store or ordering over the Internet. This gives me a more complete picture of the medications they're taking so I can appropriately warn them of the risks. We can only counsel patients about appropriate dose and potential adverse effects if we are aware of how much medication is being used.[2] Data are scarce on the prevalence of drug interactions with herbal/dietary supplements (HDS), but 9% to 19% of patients use HDS, and concurrent use with OTC analgesics is common.[38]

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WAR ON DRUGS

FDA calls for reclassification of hydrocodone products to Schedule II

According to a recent FDA announcement, FDA is recommending to the U.S. Department of Health and Human Services (HHS) that hydrocodone combination products such as Vicodin be reclassified under Schedule II, placing tighter controls on the pain medications. Hydrocodone is currently a Schedule III drug.

"This determination comes after a thorough analysis of extensive scientific literature, review of hundreds of public comments on the issue, and several public meetings," said Janet Woodcock, MD, director, FDA Center for Drug Evaluation and Research.

This month, FDA will formally submit to HHS its recommendation for the product reclassifications. The agency expects agreement from the National Institute on Drug Abuse. The Drug Enforcement Agency will make the final decision.

Early in 2013, FDA's Drug Safety and Risk Management Advisory Committee favored reclassification in a 19-10 vote. FDA had rejected a similar request for reclassification in 2008.

In March, a bipartisan bill was introduced to reclassify hydrocodone drugs, moving them from Schedule III to Schedule II of the Controlled Substances Act.

Pharmacy associations respond

The National Association of Chain Drug Stores (NACDS) continues to oppose the transfer of hydrocodone products to Schedule II, citing "the loss of pain control for millions of Americans."

In February 2013, NACDS, the National Community Pharmacists Association (NCPA), the Long Term Care Pharmacy Alliance, other professional healthcare groups, and patient advocacy groups sent a letter to FDA Commissioner Margaret A. Hamburg, MD, stating that "No evidence currently exists to show that reclassifying hydrocodone will curb misuse and abuse of pain medications. In contrast, there is evidence that rescheduling medications to higher classifications can reduce patient access to medications and cause harm."

NACDS President and CEO Steven C. Anderson, IOM, said in September that pharmacies have two main objectives when tackling the problems of prescription drug abuse. "They have to be part of the solution by working with law enforcement officials to stop prescription drug abuse, but they also have to maintain their responsibilities to patients by making sure they receive the medications they legitimately need."

NACDS suggests that Congress pass the Senate Bill 1277, the "Combatting Prescription Drug Abuse Act," introduced by Senator Barbara Boxer (D-Calif). It would establish a commission for the coordination of efforts to reduce prescription drug abuse.

NCPA CEO B. Douglas Hoey, RPh, MBA, has issued a statement, calling for greater education efforts for prescribers, electronic prescription-drug monitoring programs and tracking systems, and the closing of rogue pain clinics as first steps toward combating prescription drug abuse, while still providing access to needed pain medications.

– Julia Talsma, Content Channel Director

CHOLESTEROL CONTROVERSY

New ACC, AHA guidelines urge statin use for 33 million more Americans

The American College of Cardiology (ACC) and the American Heart Association (AHA) have issued new guidelines recommending statin therapy for approximately 33 million Americans who do not have cardiovascular disease (CVD), but have LDL cholesterol between 70 mg/dL and 189 mg/dL, and an estimated 10-year CV risk of 7.5% or higher.

The new cholesterol recommendations identify four major groups of adults who could benefit from moderate- to high-intensity statin therapy: patients who are 75 years and younger with clinical CVD; patients with LDL cholesterol of 190 mg/dL or more; patients with type 1 and 2 diabetes who are 40 to 75 years old; and patients 40 to 75 years old with an estimated 10-year CV risk of 7.5% or more, whose LDL cholesterol is between 70 mg/dL and 189 mg/dL.

This is a major shift from the 2002 cholesterol guideline that recommended statin therapy only for individuals with a 10-year CV risk level above 20%. According to an AHA report, the old guideline did not take into account the risk for stroke, only the risk for heart disease.

"We've been undertreating people who need statin therapy in this country," said AHA volunteer Donald Lloyd-Jones, MD, a member of the expert panel for cholesterol guidelines. "Statins lower cholesterol levels, but what they really target is overall cardiovascular risk."

More newly revised guidelines

Also released were other newly revised guidelines for diet/exercise, obesity, and risk assessment, AHA announced.

A new lifestyle management guideline for individuals with elevated cholesterol and blood pressure recommends a diet that includes fruits, vegetables, whole grains, low-fat dairy products, poultry, fish, and nuts, but limits consumption of red meats and sugary food and drinks. A diet that limits sodium to 2,400 mg daily should be considered for patients with hypertension. Exercise should consist of 40 minutes of moderate to vigorous aerobic exercise three to four times per week.

Recommendations for obese patients will help clinicians identify patients who need to lose weight, will match treatment with risk profiles, offer diets for weight loss, lifestyle intervention, and counseling, as well as aid in the selection of candidates for bariatric surgery, the AHA announcement stated.

The guideline for risk assessment of CVD no longer follows the Framingham 10-year risk score estimates of coronary heart disease. New equations were developed to incorporate sex, race, age, treated/untreated systolic blood pressure level, total, and HDL-cholesterol levels, smoking status, and history of diabetes.

With the guidelines, ACC and AHA released a cholesterol "risk calculator" that immediately came under fire when researchers at Boston's Brigham and Women's Hospital released data showing that it overestimated risk of MI and stroke by 75% to 150%.

– Julia Talsma, Content Channel Director

DUAL DEGREE

Rutgers to offer country's first PharmD/MD degree

The Affordable Care Act is breeding new healthcare delivery models, and emphasizing provider integration of hospitals, physicians, and pharmacists, as well as teamwork and patient management across a continuum of care.

One of the latest examples is a dual-degree program combining a doctorate in pharmacy from Ernest Mario School of Pharmacy and a medical degree from Rutgers University's Robert Wood Johnson Medical School.

The program is the brainchild of Joseph Barone, dean and distinguished professor at the school of pharmacy, who began noticing that some of his pharmacy students were going on to medical school after graduation.

The dual degree supports Rutgers' interdisciplinary approach to education, which Barone says has been a priority for many years.

"We are not trying to produce 'super' pharmacists and physicians, but the program will enable students to better understand how drugs work," said Barone.

"In light of the Affordable Care Act, teamwork between doctors and pharmacists will be important in creating efficiencies and a higher level of care," he said.

A new breed

The two schools operate under the umbrella of the new Rutgers Biomedical and Health Sciences in New Brunswick, N.J., a recently restructured conglomerate of nine New Jersey schools. The 10-year program, scheduled to start in fall 2014, will offer instruction in basic and clinical sciences and train professionals in healthcare policy, research, and clinical diagnosis and treatment.

In addition, students will have the opportunity to participate in seminars, develop and implement research programs, share ideas representing both disciplines and participate in clinical rotations and clerkships.

Barone said that he expects the dual degree to produce a new breed of researchers and policymakers among graduates as they combine pharmacotherapy and clinical skills to help design drug trials and develop new therapies, address critical healthcare issues, and serve in academia.

The PharmD program, which targets students already enrolled in the doctorate program at the Ernest Mario School of Pharmacy, is available after two pre-professional and two professional years of training at the school of pharmacy. Students apply in the spring of their second professional year for two additional years of training, followed by a four-year medical school education.

Barone calls the program the first dual pharmacy/medical school degree program in the country. He expects three to five students to enroll each year. "I think the program will be a real game-changer in healthcare education," he said.

– Mari Edlin, Contributing Editor

MAJOR NEWS

Pharmacy deemed best college major for lucrative career

Want to guide your son or daughter toward a college major that has the best chance of leading to a good-paying job?

If your answer is yes, there's no better choice than pharmacy or pharmaceutical sciences, according to *Kiplinger Personal Finance* magazine.

The best

Kiplinger analyzed 95 college majors to determine the ones that statistics indicate will lead to the highest employment rates for both college graduates and experienced workers. It also examined the college majors that will lead to the best paychecks right out of college and that have the best prospects for job growth.

Pharmacy and pharmaceutical sciences topped *Kiplinger*'s "most lucrative" list.

Topping the magazine's list of lucrative majors were pharmacy and pharmaceutical sciences. Computer science, civil engineering, information systems management, and nursing were also in the top 5. They were followed by information systems, finance, math, information science, and construction.

The worst

The magazine also identified the worst college majors, in terms of job prospects and pay, as human services and community organization, fine arts, social work, early childhood education, and art history.

Faring slightly better, but also on the list of worst college majors, were interdisciplinary studies, studio arts, mass media, humanities, and family consumer sciences.

Pharmacy and pharmaceutical sciences were cited because of the mid-career salaries ($120,000), low mid-career unemployment rate (2.5%), and projected job growth (36.4%).

A welcoming job market

"Students in this field graduate into a welcoming job market and have the second-lowest unemployment rates on this list (after nursing)," the magazine reported. "The starting pay may fall a bit short of the national median, but by mid-career you stand to earn the highest income of any grads with our best majors."

The magazine also cited jobs other than pharmacist for which a pharmacy or pharmaceutical science major can qualify.

"But if a career behind a CVS counter isn't in the cards, a bachelor's in pharmacy can also start grooming you to work as a medical scientist, doing research to design and develop drugs," the magazine said.

– Mark Lowery, Content Editor

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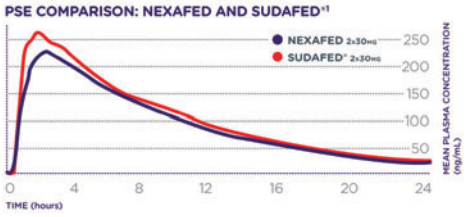

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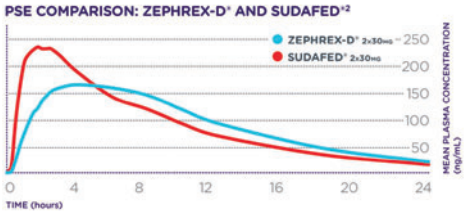

Nexafed is the only meth-deterring pseudoephedrine product:

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- With Tmax similar to that of Sudafed® immediate-release tablets[2]
- That meets the U.S. Pharmacopeial Convention (USP) standard for dissolution[1]

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acura pharmaceuticals, inc.

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References: 1. Data on file, Acura Pharmaceuticals, Inc., Palatine, IL. **2.** Brzeczko AW, Leech R, Stark JG. The advent of a new pseudoephedrine product to combat methamphetamine abuse. *Am J Drug Alcohol Abuse.* 2013;39(5):284-290.

Up front » In Depth

Jonathan C. Javitt, MD, MPH

mHealth tools: A bond between patients and pharmacists

Mobile health (mHealth) is a rapidly expanding market sector that uses mobile communication technology to link people to their medical caregivers and other health resources. Recent innovations in mHealth range from mobile-connected fitness programs to home diagnostic products, to increasingly sophisticated medical devices for the management of chronic disease. All are oriented toward lifting healthcare out of the confines of the hospital or doctor's office and delivering it any time, from anywhere.

Many chronically ill patients are accustomed to using medical monitoring equipment in their daily lives, so it's only natural that mobile-optimized versions would be useful. Many of these devices include products that people frequently purchase in pharmacies today: blood-glucose meters, scales, medication-reminder systems, or blood-pressure cuffs. Unfortunately, the information derived from the use of these products is often not tracked, stored, or shared with a patient's healthcare team in an accurate or timely way. mHealth monitoring can completely transform the way that data is collected and exchanged among a patient's support system.

Providing insight

These monitoring systems also stand out within the mHealth world because they collect validated biometric information (information derived directly a patient's own body), rather than self-reported data, which is limited in its usefulness.

For example, mHealth glucose-monitoring systems can reveal trends in an individual's blood-glucose levels that may indicate the need for education about lifestyle choices or medication adjustments. To enable this process, patients simply measure their glucose levels with a cellular-enabled meter; these readings are automatically uploaded to a database that stores the data and establishes trends over time. These readings are available to anyone with permission to view them, whether providers, caregivers, family members, or the patient's local pharmacist.

For chronically ill individuals, the advantages of these systems are clear. These technologies give patients greater convenience and the self-knowledge they need to make good decisions about their health. And by connecting patients with their care teams and loved ones through the sharing of important health data, they also offer peace of mind.

Many of these systems are very easy to use; they resemble existing medical devices and do not require additional data input or even the use of a mobile phone.

The pharmacist's role

For pharmacists, mHealth monitoring systems present an opportunity to improve the health of patients while gaining a way to further their integration as healthcare team members.

Many of these systems feature equipment, such as meters and test strips, that can be purchased at a local pharmacy. Individuals will naturally turn to pharmacists for information about the value of these systems and instructions for their use. Pharmacists, in turn, can take the opportunity to educate patients about the importance of monitoring adherence, medication compliance, and positive lifestyle choices.

For example, mHealth solutions for diabetes offer the pharmacist an opportunity to use properly credentialed diabetes education services and be compensated by most insurers. Recent experiences in the U.K. National Health Service suggest that patients may be highly receptive to the participation of their neighborhood pharmacists in their diabetes management.

Some solutions offer pharmacists the ability to review blood-glucose readings and send patients occasional helpful tips and coaching, another way to encourage patients with diabetes to stay close to their neighborhood pharmacists.

Improved profitability

mHealth monitoring systems can also help pharmacies improve their bottom lines. The availability at a pharmacy of an innovative, mobile-optimized technology has the potential to drive greater patient loyalty and optimize pharmacy spending.

This opportunity is especially significant in the case of patients with chronic conditions and related comorbidities. For example, patients living with diabetes spend eight times more than an average healthcare consumer does at the pharmacy, averaging $2,500 per year on medication, glucose monitoring products, and OTC supplies.

With the rate of chronic illness growing exponentially across a variety of populations, it stands to reason that mHealth systems designed to support these individuals will become much more common. Pharmacists who can anticipate this growth opportunity will be positioned to drive greater pharmacy spending while improving the health of their patients. DT

Dr. Jonathan Javitt *is CEO and vice chairman of Telcare, Inc. (www.telcare.com), which specializes in mobile diabetes management solutions.*

Up front
In Depth

Julia Talsma, Content Channel Director

VODI-Impact: A healthy living campus in Detroit

Pharmacists help plan, implement a healthier, safer community

More than three years ago, the Conner Creek/Osborn community of northeastern Detroit was chosen for development as the site of a healthy living campus for local residents. With a declining population of just over 80,000 individuals and one-third living in poverty, this area became the recipient of a grant for a safety-net enhancement initiative from the Kresge Foundation.

The foundation had asked for a proposal addressing the healthcare needs of a community and a social determinant. In the case of Conner Creek/Osborn, the healthcare focus was diabetes and hypertension. According to data from the 2010 City of Detroit Behavioral Risk Factor Surveillance System, 14.4% of those age 18 and older reported diabetes and 27.4% reported hypertension. The social determinant within this program became safety, because of a high level of prevailing crime that included assault and battery, vehicle thefts, and damage to property.


Nancy Lewis

Pharmacists were key to planning the needs assessment for the Voices of Detroit Initiative (VODI)-Impact: A healthy living campus. Community pharmacists provided feedback about the health of their community and helped to determine the priorities for the programs, said Nancy Lewis, PharmD, a consultant and adjunct associate research scientist, University of Michigan, College of Pharmacy.

"Pharmacists on our planning committees gave us input on specific interventions that we do for folks, which was very helpful and needed," Lewis said. "A lot of time pharmacists don't realize the role they can play in healthcare planning and policies. That was important for us."

A central hub

The healthy living campus is located in a central geographic area within the community, with an office in the community building that houses its partner, St. John Providence Health System. At the Conner Creek building, the Impact office is the place where residents are linked to various services on the campus or to partners of the program.

"We use the campus to bring in healthy living services, so that becomes the hub or safe place for people to come and receive services," said Lewis. "People who want to get involved in healthy living can find out about access to fresh food programs, fitness classes, and health information, as well as to health services."

Community pharmacists are offering services that include the promotion of medication lists and reviews of those lists. In addition, pharmacists have volunteered their time to present educational workshops and lead discussion groups on such topics as diabetes, use of insulin, and men's health. A community pharmacist also set aside a day to give immunizations at her pharmacy to Impact enrollees who request them.

Challenges

"One of the key challenges that we found was a disconnect between the residents living in that community and community-based organizations. People from the community really didn't know about the services that were available," Lewis said.

That has certainly changed with this new initiative.

"Pharmacists are a health resource for the community. On a regular basis, we offer Impact Health Day with University of Michigan pharmacy students, talking about health goals and offering blood-pressure monitoring, blood-sugar monitoring, and medication reviews with medication-list updates," she said.

In addition, VODI-Impact partners have stepped up to help the community with nutrition education, fitness activities, fresh food-share orders, and safety patrols on the campus and within the community.

Recently, VODI-Impact joined its partner, St. Johns Providence Health System, to kick off implementation of the Affordable Care Act. St. Johns has also established a good referral relationship with federally qualified health clinics, so if an Impact member needs a health referral, that can happen quickly.

Trust is also a big issue for members of the Conner Creek/Osborn community. "We found in Impact the importance of developing a relationship with the community and the importance of developing trust. It has required a great deal of effort on our part to get out and be known to people and develop individual relationships," Lewis said. "Pharmacists have a huge advantage, because they are in the community and people can see them. They have multiple interactions with people."

VODI-Impact members now number 550. As the three-year grant comes to an end this month, the Kresge Foundation has indicated an interest in continuing support for another year. Over the next year, VODI-Impact will be reporting on its outcomes, including to what extent it has been able to organize the community and bring in resources and member participation in the various activities. DT

First- and every-cycle Neulasta achieved:

- **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.

Support through every cycle

Help reduce the incidence of infection and protect your patients receiving myelosuppressive chemotherapy* from febrile neutropenia.

*Myelosuppressive chemotherapy regimens associated with a clinically significant risk of febrile neutropenia.

Neulasta® (pegfilgrastim) is administered by subcutaneous injection.

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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Neulasta® (pegfilgrastim)

Every appropriate patient. Every cycle.

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 ($AUC_{0\text{-inf}}$) 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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Up front
In Depth

Joseph Friedman, RPh, MBA

Should you establish a medical marijuana dispensary?

I know the exact moment my inner entrepreneur roared into life. It was Sunday evening, Oct. 21, 2012. I was watching a segment on *60 Minutes* about the medical marijuana industry in Colorado.

I've been interested in the medicinal benefits of botanicals since learning about them in pharmacy school. So I paid attention when California became the first state to legalize the medical use of cannabis in 1996. I continued to take notice as more states passed medical marijuana legislation.

However, the *60 Minutes* segment inspired me to turn my interest into a business. I decided to apply for one of 60 licenses to open and operate a medical marijuana dispensary in my home state of Illinois as soon as they become available in 2014.

That was my first step into an exciting new industry.

Many other steps had preceded it. I'm a registered pharmacist with an MBA and more than 15 years of pharmacy and business experience. I've held senior director of pharmacy positions with major procurement and distribution companies. I have a passion for sales, marketing, negotiations, business development, and relationship management, and have used my entrepreneurial spirit to create new business lines, call centers, retail outlets, and services — all for other people.

I decided those days were over.

Industry challenges

Starting up any new business, even in a mature industry, is complicated. However, establishing a medical marijuana dispensary in a brand-new industry already beset with significant challenges goes beyond complicated. Here are a few reasons:

Laws. Even in states that have legalized medical marijuana, licensed and registered medical marijuana growers, distributors, and patients are breaking federal laws under the Controlled Substances Act every day.

Banks. Because of warnings from the U.S. Justice Department, banks are reluctant to open bank accounts for or lend money to legal medical marijuana businesses.

Deductions. By enforcing section 280E of the tax code, the IRS denies legal medical marijuana companies the ability to take standard business deductions on their federal taxes. It's difficult to find investors for companies that can be audited and taxed out of existence.

Standards. There are no consistent standards, rules, or regulations for any aspect of the medical marijuana business. The conditions it can be used for, the amount of drug a patient can possess, where it can be cultivated – these considerations and more vary wildly from state to state.

Meetings. Beginners should expect to go to more meetings and hearings than they could ever imagine with people and agencies they never heard of before. This business requires networking on steroids.

Suppliers. Many of the cultivators (i.e., suppliers) are less than reliable. There are legions of people who claim to know how to help business owners and who are more than happy to take their money. Very few people actually know anything and are able to provide good counsel. Finding them is a challenge.

A growing industry

In spite of substantial roadblocks, state legislatures continue to pass laws legalizing medical marijuana. They want — and need — the tax revenue and jobs.

Forbes estimates that the medical marijuana market was worth $1.7 billion in 2011 and expects it to be a $9 billion industry. That doesn't count revenue from recreational use.

There may be more than 2.4 million medical marijuana patients currently registered in the United States. *Forbes* suggests that there may be 24.8 million potential patients.

Obvious candidates

The more I learn about the circumstances and challenges connected with dispensing medical marijuana, the more convinced I am that pharmacists are the best candidates to own and operate dispensaries.

We have the training, skills, experience, and patient-focused mindset. We are accustomed to adhering to regulations. We already know how to protect children, create a safe and secure environment, deal with difficult suppliers, maintain quality and inventory controls, educate patients, comply with rules and laws, and more.

In Connecticut, patients can obtain medical marijuana legally only from dispensaries licensed by the state, and only licensed pharmacists can apply for and obtain a dispensary license. The Connecticut statute also reclassified marijuana as a schedule II substance.

Whether other states and the agencies that regulate them follow the example of Connecticut or not, they should at least enlist pharmacists to help them develop rules, standards, and practices.

The National Association of Specialty Pharmacy, NASP, has established a task force to explore — and help its

Continued on pg. 40

Should you establish a medical marijuana dispensary?

Continued from pg. 39

members capitalize on — the opportunities offered by medical marijuana. Certification and insurance reimbursement are two of the items on the task force's extensive agenda.

Some back story

Marijuana in various forms has been used for medicinal, religious, and ceremonial purposes — and probably for recreational purposes as well — for thousands of years.

Marijuana is thought to have been cultivated since the dawn of agriculture 10,000 years ago. The pharmacopeia of Chinese Emperor Shen Nung, who lived circa 2,700 B.C., recommends marijuana use to treat more than 100 ailments.

Colonial Americans were ordered by the king of England to raise marijuana for export. George Washington grew marijuana at Mount Vernon.

In the United States, the criminalization of marijuana began during the 1930s. Recreational use had skyrocketed during Prohibition, in the years from 1920 to 1933. Despite opposition from the American Medical Association, Congress passed the Marijuana Tax Act in 1937. Possession of marijuana for recreational use became illegal for the first time, and an excise tax was imposed on cannabis for medical and industrial uses.

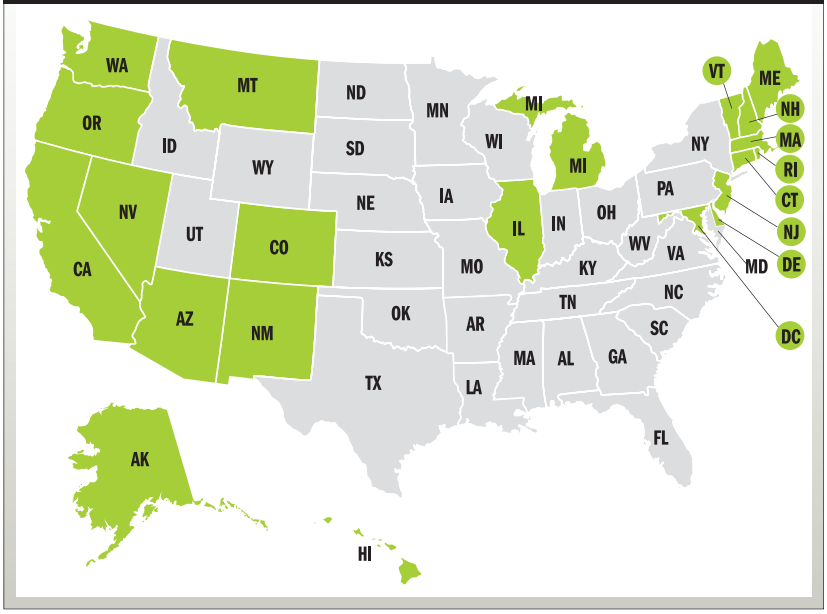
In 1969, the U.S. Supreme Court declared the 1937 law unconstitutional. in 1970, the government countered by passing the Controlled Substances Act, asserting that marijuana has no medicinal applications, is unsafe, and has a high potential for abuse. Marijuana was thereby declared a schedule I substance.

Doctors are not allowed to prescribe marijuana; they can only "suggest" it. Pharmacists endanger their licenses if they have marijuana on site.

However, as of October 2013, medical marijuana has been legalized in 20 states and Washington D.C., and more states are considering following suit.

States where medical marijuana is legal

(as of October 24, 2013)



Washington and Colorado already have legalized its recreational use.

Classification challenges

Various individuals and interest groups have been challenging the classification of marijuana for years. In August 2013, Sanjay Gupta, a respected neurosurgeon, chief medical correspondent for the CNN media network, and *60 Minutes* correspondent, joined their ranks.

In an essay for CNN, Gupta publicly apologized for his previous opposition to medical marijuana. He explained that his research has proved to him that there never had been any scientific basis for the government's claims. He went on to apologize for his part in helping the government mislead the American people for decades.

Among other points, Gupta stated that many clinical studies have established that marijuana has "very legitimate medical applications." He also stated that marijuana "doesn't have a high potential for abuse. In fact, sometimes marijuana is the only thing that works."

Medical benefits

Reliable scientific studies conducted by reputable organizations and universities have proven repeatedly that marijuana can:

- Alleviate chronic pain, especially nerve pain caused by diabetes, amputation, HIV, AIDS, multiple sclerosis, and hepatitis
- Lower intra-ocular eye pressure caused by glaucoma
- Relax muscle tension, decreasing muscle spasms and reducing shaking caused by multiple sclerosis and other neuromuscular disorders
- Act as an anti-nausea and anti-vomiting agent, especially for people receiving chemotherapy
- Stimulate the appetites of people with AIDS, cancer, and eating disorders
- Relieve acute anxiety, insomnia, and other sleep disorders

Researchers continue to discover and confirm additional medicinal uses for marijuana. For example, marijuana

Medical marijuana: Some resources

60 Minutes
A comprehensive and informative segment that describes the medical marijuana industry in Colorado, including the development of regulations and conflicts with federal agencies.
http://www.youtube.com/watch?v=sQ9JKlxGgSs

MMJ Business Daily
A comprehensive, unbiased news site about medical marijuana.
www.mmjbusinessdaily.com

National Association of Specialty Pharmacy
Nonprofit organization that advances the profession through education, certification, networking, and collaboration.
www.nasprx.org

National Center for Biotechnology Information
U.S. government-funded national resource for molecular biology information. Includes access to many public databases.
http://www.ncbi.nlm.nih.gov/pubmed (search for "medical marijuana")

National Organization for the Reform of Marijuana Laws (NORML)
This organization works to legalize the responsible use of marijuana by adults.
www.norml.org

ProCon.org
A nonprofit organization that researches and issues unbiased reports on controversial issues, such as medical marijuana.
www.medicalmarijuana.procon.org/

Project CBD
A nonprofit educational service dedicated to promoting and publicizing research into medical marijuana.
www.projectcbd.org

Smoke Screens, by Martin A. Lee
A social history of cannabis, this book describes the rapid growth of the multi-billion-dollar medical marijuana industry, scientific studies about the benefits of medical marijuana, and the efforts of local, state, and federal law enforcement agencies to maintain prohibition.

"Why I changed my mind on weed," by Dr. Sanjay Gupta
In this CNN essay, Dr. Gupta, a respected physician and media medical consultant, apologizes for his previous opposition to medical marijuana and explains why he changed his mind.
http://www.cnn.com/2013/08/08/health/gupta-changed-mind-marijuana/

may have properties that enable it to starve cancer tumors.

Catch-up needed

A recent Gallup poll showed that 58% of Americans believe that marijuana use should be legalized. The federal government's resistance to public sentiment and scientific proof is crumbling slowly.

On August 29, 2013, U.S. Attorney General Eric Holder announced that the Department of Justice would no longer enforce federal marijuana laws in states where marijuana use by adults is legal. Although he directed this statement to Washington and Colorado, it is seen as a major policy shift.

At the same time, Holder warned that states must have — and enforce — "robust controls and procedures" or face the risk of renewed federal enforcement. For example, states must prevent marijuana distribution to minors, ensure that criminals and gangs do not receive revenue from marijuana sales, and prevent marijuana from being sent to other states where it is not legal.

A 2010 memo from the IRS reminded the members of Congress that section 280E makes no exception for "medically necessary marijuana." Congress needs to amend the code and exempt medical marijuana – at least in states that have legalized it. That action would finally allow legal and licensed medical marijuana companies to deduct standard business expenses on their federal taxes.

So far, all such bills submitted to Congress have died in committee.

The vision

I have no idea whether I will be granted a license to open a medical marijuana dispensary in Illinois. But that doesn't stop me from imagining my one-of-a-kind, state-of-the-art dispensary.

My dispensary will be welcoming, patient-focused, and safe, and will be in strict compliance with all rules and regulations. It will offer various forms of medical cannabis, along with ancillary services and homeopathic remedies. There will be a comfortable seating area for community education. There will be written material and touch screens to help patients access the latest information.

If your inner entrepreneur is clamoring to be set free, consider establishing a medical marijuana dispensary. It's a challenging new field that may be a perfect choice for you. DT

Joseph Friedman *is a registered pharmacist with extensive corporate and retail experience. He received a B.S. degree in pharmacy from the College of Pharmacy, University of Illinois – Chicago and an MBA from Lake Forest Graduate School of Management. Contact him at jfriedm@comcast.net.*

Up front
In Depth

Kathryn Foxhall

Alzheimer's research: Now is the time for advocates to unite

A dozen promising trials of Alzheimer's disease could be launched today if funds were available, said Paul Aisen, MD, director of the Alzheimer's Disease Cooperative Study at the University of California, San Diego. "We know how to pick the drugs. We even know what designs we would use for the trials. But these are expensive and we don't have the money."

With a tsunami of future Alzheimer's cases facing the nation and a number of recent drug trials proving unsuccessful, an October meeting in Washington, D.C., sponsored by the Pharmaceutical Research and Manufacturers of America (PhRMA) and others, focused on how to better fund and accelerate research.

The clinical trials he referred to would focus on presymptomatic patients, said Aisen, and emphasize "anti-amyloid drugs in combinations, but extending to unrelated therapeutic approaches." The nation would be able to fund all that with $2 billion, he said.


Paul Aisen

Costs

According to the Alzheimer's Association, spending on Alzheimer's disease by the National Institutes of Health totaled about $484 million in fiscal year 2013, the equivalent of $100 "for every $29,000 Medicare and Medicaid spends, caring for individuals with Alzheimer's."

According to data from the Kaiser Family Foundation, as of 2011, long-term care, much of it involving patients with Alzheimer's disease, already accounted for roughly 30% of Medicaid expenditures.

Alzheimer's Association estimates show Medicare/Medicaid beneficiaries' Alzheimer's-related costs climbing from $122 billion in 2010 to $344 billion in 2030.

Challenges

According to PhRMA, only three new drugs for Alzheimer's disease have been approved since 1998, resulting in a 34-to-1 ratio of "failures" to successes, although failures teach researchers a great deal too.

Aisen also told meeting attendees that while the members of the Alzheimer's disease research community have developed good communications with each other, there still is no "czar" or other infrastructure to coordinate the effort. This is another example, he said, of failure to address recommendations from the 2012 National Plan to Address Alzheimer's Disease.

Reed Tuckson, MD, consultant and former chief of medical affairs for UnitedHealth Group, warned that, days into the October government shutdown, the nation was already facing the next battleground for federal dollars. In a budget-cutting process that will be hard, fast, and ugly, he said, Alzheimer's disease research advocates need to unite behind a strategically designed set of a few investigations, in spite of the fact that there is so much research to be done.

Focus

Key to research success would be finding a connection between a clinical biomarker and a clinical outcome, said Nicholas Kozauer, MD, clinical team leader in the FDA division of neurology products. He emphasized that FDA is not in a position to approve a drug solely on the basis of a biomarker such as amyloid as a surrogate.

"If anything, we have evidence, at least from the dementia stage of the disease, that affecting amyloid doesn't necessarily correlate with clinical outcomes," he said.

But once there is reassurance a biomarker is clinically meaningful, "that is going to accelerate phase 2 development significantly," he said. In Alzheimer's disease, where researchers look for small changes caused by treatment over time, being able to screen drugs more quickly will open up many avenues, he said.

In February, FDA released an Alzheimer's disease draft guidance for developing drugs for early-stage Alzheimer's.

Lifestyle

Neill Graff-Radford, MD, neurologist at the Mayo Clinic, said that research into the effects of lifestyle factors should not be forgotten. There is powerful evidence, for example, that aerobic exercise and other factors may be helpful for the brain, actually increasing the hippocampus volume. What researchers don't know is whether aerobic exercise will work in the setting of Alzheimer's pathology, he said.

A critical factor, he said, is that people are afraid of the disease, even more than they are of cancer. "If we knew that exercise could prevent Alzheimer's disease, genuinely," he said, maybe people at risk would actually exercise.

Robert Egge, the Alzheimer's Association's vice president for policy, said that advocacy for the disease now has a movement and a path forward. Positive indicators include President Obama's mention of Alzheimer's disease in the State of the Union address, the Department of Health and Human Services' emphasis on Alzheimer's in talking points about its proposed budget, and the resources NIH has directed to it from its discretionary funds.

Egge also noted indications in Congressional budget statements that Alzheimer's disease research has bipartisan support, a rare commodity these days, and grassroots lobbying has increased on Capitol Hill. DT

Kathryn Foxhall *is a healthcare journalist based in the Washington, D.C., area.*

Mark Lowery, Content Editor

One pharmacist's winning strategy for curbing robberies

Last year, Indiana held the dubious distinction of being the state with the most pharmacy robberies in America. Yet there was not a single pharmacy robbery in 2012 in St. Joseph County, Indiana, which includes South Bend.

That wasn't always the case in St. Joseph County, where in 2004 a pharmacy was robbed, on average, every six weeks. That was the year local pharmacists began aggressively working with police to create safer pharmacy environments and to apprehend criminals. Their efforts led to the arrest of more than 30 diversion and robbery suspects, the breakup of two prescription fraud rings, and the end of the armed-robbery spree in their county.

That success is chronicled in *Staring Down the Barrel: A Pharmacists' Guide to Diversion and Coping with Robbery* (AuthorHouse) by Ken Fagerman, RPh, MM. The book was published in July.

"Pharmacy violence is on the rise and a subject rarely dealt with in an open format. This book details how a group of local pharmacists began a program with police that stopped rampant pharmacy robberies and at the same time uncovered widespread, organized narcotic diversion," Fagerman said.

Fagerman is a clinical pharmacist, a former manager of infusion and retail pharmacies, an adjunct professor of pharmacology, and former president of the St. Joseph County Pharmacy Association.

Enough was enough

Two particularly disturbing incidents ignited Fagerman's decision to organize his pharmacy colleagues. The first involved an armed robbery during which a pharmacist and staff were bound and gagged. The second occurred when a pharmacist who refused to fill a suspicious prescription was threatened. That pharmacist was shown a knife and told: "I'll cut you later."

Fagerman said he found that "there was no manual or program to turn to. This book is to relay our successes, tactics, and tips so you may benefit from the South Bend experience."

The book's strategies include working with police, training pharmacists how to react, and changing the way many stores are set up.

"Just the physical setup of the stores was not conducive to crime prevention methods," said Captain Phil Trent, South Bend Police Department. "Now at least some of the pharmacies have done a better job of beefing up their prevention security."

The book also examines:

Surveillance systems. More up-to-date technology uses computer hard drives for video storage, but this data is often stored locally, so be aware that savvy thieves may take or destroy these hard drives. A dummy or decoy drive is a good idea. A comprehensive, good quality system is a must, as is one that monitors and records license plate numbers of vehicles at the drive-through window. Systems that monitor parking areas are of great value and will give police vehicle information and direction of travel. Customers may resent the invasion of privacy, but everyone's behavior improves when all parties realize their actions are being recorded.

Alarm systems. Know and use your alarm system. It's surprising how many pharmacies underuse their alarm systems or have none. Most modern alarm systems have important features that simply are not fully used, perhaps because many users don't know all the functions of which their systems are capable. A good alarm system is a lifeline to the police and could save your life.

Telephones. Insist on caller ID on incoming phone and message lines. Do not accept called-in prescriptions from unknown or blocked callers. Be aware that any gaps or deficiencies in your system may be purposely exploited by diversion suspects. In some cases, these callers may be working with insiders at your location.

Pharmacy Crime Watch (PCW) program. The most effective tool to counter pharmacy threats is a PCW. By forming a PCW and a partnership with police, you can learn what evidence or information local police need to make an arrest. Over time, you can also educate police on what constitutes fraud and forgery. In some diversion cases, this may mean allowing a perpetrator to get away with filled prescriptions while the police make a case against him or her. It may also mean filling a prescription and letting the arrest take place while the suspect is in possession of the prescription. Work with and learn from local police what constitutes an actionable case.

Prescription monitoring programs. Support and use your state programs, and encourage prescribers to do so as well. These programs are of great value and will aid in the identification of in-office diversion by prescriber office staff. Police detectives are usually very discreet in the investigation and prosecution of these occurrences. Be patient, maintain absolute silence about any details, and follow police directives. Request that your identity be withheld, and take steps to avoid revealing your involvement. DT

GETTY IMAGES / E+ / HUGO CHANG

Julia Talsma, Content Channel Director

Pharmacists face tougher 2014

ACA, shrinking margins, drug shortages put the squeeze on community, hospital pharmacies

Pharmacists in the community setting (64%) anticipate a slightly tougher business climate next year, with retail sales remaining the same or increasing, compared to 2013 estimates (66%). However, estimates of net profits in the community pharmacy setting in 2014 are on par with those of 2013, with approximately half of those surveyed expecting net profits to remain the same or increase, according to respondents to *Drug Topics*' latest Business Outlook Survey.

Expectations for hospital pharmacy have dropped slightly. Last year 70% of respondents expressed a positive outlook; this year, 67% expect the pharmacy department to reach its institution's financial goals for contributions to net hospital revenues.

These were some of the findings from *Drug Topics*' 2014 Business Outlook Survey, an annual survey of more than 600 community pharmacists and approximately 300 hospital pharmacists, which examines the current business climate and future prospects for pharmacists. This year's survey was fielded for two weeks in November 2013.

Community pharmacists

Community pharmacists (n=639) ranked the top five factors that contributed positively to their businesses last year as follows **(Figure 1)**:

1. Major brand-name drugs going off patent
2. Increase of electronic prescriptions
3. Immunization certification
4. Medication therapy management
5. Medicare Part D

Compared with last year's survey answers, responses showed little difference, except that this year MTM made the list and Medicare Part D edged out healthcare reform.

The biggest challenges that community pharmacists listed for 2014 (**Figure 2**) were:

1. Competition from mail-order pharmacies
2. Healthcare reform
3. Decrease in state Medicaid rates and MAC and FUL
4. Preferred pharmacy networks for Medicare Part D
5. PBM practices

Impact of Medicare Part D

When Medicare Part D was implemented in 2006, it was considered a good program for seniors and pharmacies alike. At the time, seniors thought that they no longer had to worry about obtaining medications at an affordable rate when they used generic drugs. Community pharmacies saw increased business.

Now, however, Medicare beneficiaries are enrolling in plans promoting preferred pharmacy networks/mail-order pharmacies, and this has had a negative impact on some community pharmacies, according to respondents to the *Drug Topics* survey.

"Reimbursement does not keep up with increased drug cost." "Medicare Part D cuts into more favorable reimbursement from state Medicaid." "Reduced MAC levels and increases in number of Rxs have occurred." "It is very time-consuming. Bookkeeping, billing, and record-keeping are a nightmare," several readers responded.

"Medicare Part D is a horrible plan, both for seniors and pharmacies. However, it is a wonderful plan for the insurance companies who were allowed to write the law for Medicare Part D," a retail pharmacist said.

"For 2014, I cannot enroll in any network and be considered a 'preferred' pharmacy. I've already received dozens of greeting cards of regret from patients who will not be able to use my pharmacy next year," reported one community pharmacist.

Helping seniors

Some survey respondents did note that Medicare Part D has helped seniors fill their prescriptions consistently, because the drugs are more affordable with this government subsidy. Medicare beneficiaries with Medicare Part D coverage have greater access to pharmacies, consultations with pharmacists, and medication therapy management (MTM).

Other pharmacists responded that increased sales and drug coverage have increased business, but resulted in lower net profit for pharmacies. In addition, the dual eligibles, those eligible for state Medicaid and Medicare, have had an impact on business, with much lower dispensing fees resulting when Medicaid beneficiaries were switched to Medicare.

When seniors switch plans, another problem with Medicare Part D plans arises, said one survey respondent. "Each plan operates its own fee schedule and step therapy requirements. When patients change from one plan to another, step therapies must be redone, which wastes time and resources, not to mention affecting the patient, who doesn't get proper treatment."

However, one pharmacist from a chain pharmacy noted that being a preferred pharmacy chain has been positive. "We are able to provide competitive prices and provide patients a cost-saving advantage, serving a large population of patients on Medicare Part D. "

FIGURE 1

Positive factors affecting community pharmacy in 2013

1. Major brand-name drugs going off patent
2. Increase of electronic prescriptions
3. Immunization certification
4. Medication therapy management
5. Medicare Part D

Source: Drug Topics' *2014 Business Outlook Survey*

FIGURE 2

Challenges for community pharmacists in 2014

1. Competition from mail-order pharmacies
2. Healthcare reform
3. Decrease in state Medicaid rates and MAC and FUL
4. Preferred pharmacy networks for Medicare Part D
5. PBM practices

Source: Drug Topics' *2014 Business Outlook Survey*

Another community pharmacist summed up the pros and cons. "The positive aspects are that prescription healthcare is available for seniors, most generics are cheap, and immunizations are covered at the pharmacy. The negatives are two major loopholes — the donut hole and changing formularies once patients sign up. Also, the customer service on insurance cards is a joke. Patients cannot change plans but once a year, even after finding out that they were misrepresented after signing."

MTM services

About the same percentage of pharmacies (43%) as in 2012 offered MTM services in 2013 under Medicare Part D. Unfortunately, only 25% of the 626 respondents are being paid for these services. Of these, the majority of pharmacists delivering MTM (45%) received between $0 and $249 for these services. Thirty-one percent reported payments between $250 to $999, 20% reported payments between $1,000 to $4,999, and 5% reported $5,000 and above.

Some were concerned about their ability to deliver MTM services. One respondent noted, "We need restructuring in the retail setting in order to make MTM and immunizations work efficiently."

Frustrations in retail pharmacy

When retail pharmacists were asked whether they were satisfied with the way their pharmacy associations have represented them in 2013, 35% responded no, 34% responded yes, and 31% said they didn't know.

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Pharmacists face tougher 2014

Continued from pg. 49

A number of state associations were lauded for their leadership in formulating national policies. "The Arkansas Pharmacist Association is one of the leaders in the questioning and formulating of national policies. The association places the patient first and shows that the PBMs are killing business and government that offer Rx programs by their greed."

A survey respondent from Pennsylvania was pleased with the state association. "The Pennsylvania Pharmacist Association has an excellent CEO who has accomplished a great deal during her tenure, both within the profession and with her relationship with state government."

Others thanked the national pharmacy associations. "The American Pharmacists Association collaboration with the American Society of Health-System Pharmacists and the National Community Pharmacists Association are empowering pharmacists as healthcare providers. State associations' effectiveness hinges on national groups."

A California pharmacist was pleased with the California Pharmacists Association because "the association did everything it could to get pharmacists recognized as providers. We were successful. Hopefully, it can become a nationwide policy."

One respondent from Michigan was dissatisfied with the state association, citing lack of support for stress and work overload. "I have worked in retail pharmacy for 33 years and I burned out because of no help. The state association has done nothing to mandate a manageable pharmacist-to-tech ratio. I am very disheartened about retail pharmacy. I used to really enjoy it and took pride in my profession. These [working conditions] put the public at risk, with many mistakes occurring when a pharmacist has low or no staff."

Other community pharmacists are also demoralized by working conditions. "After years of disappointment, I no longer follow what [the associations] do. They seek [provider] status while working conditions have worsened for retail pharmacists," said one survey respondent. "Extensive lowering of tech help hours is putting a lot of undue pressure on pharmacists. No association seems to be concerned with deterioration of workplace conditions for retail chain pharmacists," another pharmacist said.

Hospital pharmacists

Approximately 67% of hospital pharmacists (n=298) reported in the survey that the business climate was good to excellent, as it related to their expectation of reaching their financial goals for the year. This was slightly lower than expectations expressed in 2012, with approximately 70% optimistic about that year. Almost two-thirds expected to stay within budget for 2013, compared to approximately 72% last year.

Next year, 41% of hospital pharmacists expect their 2014 drug budgets to increase, on par with last year. However, almost 15% expect the 2014 drug budget to decrease, compared to 12% last year. Approximately 35% expect the 2014 drug budget to remain the same, compared to 43% last year.

In terms of 2014 salaries for hospital pharmacists, only 22% expect salaries to increase, whereas 62% expect them to remain the same, and 11% expect a decrease in compensation. Last year, approximately 30% expected pharmacist salaries in the hospital setting to increase, according to last year's survey results.

In terms of 2014 pharmacy technician salaries, only 31% expect increases, 60% expect the salaries to remain the same, and 4% expect them to decline. In last year's survey, 34% of the survey respondents expected pharmacy technician salaries to increase, 58% expected them to remain the same, and 2% expected declines.

Hospital pharmacists are also bracing for possible layoffs in 2014. Almost 18% expect the number of pharmacists in their departments to decrease next year, compared with only 10% who expected decreases in 2013. However, approximately 15% expect pharmacist staffing in their departments to increase in 2014, compared to only 12% who expected pharmacist staffing to climb last year.

According to 24% of survey respondents, pharmacy technician staffing numbers are also expected to climb in 2014. About 64% expect pharmacy tech levels to remain the same in 2014, and 8% expect them to decline.

Improving patient care

Some of the big concerns on the minds of hospital pharmacists include continuing drug shortages, the impact of the Affordable Care Act, cutbacks in state Medicaid reimbursement, FDA's crackdown on compounding facilities, and penalization of hospitals for readmissions within the 30-day discharge period **(Figure 3)**.

The top five actions that hospital pharmacies took in 2013 to improve patient care **(Figure 4)** were:

1. Intensified efforts to reduce drug errors
2. Steps to document pharmacist interventions
3. Initiatives to reduce hospital-acquired infections
4. Reconciliation of medications for incoming and outgoing patients
5. Encouragement of certification of pharmacy technicians

The top five actions that respondents expect hospital pharmacies to perform in 2014 to improve patient care are the same as last year, except that medication reconciliation moves up to third place and actions to reduce hospital-acquired infections moves to fourth place.

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MEDICATION SAFETY Tracey Walker, Contributing Editor

Antipsychotics increase T2DM risk for children and young people

Children and young people taking antipsychotics appear to be three times more likely to develop type 2 diabetes, according to a study published by *JAMA Psychiatry*, a *JAMA* Network publication.

Large cohort showed significant risk

In a retrospective cohort study of the Tennessee Medicaid program that surveyed 28,858 recent initiators of antipsychotic drugs and 14,429 matched controls, William V. Bobo, MD, MPH, of the Vanderbilt University School of Medicine, Nashville, found a threefold risk of new-onset, treated, type 2 diabetes for children and young people from 6 to 24 years of age who were prescribed antipsychotic drugs, compared with a matched control group of patients who initiated other psychotropic medications.

The cohort excluded patients who had previously received a diagnosis of diabetes, schizophrenia, or other conditions for which antipsychotics are generally recognized as the only therapy.

The control group medications included mood stabilizers (e.g., lithium), antidepressants, psychostimulants, μ-agonists (for diagnosed attention-deficit/hyperactivity disorder or other behavior problems), and benzodiazepines (with psychiatric diagnosis).

During follow-up, researchers noted 106 incident cases of type 2 diabetes (18.9 cases per 10,000 person-years). The mean age of the patients was 16.7 years, and 37% of participants were male.

Use of antipsychotic drugs was associated with a threefold increased risk of type 2 diabetes (hazard ratio [HR], 3.03 [95% CI=1.73–5.32]), which was apparent within the first year of follow-up (HR=2.49 [95% CI=1.27–4.88]). The increased risk remained for up to one year after antipsychotic use was discontinued (HR=2.57) the study reported.

Need for caution

"This study was motivated by reports of increased type 2 diabetes risk associated with some antipsychotic drugs in adults, and clinical studies in youth showing adverse changes in markers of type 2 diabetes risk, such as weight gain, during treatment with some antipsychotics," said Bobo.

"Our findings highlight the need for caution when considering antipsychotics for non-primary indications, and to weigh risks and benefits of antipsychotic treatment for every case, factoring in the potential for treatment-emergent type 2 diabetes," Bobo said. "If antipsychotic treatment is deemed the best option among all reasonable choices, frequently assessing body weight and checking glucose and lipid levels is needed." DT

Use of antipsychotic prescriptions in nursing homes declines

Eleven states have reduced by at least 15% the use of antipsychotic prescriptions in nursing-home residents, meeting a partnership goal set by the Centers for Medicare and Medicaid Services (CMS) last year.

In 2012, CMS introduced the National Partnership to Improve Dementia Care, with a goal of reducing antipsychotic drug use by 15% by the end of this year. Data released on the government website Nursing Home Compare (*www.medicare.gov/nursinghomecompare*) by CMS demonstrated that the goal was met or exceeded by Alabama, Delaware, Georgia, Kentucky, Maine, North Carolina, Oklahoma, Rhode Island, South Carolina, Tennessee, and Vermont.

More patient-centered treatment

The nursing homes using fewer antipsychotics are providing more patient-centered treatment for dementia and other behavioral healthcare, according to data posted at Nursing Home Compare. In 2010, the data showed that more than 17% of nursing home residents had received daily doses of antipsychotic medications that exceeded recommended levels.

"This important partnership to improve dementia care in nursing homes is yielding results," said Dr. Patrick Conway, CMS chief medical officer and director of the Center for Clinical Standards and Quality. "We will continue to work with clinicians, caregivers, and communities to improve care and eliminate harm for people living with dementia."

The data also show that long-term nursing-home residents have benefited from the initiative, as the national prevalence of antipsychotic use in this patient population has been reduced by 9.1% in the first quarter of 2013, compared to the last quarter of 2011. Also, about 30,000 nursing home residents in the United States are no longer receiving these medications.

For additional information about the Partnership efforts, visit the website Advancing Excellence in America's Nursing Homes (*www.nhqualitycampaign.org*). DT

– Julia Talsma, Content Channel Director

Pharmacists face tougher 2014

Continued from pg. 50

FIGURE 3

Challenges for hospital pharmacists in 2014

1. Continuing drug shortages
2. Impact of the Affordable Care Act
3. Cutbacks in state Medicaid reimbursement
4. FDA's crackdown on compounding facilities
5. Hospital penalization for readmissions within 30-day discharge period

Source: Drug Topics' 2014 Business Outlook Survey

FIGURE 4

Top five actions taken by hospital pharmacies in 2013 to improve patient care

1. Intensified efforts to reduce drug errors
2. Steps to document pharmacist interventions
3. Initiatives to reduce hospital-acquired infections
4. Reconciliation of medications for incoming and outgoing patients
5. Encouragement of certification of pharmacy technicians

Source: Drug Topics' 2014 Business Outlook Survey

Satisfaction with associations

Approximately 40% of hospital pharmacists surveyed said they were satisfied with the pharmacy associations, up from only 35% last year. Some pharmacists stated that they were pleased with the work of the American Society of Health-System Pharmacists (ASHP), because the society is fighting for the role of pharmacists in delivering healthcare and is an excellent resource for drug shortages.

"ASHP works well with the FDA and Congress to help refine legislation to improve regulatory requirements," noted one hospital pharmacist. "ASHP and CSHP have been very active and vocal in events and legislation around the new compounding law and obtaining provider status for pharmacists," said another.

Some respondents worried that the number of new pharmacy graduates is leading to an oversupply of pharmacists. "Organizations have not addressed the oversupply [of pharmacists]. This should have been addressed 5+ years ago," said one pharmacist. "With the cutbacks we encountered this year, I did not see any assistance from our organizations," another pharmacist said.

Advocacy for provider status is necessary, said a pharmacist. Another respondent agreed: "Bottom line is, we need provider status. Without this, pharmacy cannot be recognized or participate on a meaningful level in patient care." DT

MEDICATION SAFETY Julia Talsma, Content Channel Director

High-dose isotretinoin reduces risk of acne vulgaris relapse

Higher doses of isotretinoin can effectively treat patients with acne vulgaris and reduce the relapse rate without significantly increasing adverse events, according to a recent report published in *JAMA Dermatology*.

Rachel C. Blasiak, MD, MPH, and her colleagues from the department of dermatology, School of Medicine, University of North Carolina at Chapel Hill, reviewed the medical records of patients at their institution and discovered that lower doses of the drug were associated with higher relapse and retrial rates. The researchers then conducted a prospective observational study of 180 patients with severe nodular-cystic acne, to determine the effectiveness and safety of higher cumulative doses of isotretinoin (220 mg/kg or more).

Of the 180 patients, 116 (64%) completed the study and follow-up survey 12 months after the treatment. Approximately 52% were women, the mean age was 19.3 years, and the majority of participants were white (74%). The mean cumulative dose of isotretinoin was 264.3 mg/kg, with a mean treatment period of 6.3 months. In the lower-dose group, the mean cumulative dose was 170.8 mg/kg, and in the higher- dose group, the mean cumulative dose was 309.8 mg/kg. Treatments began August 1, 2008 and continued through August 31, 2009.

Results

At the time of the 12-month follow-up, the relapse rate for patients in the high-dose group was lower (26.6%) than that of patients in the low-dose group (43.8%), after adjustment for age, sex, race, treating physician, and treatment duration. Most patients (97%) reported in the survey that their condition had improved with the isotretinoin treatment, and more than 55% did not need any further treatments with acne medication. At the 12-month follow-up, approximately 25% were treated with topical prescriptions, almost 15% used an over-the-counter medication, 1.7% were receiving an oral antibiotic, and 0.9% were being retreated with isotretinoin.

"Of the patients in the lower-dose group, 42.3% were given a prescription for another acne medication after completing isotretinoin compared with 28.1% in the high-dose group," Blasiak wrote. "In the lower-dose group, 12.8% of patients reported using over-the-counter acne treatment compared with 16.2% of patients in the high-dose group. This difference was not statistically significant (P=.23)."

Adverse events

In the study, 14% of patients had laboratory abnormalities, with most occurring in the higher-dose group. Elevated liver enzyme levels were seen in the higher-dose group, with 6.4% having elevated aspartate aminotransferase (AST) levels and 1.3% having elevated alanine aminotransferase (ALT) levels. In this higher-dose group, 1.3% also had elevated cholesterol levels and 11.5% had elevated triglycerides. In the lower-dose group, 5.3% had elevated triglycerides.

Other adverse effects during treatment included cheilitis and xerosis, which was reported by most of the patients in both treatment groups. Patients in the higher-dose group also reported retinoid dermatitis at higher rates (53.8%) than those of the patients in the lower-dose group (31.6%). Systemic effects included arthralgias, myalgias, and epistaxis.

After the 12-month follow-up, patients continued to report cheilitis, xerosis, and headaches, with both groups experiencing similar rates.

"At the 12-month follow-up, the percentage of patients reporting rash decreased to less than 10%, with no statistically significant difference between the dosing groups, suggesting that isotretinoin has a transient, dose-dependent effect," Blasiak wrote.

Most patients (97%) reported that their condition had improved with the isotretinoin treatment, and more than 55% did not need any further treatments with acne medication.

"At one year after completion of isotretinoin therapy, we found that patients in the high-dose group had a significantly decreased risk of relapse, which was defined as the need for prescription acne medication. Our overall rate of retrial or retreatment with a second course of isotretinoin was so low that we are unable to draw conclusions about the effect of dose on retrial rate," she concluded. DT

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NEW DRUG REVIEW Kathryn Wheeler, PharmD

FDA approves new once-daily treatment option for HIV

FDA approved dolutegravir (Tivicay, GlaxoSmithKline) in August 2013, for treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older and weighing at least 40 kg, as part of combination antiretroviral therapy. Dolutegravir is an integrase strand transfer inhibitor (INSTI), which prohibits HIV-1 virus multiplication by interfering with HIV integrase, an enzyme required for viral replication. Dolutegravir is indicated for treatment of both INSTI-naïve and INSTI-experienced adults, but is indicated for pediatric patients only if they are INSTI-naive. A new, once-daily option, dolutegravir may allow improved personalization of a patient's medication regimen.

Efficacy

FDA based its approval of dolutegravir for adults on four Phase III trials. In the studies, patients received dolutegravir or raltegravir, plus additional appropriate antiretroviral therapy.

Two trials, SPRING-2 (n=822) and SINGLE (n=833) evaluated once-daily dolutegravir in INSTI treatment-naïve patients. By 48 weeks, dolutegravir demonstrated statistically equal or superior virological suppression, achieving <50 copies/mL of HIV-1 RNA in participants, vs. raltegravir comparison regimens.

Use of dolutegravir in treatment-experienced patients was investigated in two studies, SAILING (n=719) and VIKING-3 (n=183). In both studies, the addition of dolutegravir to patients' background therapy improved virologic suppression at 24 weeks. VIKING-3 investigated the use of twice-daily dolutegravir in patients with multidrug-resistant infection, including resistance to other approved integrase inhibitors (raltegravir, elvitegravir). Subjects with INSTI resistance Q148 and two or more additional INSTI resistance substitutions demonstrated poor virologic response with the addition of twice-daily dolutegravir treatment to their background regimen.

FDA based its approval for use of dolutegravir as part of combination antiretroviral therapy in pediatric patients ≥12 years of age and weighing a minimum of 40 kg on a 24-week open-label trial of INSTI-naïve participants. Findings were similar to those for adults: At week 24, 70% of participants taking dolutegravir demonstrated viral suppression by achieving a viral load of <50 copies/mL, with improved CD4+ cell count compared to baseline levels. Dolutegravir therapy has not been studied in INSTI treatment-experienced pediatric patients and is not indicated for this patient population.

Safety

In trials, dolutegravir was well tolerated. The most common adverse reactions occurring with moderate-to-severe intensity and a frequency of at least 2% were headache and insomnia. Rare but serious adverse effects demonstrated with this therapy include redistribution or accumulation of body fat, immune reconstitution syndrome, and hypersensitivity reactions. Patients who have experienced a serious hypersensitivity reaction should discontinue the medication and avoid rechallenge with the drug to prevent progression to a life-threatening reaction. Patients with hepatitis B and/or C co-infection may be at increased risk for worsening liver enzyme elevations. Baseline laboratory tests should be performed before therapy is initiated and should be monitored periodically throughout treatment. Dolutegravir should be prescribed to geriatric patients with caution, as this group was not represented in trials sufficiently to permit identification of differences in response to the medication. Patients taking dofetilide should not take dolutegravir. This combination is contraindicated due to the increase in dofetilide levels and the potential for serious adverse effects. Dolutegravir is classified as pregnancy category B.

Dosage

In adult patients without INSTI resistance, the daily dose of dolutegravir is 50 mg orally. Dolutegravir 50 mg twice daily is recommended for patients with INSTI resistance. The recommended dosage for pediatric patients is 50 mg daily. There are no dosing adjustments necessary for patients with renal or hepatic impairment. There are several clinically significant drug interactions that require dosing adjustments or avoidance of coadministration. Strong inducers of CYP3A4 and UGT1A1 may reduce plasma concentrations of dolutegravir and necessitate a dose adjustment. The full prescribing information provides a chart of interactions with clinical comments and recommendations. Dolutegravir may be taken with or without food but should be administered two hours before or six hours after administration of polyvalent medications. Dolutegravir is highly plasma protein-bound (98.9%). DT

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ANTICOAGULATION THERAPIES Anna D. Garrett, PharmD, BCPS

Dabigatran vs. warfarin in patients with mechanical heart valves

Patients with mechanical heart valves are at high risk for thrombotic events and require life-long treatment with anticoagulation. Warfarin has historically been the drug of choice for these patients, but the development of target-specific anticoagulants has raised the question of possible use in this population.

A recent phase 2 dose-validation study included two populations of patients: those who had undergone aortic or mitral-valve replacement within the past seven days and those who had undergone such replacement at least three months earlier.

Patients were randomly assigned in a 2:1 ratio to receive either dabigatran or warfarin. Selection of the initial dabigatran dose (150, 220, or 300 mg twice daily) was based on kidney function. Doses were adjusted to obtain a trough plasma level of at least 50 ng/mL. The warfarin dose was adjusted to obtain an international normalized ratio of 2-3 or 2.5-3.5 on the basis of thromboembolic risk. The primary end point was the trough plasma level of dabigatran.

The trial was terminated prematurely after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group.

In the as-treated analysis, either dose adjustment or discontinuation of dabigatran was required in 52 of 162 patients (32%). Ischemic or unspecified stroke occurred in 9 patients (5%) in the dabigatran group and in no patients in the warfarin group. Major bleeding (all of which was pericardial) occurred in seven patients (4%) and two patients (2%), respectively.

Source: Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. *2013;369:1206–1214.*

ASCO updates recommendations for VTE prophylaxis, treatment for patients with cancer

A 2013 update by the American Society of Clinical Oncologists adds two new recommendations for VTE prophylaxis and cancer.

The first focuses on communication between the patient and provider, and stresses that all patients with cancer be educated about the risks of VTE and given clear information about its signs and symptoms. Two recent patient surveys found that fewer than 50% of patients are aware that malignancy carries increased risk of VTE.

The second new recommendation suggests that patients with cancer be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter.

Slight changes were made to the remaining recommendations after the panel considered all evidence published since the guidelines were issued in 2007. Routine use of thromboprophylaxis is still not recommended for ambulatory patients, despite trials that have shown benefit, because it is not cost-effective. The exception to this is for multiple myeloma patients who are receiving thalidomide or lenalidomide along with chemotherapy and/or dexamethasone.

Source: Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. *2013:2189–2204.*

Major dabigatran bleeding events require less intensive management

A recently published comparison of the management and prognosis of patients with major bleeding events on warfarin or dabigatran concluded that patients treated with dabigatran required less intensive management.

Two independent investigators reviewed bleeding reports from 1,034 individuals with 1,121 major bleeds. Patients with major bleeds on dabigatran were older, had lower creatinine clearance, and more frequently used aspirin or nonsteroidal anti-inflammatory agents than did those on warfarin.

The 30-day mortality after the first major bleed tended to be lower in the dabigatran group (9.1%) than in the warfarin group (13.0%). Major bleeds in dabigatran patients were more frequently treated with blood transfusions (61%) than bleeds in warfarin patients (42%) and less frequently with plasma (dabigatran, 19.8%; warfarin, 30.2%). Patients who experienced a bleed had shorter stays in the intensive care unit if they had previously received dabigatran (mean 1.6 nights), compared to those who had received warfarin (mean 2.7 nights).

Source: Majeed A, Hwang H, Connolly SJ, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. Circulation. *2013;CIRCULATIONAHA.113.002332; published online before print, September 30, 2013.* DT

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EDUCATIONAL OBJECTIVES

Goal: To enable pharmacists to discuss the impact of adherence and health maintenance in providing medication therapy management for patients with multiple sclerosis (MS).

After participating in this activity, pharmacists will be able to:

- Identify barriers to medication adherence in patients being treated for MS
- Describe methods for optimizing medication adherence in MS
- Recognize cost-mitigating strategies in treatment of MS
- Identify appropriate resources for pharmacists in managing patients with MS
- Discuss health maintenance recommendations for patients with MS

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

ACPE #0009-9999-13-096-H01-P

Grant Funding: None

Activity Fee: There is no fee for this activity.

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Expiration date: 12/10/2015

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IMAGE: THINKSTOCK / ISTOCK

Medication therapy management considerations for improving patient adherence and health maintenance in multiple sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic autoimmune disease resulting in neural demyelination and chronic disability. Disease-modifying therapies (DMTs) are used to slow disease progression of the disease and minimize the number and severity of disease flares; however, DMTs are expensive, have a wide range of potential adverse drug reactions associated with their use, and may not provide measurable improvements in patient's quality of life. As a result, nonadherence early in therapy is a common reason for treatment failure in patients with MS. Pharmacists can play a critical role in improving patient outcomes in MS by recognizing early signs of nonadherence and identifying the causes in individual patients. Pharmacists can minimize the risk of nonadherence through targeted patient education, management and prevention of adverse events, and implementation of cost-mitigation strategies. Pharmacists may also play an active role in recommending appropriate non-pharmacologic and pharmacologic health maintenance plans, including dietary and exercise regimens and vaccinations. Through education and referral, pharmacists may help maintain the needs of patients with MS and improving patient outcomes and quality of life.

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Editor's note: This is the second article in a two-part series. Last month, we published "Improving patient outcomes in multiple sclerosis: Considerations for medication therapy management."

Multiple sclerosis (MS) is a chronic autoimmune disease resulting in neural demyelination and chronic disability. The onset of MS occurs typically between 20 and 50 years of age, suggesting that the duration of disability and lifetime cost of care is often much greater than that for other more common neurologic diseases beginning later in life.[1-3] It is difficult to assess the total cost of MS to the healthcare system; however, estimates from health insurance plans and patient surveys suggest that direct treatment costs per patient range from approximately $12,000 to $30,000 annually.[3,4] Additional data indicate that the cost of a single exacerbation may approximate $250 to $13,000, depending on the severity of the exacerbation.[5] Moreover, it is important to note that these estimates are from patient care data from the early 2000s. With the recent approval of multiple new and costly disease-modifying therapies (DMTs) for treatment of MS, these estimates may be much greater for today's patients. One of the best methods for reducing the cost of care in MS is to improve patient adherence to therapy over time.[6] Pharmacists providing medication management services are in a unique position to positively impact patient adherence and ultimately minimize costs to the patient and the healthcare system. This is the second article in a two-part series aimed at defining the role of medication therapy management (MTM) in improving outcomes for patients with MS.

Adherence and persistence in MS

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Special Interest Group defines adherence as the percent of medication doses over a given time frame that are taken as directed by the prescriber.[7] In contrast, persistence is defined as the total number of days that a patient takes a medication over a given time frame. Both adherence and persistence have an impact on patient outcomes in MS and may ultimately impact cost of care. There is limited evidence evaluating the rate of adherence and typical persistence patterns for patients using DMTs in the treatment of MS; however, current data suggest that adherence rates among these patients can be low, although the rates with newer therapies are not available. A review of numerous studies evaluating the use of interferon products and glatiramer acetate suggests that the rate of adherence ranges between 41% and 88%, but these rates could not be linked to an individual agent or route of administration.[8] Additionally, in a study aimed to evaluate the reasons for nonadherence to DMTs, researchers found nonadherence rates between 36% and 39%, providing a more concerning picture of adherence in MS.[9] Finally, other results show that patients who stop therapy are most likely to do so in the first two years of therapy.[10]

TABLE 1

REPORTED REASONS FOR NONADHERENCE TO DMTS

- Forgetting to take medication
- Unrealistic expectations for medication
- Medication fatigue
- Adverse drug reactions (fatigue, injection site reactions)
- Depression
- Injection fear or phobia
- Cost
- Lack of benefit from medication
- Complexity of regimen
- Lack of support

Abbreviation: DMTs, disease-modifying therapies

Source: Ref 9,10

Reasons for medication nonadherence are provided in **Table 1**.[9,10] These reasons, however, will vary by patient.

Forgetting to take medication. Because patients are far more likely to become nonadherent or stop DMTs early in therapy, pharmacists must be diligent and proactive in educating patients about the importance of adherence as soon as these therapies are initiated. Targeted discussions about the goals that can be reached with DMTs, appropriate expectations for patients receiving DMTs, and management of mild adverse events can play a major role in preventing nonadherence, but it is important to recognize that the most common reason for nonadherence to DMTs is forgetfulness.[9] Pharmacists may utilize the same tools used in helping patients with other disease states overcome this problem. Some common methods for helping patients remember to take their medications include use of pill boxes when utilizing oral therapies, such as fingolimod, teriflunomide, and dimethyl fumarate. For self-injected therapies, such as glatiramer acetate, patients may need to utilize specific reminders and memory aids such as alarms and paper or electronic calendar tools, or simply find ways to associate the administration of the drug with another common task such as brushing their teeth prior to bedtime. Similarly, for medications administered in an infusion center, patients may benefit from calendar reminders and associations with specific events. Further, patients may

One of the best methods for reducing the cost of care in MS is to improve patient adherence to therapy over time.

TABLE 2

MANAGEMENT AND PATIENT EDUCATION FOR ADRS WITH DISEASE-MODIFYING THERAPIES

Drug therapy	Adverse reaction	Management strategies
Interferon beta	Injection-site reactions and necrosis	Ice injection site up to 15 min prior and 15 min after injection Allow product to come to room temperature before injecting Topical hydrocortisone 1% may be used after administration Rotate injection sites when possible (inject in thighs or buttocks) Use aseptic technique Wash hands thoroughly Clean injection site with alcohol or soap and water Acetaminophen or NSAID dosing prior to injection
	Flu-like symptoms	Ensure appropriate titration of therapy (25%-50% of target dose for 2 wk before maximizing to full dose) Administer NSAIDs starting immediately prior to and for 24 hr post injection Counsel patient that symptoms may resolve with continued use (3-6 mo)
	Depression	Depression unlikely to resolve with continued use Initiate antidepressant, when needed, preferably SSRI Refractory depression: Consider a different DMT
Glatiramer acetate	Injection-site reactions	Ice injection site up to 15 min prior, up to 15 min after administering injection Rotate injection sites to 1 of following: Back of upper arm, within 2 in of naval, area on side above hip, front of leg ≥ 2 in above knee and 2 in below groin Topical anesthetics may be used
	Systemic reactions (flushing, palpitations, shortness of breath, chest tightness)	Associated with any dose With recurrent episodes, may decrease dose by 75% for week following reaction, then return to full dose
Natalizumab	Signs and symptoms of PML: sudden vision loss, loss of strength, difficulty concentrating NOTE: Symptoms may mimic those of a relapse, so patients must contact physician immediately to avoid missed diagnosis of PML	Therapy must be stopped if PML suspected
	Hypersensitivity reactions	Stop infusion and give diphenhydramine Give IV steroids
Dimethyl fumarate	Flushing Gastrointestinal upset	Patients may take with food to minimize these effects Both will likely resolve with continued use

Abbreviations: ADRs, adverse drug reactions; DMT, disease-modifying therapy; IV, intravenous; min, minutes; MS, multiple sclerosis; NSAID, nonsteroidal anti-inflammatory drug; PML, progressive multifocal leukoencephalopathy; SSRI, selective serotonin reuptake inhibitor.

Source: Ref 11-18

find it beneficial to involve family members or caregivers in helping them to remember their medications. This can provide the patient with both the necessary reminders and a greater sense of support from loved ones. In addition, family members may appreciate the ability to assist with reminders as this can give a sense of empowerment to those who are unsure how to best help a loved one with MS.

Unrealistic expectations, lack of benefit, medication fatigue. DMTs should be initiated in all patients who have a confirmed diagnosis of MS, and the goal of therapy is to minimize or stop disease progression and prevent or slow the risk of long-term disability. A great deal of data support that these agents can be effective in decreasing the number and severity of exacerbations as well as decreasing the risk of permanent disability after each attack. Many DMTs, however, have been shown to have little or no impact on the quality of life in a patient with MS. Therefore, much like patients with type 2 diabetes, patients with MS may not immediately recognize the benefit of maintaining treatment with DMTs. If patients are also experiencing significant adverse events while on therapy, the obvious decision for many patients will be that the benefit is not

worth the price. This may ultimately result in patients stopping therapy due to a perceived lack of effect.

To combat this reason for nonadherence or therapy cessation, the pharmacist should initiate discussions early about what a patient may expect from DMTs. It is important to explore the patient's current perceptions and make corrections to unrealistic expectations. Pharmacists must acknowledge that patients may see no benefit and emphasize that relapses and exacerbations of MS may, and likely will, still occur while on DMTs. Emphasis should be placed on the role of preventing progression rather than curing existing symptoms. Pharmacists can help educate patients by stressing that therapy will help maintain the current functional status and diminish the severity of relapses. It can be helpful to work with patients to identify realistic short-term and long-term personal goals, as these may be a driving force in helping patients maintain uncomfortable, inconvenient, and costly therapies. This can also be a beneficial strategy in assisting patients who are experiencing therapy fatigue. Many patients with MS are on multiple medications with a wide array of adverse effects. This can lead to frustration with therapy as patients may initially feel healthier after discontinuing therapy than while on therapy. As with helping patients remember to take medications, having family members and caregivers involved in the discussion may also improve outcomes. Family members who are well educated about the disease state and therapies may be a great source of consistent support and reminders when the burden of therapy threatens the patient's adherence.

Adverse drug reactions. Adverse drug reactions may also play a significant role in whether a patient continues with therapy. **Table 2** identifies specific strategies in helping patients overcome more common or inconvenient adverse effects with therapies.[11-18] If self-management is not appropriate, pharmacists can encourage the patient to contact the prescriber immediately to avoid or minimize delays in therapy.

Most common adverse events reported as reasons for discontinuation are fatigue, depression, and flu-like symptoms, specifically with interferon therapies. All of these adverse effects are common and can be managed both through nonpharmacologic therapies and appropriate pharmacologic management.

Fatigue is a symptom that many patients report both as a result of their MS and their medication therapy. Patients may lessen the impact of this often unavoidable problem by preparing and anticipating times of increased fatigue. To avoid worsening symptoms, patients can be educated about the benefits of having a scheduled, restful night of sleep. Consistent bed times and wake times may help prevent compounding fatigue with too little sleep. Taking breaks periodically during a busy work day and avoiding excess stress can be helpful. Maintaining a healthful diet and regular exercise routine may also help maintain appropriate baseline energy levels. In addition, patients may wish to schedule medications that worsen fatigue at a time of day or week that allows for more flexibility. For example, if a patient is consistently fatigued after a monthly natalizumab infusion, they can seek to schedule the infusion prior to a weekend at home or prior to less busy days at work.

TABLE 3

ADHERENCE ASSESSMENT TECHNIQUES

- Patient inquiry/self-reports
- Monitoring efficacy of therapy
- Monitoring for significant decrease in adverse effect
- Caregiver report
- Patient medication/adverse effect diaries
- Prescription refill records for non-DMT and/or DMT for overall adherence

Abbreviation: DMT, disease-modifying therapy.

Source: Ref 19

Several predictors of medication adherence have been identified in patients with MS, including high sense of self-efficacy, feelings of hope, and high self-esteem.

Also of particular importance is educating about and recognizing signs and symptoms of depression. Depression is often seen in conjunction with MS, but its frequency and severity may be impacted through concomitant use of interferon products. Patients should be educated on initiation of therapy and frequently monitored both by family/caregivers and healthcare professionals. Use of common depression assessment tools or inventories, such as Beck's Depression Scale, may be an appropriate screen for each patient encounter. Patients can also benefit from specific education on recognizing signs and symptoms such as irritability, withdrawal from social situations,

Pause&Ponder

How might your pharmacy be better equipped to fill the educational needs of a patient with MS?

loss of focus or concentration, deep sadness, and thoughts of suicide. If patients or caregivers suspect depression, an immediate referral to a physician on the healthcare team is warranted. In addition, both patients and caregivers may benefit from ongoing cognitive behavioral therapy as a means of managing the stress of chronic illness.

Injection fear/anxiety. Fear of injections has been an area of concern for patients with MS. Until recent years, all DMTs were administered intravenously or subcutaneously. For patients who have a needle phobia or anxiety associated with injections, there are now three oral alternatives that physicians may consider. For patients who have responded to or require an injected formulation, however, needle fears can be addressed using several techniques. Often fear associated with injections can be attributed to lack of understanding of the process. Many patients may benefit sufficiently from a good education on administration techniques. Others may feel more comfortable when their caregivers are given multiple opportunities to practice injections with a healthcare provider prior to self-administration. Patients can benefit from time set aside with the pharmacist for several scheduled visits when initially learning injection techniques. For patients whose fears are not allayed by education and practice, serious consideration can be given to referral for relaxation techniques as a means of relaxing prior to and during administration.[19] Use of these techniques can be particularly beneficial when infusion is necessary and administration time can be extended.

Recognizing nonadherence

Several predictors of medication adherence have been identified in patients with MS, including high sense of self-efficacy, feelings of hope, and high self-esteem.[19] These characteristics and feelings can be fostered through frequent education and contact with healthcare providers highly interested in the success of the patient's therapy. Despite these interactions, patients may still have lapses in adherence or choose to discontinue therapy without notifying a healthcare provider. Pharmacists may be able to detect nonadherence and help correct the barriers if nonadherence is identified. Several characteristics of a patient may trigger an inquiry into nonadherence. Anytime a patient has loss of or diminished response to therapy, significant periods of absence from the healthcare setting, or nonadherence identified through refill of non-MS drugs, pharmacists should take the opportunity to discuss the role of adherence in therapy success. Direct questions that indicate a response other than yes or no can be very helpful in getting to the root of nonadherence. For example, when inquiring about medication use, rather than asking, "Have you missed your medication this month?" a pharmacist might ask, "How many times have you missed your medication this month?" By asking a question that requires the patient to quantify the number of missed doses, you provide a safer environment for discussing adherence. The latter question assumes a baseline nonadherence and takes the negative judgment off of the patient. Other means of assessing patient adherence by pharmacists are provided in **Table 3**.

Of course, no amount of questioning or education will be beneficial if the patient does not have a positive relationship with a caregiver. From the onset of MTM, pharmacists must take the opportunity to build a relationship with the patient based on mutual respect and trust. Avoid scolding or belittling tones but provide ample education based on the patient's baseline knowledge. Address all questions from the patient with respect and confidentiality, and recognize the role of the caregiver in each patient's healthcare needs. Ask clear questions from the start about what information can be stated in front of a caregiver and about how involved caregivers should be in the education and disease state management. Each patient must be treated as an individual. The pharmacist must ultimately show a desire to optimize the patient's health-related needs.

Pause&Ponder

How might you educate a patient with MS who does not wish to receive an annual flu vaccine due to risk of acquiring the flu from the vaccine?

Cost-mitigation strategies

The cost of therapy for MS can be overwhelming for patients, especially for those with suboptimal healthcare coverage. Minimizing the cost of therapy with MS, outside of DMT coverage, is best achieved through managing the patient's overall health. In addition, maintaining adherence to DMTs can be one of the most effective ways to lower the overall cost to the patient. Use of DMTs can be as much managed by the tiering of drug therapy in health coverage entities as by the neurologist recommending therapy. This may leave patients and caregivers paying a large component of the cost of medication. Whereas many neurologists will offer patients assistance with navigating patient access programs, this task cannot be assumed by the pharmacist. A pharmacist can play an active role in seeking out assistance through drug company programs specific to individual therapies. Programs are accessible through individual websites for the manufacturer or through searching the nonprofit website *www.needymeds.org*.[20]

For pharmacists, understanding the basic criteria described in each program will help them refer appropriate patients to these benefits.

Health maintenance in MS

Maintaining overall health is critical to

TEST QUESTIONS

1. What is the typical age of onset for patients with multiple sclerosis (MS)?
- **a.** 10–20 years of age
- **b.** 20–50 years of age
- **c.** 50–70 years of age
- **d.** >65 years of age
- **e.** MS is equally likely to occur in all age groups.

2. Which following statement most accurately represents the cost associated with MS?
- a. Healthcare cost to patients with MS can be best minimized by selecting the least-expensive disease-modifying therapy (DMT).
- b. Patients with MS have an estimated total annual cost of $12,000–$30,000.
- c. Adverse drug reactions are the most common reason for increase in healthcare costs to patients with MS.
- d. Each exacerbation of MS may cost a patient up to $500 annually.
- e. Healthcare costs for MS will likely decrease with the advent of new DMTs.

3. When is a patient at highest risk of nonadherence with their MS therapy?
- **a.** Within the first 2 years
- **b.** Between 2–5 years of therapy
- **c.** Between 5–10 years of therapy
- **d.** >10 years of therapy
- **e.** Adherence is equally problematic across all time frames.

4. Persistence of medication therapy is defined as:
- **a.** The number of missed medication doses over a given time frame
- **b.** The number of days a medication is taken over a given time frame
- **c.** The number of duplicate doses taken over a given time frame
- **d.** The continued use of therapy despite discontinuation by a physician
- **e.** Stopping therapy due to cost concerns

5. Adherence to medication therapy is defined as:
- **a.** The number of missed medication doses over a given time frame
- **b.** The number of days a medication is taken over a given time frame
- **c.** The number of duplicate doses taken over a given time frame
- **d.** The continued use of therapy despite discontinuation by a physician
- **e.** Stopping therapy due to cost concerns

6. The rate of adherence across all DMTs in patients with MS range between:
- **a.** Approximately 10% and 20%
- **b.** Approximately 30% and 40%
- **c.** Approximately 50% and 60%
- **d.** Approximately 80% and 90%
- **e.** 100%

7. What is the most common cause of medication nonadherence to DMTs in patients with MS?
- **a.** Adverse effects **b.** Forgetfulness
- **c.** Cost **d.** Lack of perceived benefit
- **e.** Lack of access to specialty pharmacies

Continued on pg. 64

the effective management of a patient with MS. Even though drug therapy is often a point of focus due to the multiple medications involved, broad range of adverse effects, and high cost, the importance of a healthy, well-balanced diet and exercise program must not be underestimated. Early literature on MS suggests that physical inactivity and sedentary lifestyle place patients with MS at increased risk for obesity. This has led to much research on optimizing diet and exercise for patients with MS. Investigators have found that exercise and management of stress play a role in improving functional ability and health-related quality of life. A healthy diet plays a similar role but has a stronger effect on patients with higher levels of disability.[21] Pharmacists can encourage continued maintenance of weight or weight loss through diet and exercise programs. Community resources such as local fitness centers and weight management programs can serve as places for referral for patients and can augment the education provided. In addition to the MS, it will be important to consider any concomitant disease states such as hypertension, hyperlipidemia, and type 2 diabetes when making dietary recommendations. These secondary disease states may play a pivotal role in dietary restrictions or guidelines.

Apart from the role of pharmacists in weight and health management, they play an ever-growing role in vaccine recommendations and administration. As with many autoimmune diseases, patients with MS taking DMTs may be at increased risk of infection and worsening outcomes if infection occurs. Pharmacists should encourage patients to receive their annual inactivated influenza vaccines. Live attenuated vaccines should be avoided in patients receiving most DMTs. Pharmacists may also inquire about the dates of the last pertussis vaccine and pneumonia vaccine the patient has received to ensure adequate coverage based on Centers for Disease Control and Prevention (CDC) recommendations. Up-to-date vaccine information can be obtained at *www.cdc.gov/vaccines/*.[22]

Conclusion

Patients with MS have many new options for improving overall health and preventing disease progression. As with many chronic diseases, however, patient adherence can have a huge impact on the success of treatment. Pharmacists providing medication therapy management to patients with MS have the knowledge and expertise to educate patients about minimizing this risk. In addition, frequent interaction with a pharmacist as a caring healthcare provider can help increase patient self-efficacy and self-esteem, both of which decrease the risk of nonadherence. Pharmacists may also be helpful in identifying existing nonadherence and managing prevailing barriers. Finally, through education and referral, pharmacists may help maintain the other healthcare needs of patients with MS, ultimately improving patient outcomes and quality of life.•

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Test Questions

Continued from pg. 63

8. All of the following have been identified as reasons for nonadherence except:
- **a.** Adverse effects
- **b.** Forgetfulness
- **c.** Cost
- **d.** Lack of perceived benefit
- **e.** Lack of access to specialty pharmacies

9. Patients who forget to take their DMT therapy may benefit from which of the following?
- **a.** Adherence reminders such as pill boxes or alarms
- **b.** Involvement of a caregiver in helping with adherence
- **c.** Associating medication administration with another common event, such as brushing teeth
- **d.** Education about the importance of adherence
- **e.** All of the above

10. Identify which of the following is an appropriate recommendation for self-management of injection site reactions with glatiramer acetate:
- **a.** Apply warm compresses to injection site 15 minutes prior to injection
- **b.** Allow product to come to room temperature before injecting
- **c.** Avoid topical hydrocortisone 1% after administration due to risk of diminished effect of DMT
- **d.** Choose one injection site for continued use to help build resistance to reactions
- **e.** Apply pressure to site for approximately 5 minutes after injection

11. Which of the following is an appropriate method for minimizing risk of flu-like symptoms with interferon agents?
- **a.** Ensure appropriate titration of therapy
- **b.** Administer prednisone starting immediately prior to and for 24 hour post injection
- **c.** Take half of the dose in the morning and the second half in the evening
- **d.** Apply ice to injection site 15 minutes prior to injection
- **e.** Apply warm compresses to injection site 15 minutes prior to injection

12. Which of the following is a method for minimizing fear of needles in patients receiving injectable DMTs?
- **a.** Avoidance of all intravenous products
- **b.** Use of subcutaneous rather than intravenous therapies
- **c.** Icing area 15 min prior to injection
- **d.** Use of benzodiazepines prior to administration
- **e.** Cognitive behavioral therapy

13. Which of the following is true regarding depression in patients receiving interferon therapy?
- **a.** Depression associated with interferon products is temporary and will resolve with continued use.
- **b.** Depression with interferon will not respond to treatment with medications.
- **c.** Depression with interferon therapy warrants discontinuation of therapy.
- **d.** Patients taking interferon should be screened frequently for depression.
- **e.** Patients taking interferon would benefit from therapy with St. John's Wort.

14. GG is a 32-year-old female diagnosed with MS. She comes into your pharmacy for follow-up with her medication therapy management appointment. She reports having difficulty remembering to take her fingolimod. Which of the following is an appropriate response for GG?
- **a.** GG should be counseled that adherence is important for the DMT to improve quality of life.
- **b.** Missed doses may not be a concern with this agent because of its extended half-life.
- **c.** GG may benefit from use of an alarm to remind her to take her medications.
- **d.** GG is clearly unable to take daily medications, so she should be switched to a less frequently dosed medication.
- **e.** Nonadherence to DMTs is not a concern and should be assumed for all patients.

15. Which of the following is true of fatigue associated with MS?
- **a.** Fatigue is a common symptom of MS and cannot be controlled.
- **b.** Fatigue is a common adverse effect with DMTs and cannot be controlled.
- **c.** Patients experiencing fatigue may benefit from drug holidays from DMTs.
- **d.** Regular exercise and consistent sleep patterns may combat extreme fatigue.
- **e.** Fatigue from drug therapy may be a reason for drug discontinuation.

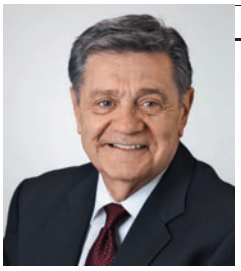
16. Which of the following is an appropriate method for assessing adherence in patients?
- **a.** Medication diaries
- **b.** Reports from caregivers
- **c.** Patient self-reports
- **d.** Refill records
- **e.** All of the above

17. KL comes to your pharmacy regularly for refills on her antihypertensive therapy. You notice that she has not been obtaining her refills regularly and express concern. KL states that her MS symptoms have been particularly severe for the past few months, so she has not been able to come in for refills. You suspect that KL may also be nonadherent with her MS medications. How should you best inquire about adherence with KL?
- **a.** Ask, "Have you missed any of your medications for MS in the past month?"
- **b.** Ask, "How many times have you missed your medication for MS in the past month?"
- **c.** Ask, "Have you been skipping your medication for MS?"
- **d.** Do not ask about adherence directly as it will be awkward for the patient.
- **e.** Do not ask about adherence as adherence should be assumed.

18. What is the best method for minimizing costs associated with therapy for MS?
- **a.** Changing DMT to a less-expensive DMT
- **b.** Only recommend drugs that are tier 1 in a prescription coverage plan
- **c.** Optimize adherence and persistence of drug therapy
- **d.** Utilize drug holidays to minimize frequency of expensive medication use
- **e.** Discontinue the DMT as this will not improve quality of life

19. Which of the following is true regarding health maintenance in patients with MS?
- **a.** Patients with MS are less likely to have problems with obesity than patients without MS.
- **b.** Patients with MS will most benefit from a diet low in potassium.
- **c.** Patients with MS will most benefit from a diet high in protein.
- **d.** Exercise may improve health-related quality of life.
- **e.** Exercise is not a realistic expectation for patients with MS.

20. Which of the following is true regarding vaccinations for patients with MS?
- **a.** Patients with MS receiving DMTs are not candidates for vaccinations due to increased risk of adverse effects from the vaccine.
- **b.** Patients with MS receiving DMTs are not candidates for vaccinations because they are less likely to develop immunity.
- **c.** Patients with MS receiving DMTs should receive the live attenuated flu vaccine annually.
- **d.** Patients with MS receiving DMTs should receive the inactivated influenza vaccine annually.
- **e.** Patients with MS should receive 2 doses of the flu vaccine to ensure full response to vaccine.



ETHICAL DECISION-MAKING IN PHARMACY Kenneth R. Baker, BS Pharm, JD

Justice in the distribution of health resources

I teach a course titled "Ethical Decision-Making" at Midwestern University College of Pharmacy in Glendale, Arizona. Nonetheless, I confess I have struggled to understand how pharmacists can in any practical way assume responsibility for the eighth article of the Pharmacist Code of Ethics (*http://www.pharmacist.com/code-ethics*).

That one comes last, and it is sometimes easy merely to recite the words without giving too much thought to what they mean for pharmacists in daily practice and life. The eighth article reads:

A pharmacist seeks justice in the distribution of health resources.

When health resources are allocated, a pharmacist is fair and equitable, balancing the needs of patients and society.

It seems unlikely that it simply means we should allocate a drug that is temporarily in low supply among patients throughout the period of shortage. Does it mean, as seems more likely, that a patient with a minimum-wage job and no health insurance should have access to medications that are the same as — or at least similar to — those available to our other patients?

A different type of commodity

Healthcare is unlike most other commodities. In most cases, medication and medical treatment are not luxuries. Patients use healthcare services not because they want to, but because they must.

Healthcare, including the distribution of prescription drugs, is allocated upon the basis of one's ability to pay — or to get someone else to pay. If someone has no money, of course, welfare provides. If patients have a lot of money, meaning they earn livable wages, they have insurance.

We are now struggling with what to do with those in the middle — those who make too much money to receive welfare but not enough to be able to choose both food and drugs.

Providers in the middle

We are arguing in this country about the Affordable Care Act, passed by one political party and opposed by the other. Those who support the law are trying desperately to implement what even they agree is a less-than-perfect system of health insurance. Those opposed to the ACA appear to be desperately trying to destroy it before it has an opportunity to work.

Pharmacists and the healthcare community are also in the middle. Few pharmacists believe that patients who can be treated with the wonder drugs we oversee should have to go untreated or die because they are neither poor enough nor rich enough to receive them. Nor can we, as business operators, fill prescriptions without payment. To say, "Let charities provide" is a haphazard and inefficient answer.

In the United States, the system of payment for healthcare services, meaning primarily insurance, has grown haphazardly, without an overall plan or goal. If an efficient system of payment for healthcare had been planned, it is unlikely that the companies we work for would have been put in charge of deciding which and how much insurance we need. Rather, using principles of the free market, we each would have been able to make those decisions for ourselves. Instead there evolved an employer-based system of socialized medicine in which the centralized planning is performed by the boss.

Professional responsibility

Whether we as pharmacists support the ACA as the best answer available or oppose it as the worst answer available, we should work together to solve the underlying problems. If the ACA isn't the best answer, it is incumbent upon us either to help to fix it or to work to implement an alternative that is better.

Perhaps government should not be a major part of the solution. If not, what should be?

If this eighth article of the pharmacists' ethical code has meaning, it must lead us to agree that all patients need access to the essential prescription drugs required to treat their symptoms.

We as pharmacists should raise our voices, individually or collectively, demanding either to fix the problems with the ACA or to propose workable alternatives. DT

These articles are not intended as legal advice and should not be used as such. When a legal question arises, the pharmacist should consult with an attorney familiar with pharmacy law in his or her state.

Ken Baker *is a pharmacist and an attorney consulting in the areas of pharmacy error reduction, communication, and risk management. Mr. Baker is an attorney of counsel with the Arizona law firm of Renaud Cook Drury Mesaros, Pa. Contact him by e-mail at ken@kenbakerconsulting.com.*

LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

California Governor Brown vetoes biosimilar substitution bill

Battles continue over pharmacist substitution procedures

In October 2013, Governor Jerry Brown of California vetoed Senate Bill 598 (SB 598). The failed SB 598 would have changed California's pharmacy law to require, in part, any pharmacy to notify the prescribing healthcare professional within five business days as to whether the prescription dispensed was a biological product or an interchangeable biosimilar. It would have permitted the pharmacy, alternatively, to document the information in an interoperable patient record system accessible by the prescriber.

Across the country

The Biologics Price Competition and Innovation Act of 2009 (BPCIA), which is included in the Affordable Care Act, provides for biosimilar substitution and interchange of biological products, as set forth in Section 351(k) of the BPCIA. Since that passage, many states have introduced legislation in anticipation of pharmacy handling of such substitution.

Notably, FDA still has not approved or accepted a biosimilar biological product or application. Nevertheless, it is widely thought that biosimilars will be treated much like traditional drugs, with branded-to-generic substitutions providing broad market penetration of generics when available. Third-party payors and PBMs are likely to welcome the reduced costs associated with biosimilars. It is thought that the marketplace will be motivated to move forward quickly on this front.

In California

California's State Assembly and State Senate passed SB 598 without issue. However, when Governor Brown received SB 598, a flurry of opposition from the marketplace hampered his approval of the bill. Several dozen marketplace stakeholders urged him to veto SB 598. The list of opposing bodies includes AARP, CalPERS, California Pharmacists Association, California Association of Health Plans, California Retailers Association, California Correctional Health Care Services, CVS Caremark, Express Scripts Inc., Kaiser Permanente, Pacific Business Group on Health, Walgreens, The Generic Pharmaceutical Association (GPhA), and nine state labor unions. GPhA argued that SB 598 would interfere with California's ability to save billions of healthcare dollars over 10 years through biosimilar substitution.

The governor's decision

Governor Brown's reasons for vetoing SB 598 were itemized in a letter to the California State Senate. It stated:

"Senate Bill 598 would effect two changes to our state's pharmacy law. First, it would allow interchangeable 'biosimilar' drugs to be substituted for biologic drugs, once these interchangeable drugs are approved by the federal Food and Drug Administration (FDA). This is a policy I strongly support.

"Second, it requires pharmacists to send notifications back to prescribers about which drug was dispensed. This requirement, which on its face looks reasonable, is for some reason highly controversial. Doctors with whom I have spoken would welcome this information. CalPERS and other large purchasers warn that the requirement itself would cast doubt on the safety and desirability of more cost-effective alternatives to biologics.

"The FDA, which has jurisdiction for approving all drugs, has not yet determined what standards will be required for biosimilars to meet the higher threshold of 'interchangeability.' Given this fact, to require physician notification at this point strikes me as premature.

"For these reasons, I am returning SB 598 without my signature."

More to come

The first year of controversy at the state legislative level is coming to a close. In general, health insurers and generic drug companies have edged out brand-name drugmakers.

The arguments surround the manner in which pharmacists are able to dispense the cheaper versions of biotechnology drugs, which are otherwise generally high-touch pharmaceuticals. Although the BPCIA calls for the approval of copycat biologics, the substitution laws that enable a pharmacist to dispense the biologic prescription are governed at the state level and enforced by a board of pharmacy. 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 a partner and head of the drug and pharmacy legal practice at Roetzel and Andress LPA. He is also vice-chairman of the Illinois State Board of Pharmacy. Contact Ned at 312-582-1676 or at nmilenkovich@ralaw.com.*

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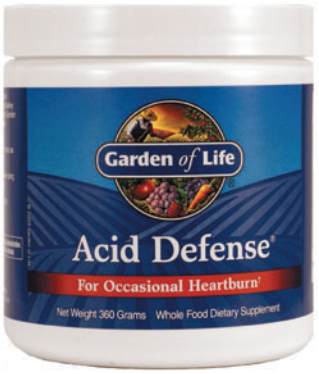

Acid Defense by Garden of Life helps relieve heartburn.

Martha Stewart Essentials for Digestive Health provides a blend of enzymes for healthy digestion.

Zantac 150 Cool Mint Tablets take aim at heartburn and acid indigestion.

PHOTOS COURTESY OF GARDEN OF LIFE / MARTHA STEWART ESSENTIALS / BOEHRINGER INGELHEIM

OTC

Good digestive health within reach

JULIA TALSMA, CONTENT CHANNEL DIRECTOR

If you want good digestive health, eat right and exercise. However, that really is not always possible; sometimes we overindulge or stray from our healthy goals. To get back on track, consumers may have to search for just the right product to quiet that upset stomach and heartburn, relieve bothersome constipation, or promote good digestive balance. Here are some helpful products to recommend to your patients.

Digestion support

According to the literature, heartburn affects about 40% of adults on a monthly basis, 7% to 30% on a weekly basis, and 7% to 10% on a daily basis. To combat this problem, Garden of Life offers **Acid Defense** for occasional heartburn relief. Its Stomach Soothe Enzyme Blend includes barley grass, beet, and carrot juice concentrates. The company suggests mixing one heaping teaspoon of Acid Defense with 8 oz of water or juice for easier ingestion.

To settle the occasional upset stomach, Nature's Sunshine offers **Stomach Comfort** tablets with calcium carbonate to help buffer acid. Other ingredients include alginic acid from brown seaweed, papaya fruit, guar gum, slippery elm bark, ginger rhizome, licorice root concentrate, and caseinate powder. For optimal pH balancing, the recommended dose is one to two tablets taken between meals.

Martha Stewart has also joined the digestive health arena, with a new supplement line that includes **Martha Stewart Essentials for Digestive Health**. The Digestive Health capsules provide a blend of enzymes to aid digestion of carbohydrates, proteins, and fats. These capsules are recommended for adults 18 years of age and older. Two can be taken daily with a meal.

For vegetarians and others seeking a gluten-free option, Country Life has developed a **Tropical Papaya** enzyme supplement, which the company says promotes healthy protein digestion. Adults can consume two to four wafers after every meal. A four-wafer serving contains 22 mg of papaya, 24 mg of mylase and protease, and 28 mg of papain.

For patients who need a strong, fast-acting product for prevention and relief of heartburn and acid indigestion, Boehringer Ingelheim has produced **Maximum Strength Zantac 150 Cool Mint Tablets**, a clinically proven formulation that contains ranitidine. The effect can be felt approximately 30 minutes after administration and may last for up to 12 hours, the manufacturer says. Individuals 12 years of age and older can take one tablet twice daily before or after eating.

Fiber options

Consumers requiring a good source of fiber can try Now Foods' **Whole Psyllium Husks**, a dietary supplement that the company calls a convenient way to increase dietary fiber intake. The bulking agent can be used daily, starting with one level teaspoon mixed in 12 oz of water or juice. The dose can gradually increase to two teaspoons, which offer 7 g of dietary fiber, 6 g of which are soluble.

Another option for adding bulk to the diet is Nature's Sunshine **Psyllium Hulls Combination**. For adults, the

Now Foods' **Whole Psyllium Husks** offer a convenient way to increase dietary fiber intake.

Nature Made's **Triple Probiotic** delivers live probiotics to the gut and supports optimal absorption.

PHOTOS COURTESY OF NOW FOODS / NATURE MADE

recommended dose is two teaspoons in water or juice. For children six years of age and older, a quarter-teaspoon can be mixed in half a glass of water or juice for daily consumption. This product contains psyllium seed hulls, hibiscus flowers, and licorice root.

Garden of Life's **Super Seed** is a whole-food formula containing flax seeds, sprouted grains, and legumes, helpful for the support of normal gut flora, regular bowel function, and overall health, the company says. Two daily servings provide half the daily value for fiber, with each serving containing six g of fiber. The company suggests mixing one scoop with any food or beverage, such as smoothies, vegetable or fruit juices, cereal, yogurt, or soup. "Super Seed was formulated to include naturally occurring soluble and insoluble fiber from carefully selected grains, seeds, and legumes that are easy on the gastrointestinal system," the manufacturer's website states. "Super Seed does not include psyllium husk, which provides no nutritional value."

Probiotics

Nature Made's **Triple Probiotic** is a blend of three probiotics and essential vitamins and minerals that help to support one's immune system, the company says. The three-layered caplet should be taken daily, two hours before or after other medications, with

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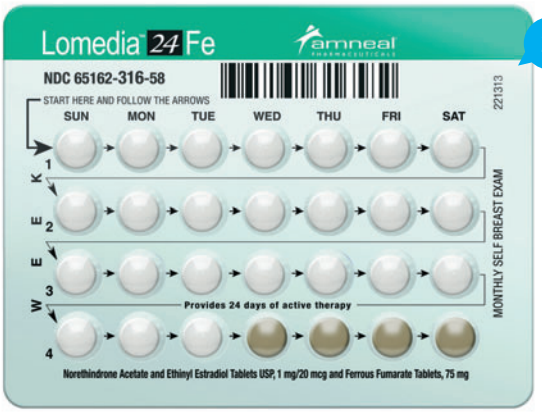
RX & OTC

New Products

JULIANNE STEIN, CONTENT CHANNEL MANAGER

1



2

RX CARE

NEW Rx

GlaxoSmithKline and Theravance have announced that **Breo Ellipta [1]**, the first once-daily prescription medicine for chronic obstructive pulmonary disease (COPD), is now available to U.S. pharmacies nationwide. A new treatment option for COPD patients, estimated at 27 million people in the United States alone, it was approved by FDA in May. The product combines the inhaled corticosteroid fluticasone furoate and the long-acting beta$_2$-adrenergic agonist vilanterol (100/25 µg). It is indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. It is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. It is not indicated for the relief of acute bronchospasm or for the treatment of asthma. Breo Ellipta labeling includes a boxed warning and a medication guide. **(us.gsk.com)**

In October, Mission Pharmacal announced the launch of **Aquoral**, a protective oral spray that moistens and lubricates the mouth for up to four hours. Dry mouth, or xerostomia, causes about 25 million Americans to experience decreased production of saliva, a condition common in older adults as well as those taking certain prescription medications. Symptoms of dry mouth include an uncomfortable dry (cottony), sticky, or burning sensation in the mouth. Dry mouth can also cause cracked lips, dry tongue, mouth sores and ulcers, mouth infections, and dental decay. Aquoral uses oxidized glycerol triesters in a patented, plant-derived, lipid-based technology designed to function similarly to human saliva, to form a protective barrier on the oral mucosa that lasts longer than water-based remedies. According to the manufacturer, even though patients need a prescription for Aquoral, it is a nondrug medical device that has been shown to be more effective and longer-lasting than an artificial saliva substitute. Aquoral will launch with a special patient savings card; to make the product more affordable to patients, the card will offer up to $75 savings on their first prescription and $40 on future refills, meaning that that most patients will pay no more than $25 for a six- to eight-week supply of Aquoral. **(www.aquoral.com)**

Actelion has announced that **Valchlor**, the first and only FDA-approved topical formulation of mechlorethamine, is now available to patients in the United States. A once-daily topical gel, the product is an alkylating drug indicated to treat patients with stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) who have received prior skin-directed therapy. An orphan drug that was acquired by Actelion in September as part of a merger with Ceptaris Therapeutics, Valchlor is priced at $2,900 per tube. At this time distribution in the United States is limited to Accredo Specialty Pharmacy, which, upon receipt of the prescription, contacts patients and arranges for mail-order delivery at an agreed-upon time, when a recipient will be available. Actelion has established Valchlor Support, an assistance program to help eligible patients successfully start and remain on Valchlor therapy. The program includes reimbursement and financial support for eligible patients, as well as disease and product information. **(www.valchlor.com)**

New generics

Next month, Amneal will launch **norethindrone acetate and ethinyl estradiol tablets, USP, 1 mg/20 µg, and ferrous fumarate tablets, 75 mg [2]**, its AB-rated generic for Loestrin 24 Fe, the manufacture of which was discontinued by Warner Chilcott in July 2013, which replaced it with a chewable product. Amneal's exclusive first-to-file generic equivalent for this brand will be sold under the name Lomedia 24 Fe. Amneal wants patients to know that they will be able to swallow the pill whole just as they did Loestrin 24 Fe. Amneal plans to sell the product to wholesalers and distributors, and direct to the trade. The company expects

Continued on pg. 72

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Good digestive health within reach

Continued from pg. 69

PHOTO COURTESY OF GARDEN OF LIFE

Primal Defense Kids by Garden of Life offers four species of probiotic cultures for children three years of age and older.

cold or room-temperature liquids, and should be taken with food. The Triple Probiotic, which has no preservatives or artificial flavors, delivers live probiotics to the gut and releases vitamins and minerals for optimal absorption of nutrients.

Advanced Enzyme Optima by Rainbow Light provides broad-spectrum plant enzymes, herbs, prebiotics, and probiotics to help with digestion by breaking down all types of food, including complex proteins and carbohydrates, says the company, and is perfect for consumption by vegetarians and vegans. Free of animal products, it contains 11 plant enzymes, such as amylase and bromelain, and a digestive blend of extra-fibrous herbs, such as ginger, peppermint, fennel, and turmeric, to alleviate any gas or bloating. *Lactobacillus sporogenes* helps promote gut health. The product has no gluten, soy, yeast, milk, eggs, nuts, fish, or shellfish.

For children who need probiotics, Garden of Life's **Primal Defense Kids** contains a four billion live cell count of four species of probiotic cultures, including *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, and *Saccharomyces boulardii*. Each has been clinically studied in children, the company states. Primal Defense Kids is safe and effective for children three years of age and older. The recommended dose is a quarter teaspoon added to food or beverage once daily, which can be increased to a half-teaspoon if needed. DT

New products

Continued from pg. 70

its new generic product to be in pharmacies the first week of January 2014. **(www.amneal.com)**

BD Rx has announced that FDA has approved the fourth drug in the BD Simplist generic product line of prefilled injectables. **Morphine sulfate injection, USP** is indicated for the management of pain not responsive to non-narcotic analgesics. The product will be available in the most common strengths: 2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL and 10 mg/mL. Production began in November, with distribution to commence early in 2014. The first three drugs in the series, all launched in the past year, are diphenhydramine hydrochloride injection, USP; metoclopramide injection, USP; and ondansetron injection, USP 4 mg/2 mL (2 mg/2 mL). BD Rx plans to launch as many as 20 to 30 drugs in the BD Simplist prefilled injectables product line in years to come, with a focus on therapeutic categories primarily used by clinicians in hospital and surgical center settings, including pain management, anesthetics, cardiovascular agents, and antiemetics. **(www.bd.com)**

NEW OTC

On January 1, 2014, American MD Labs will announce the launch of its **HA85 PUR Relief [3]** series of professional skin formulations for patients who are undergoing or recovering from chemotherapy and radiation treatments. HA85 is the first FDA-registered topical product to address the specific skin-care needs of these patients. The product assists in the process of burn relief; hydration of dry, cracked skin; and overall wound healing. The product's effectiveness derives from hyaluronan or hyaluronic acid, an essential polysaccharide that is one of the key components in which cells and fibrous constituents such as collagen and elastin are embedded in the skin. Hyaluronic acid binds 1,000 times its weight in water, which helps to control skin-tissue hydration by providing a water reservoir for the cells. HA85 also employs allantoin, a natural chemical compound, as an anti-irritant and skin protectant to help minimize damage to patients suffering from chemotherapy and radiation treatments. Allantoin also increases the water content of the extracellular matrix and promotes cell replication and wound-healing from burns. The products in the HA85 PUR Relief Professional Series will be available in both gel and spray applications. Each product produced by this brand is dermatologist-tested and -approved, and backed by independent clinical studies. The products contain no harsh chemicals, parabens, PEGs, glycols, sulfates, petrochemicals, synthetic fragrances, or artificial dyes. These products are available now through the company website; distribution will expand after the first of the year to oncology clinics, hospitals, medi-spas, pharmacies, and online websites. The price is $45, and one unit of product lasts about six weeks. **(www.purrelief.com)**

Boiron has added a new pediatric cough-cold item to its lineup. **Children's Chestal Cold & Cough**, a multi-symptom syrup formula, targets symptoms of the common cold such as nasal and chest congestion, cough, runny or stuffy nose, sneezing, and minor sore throat. Now that manufacturers of antihistamines and decongestants have relabeled their products for children four years of age and older, the company says, it provides parents with a natural alternative for children three years of age and older. **(http://bit.ly/chestal)**

NEW DEVICE

Novo Nordisk announced in November that FDA has granted 510(k) clearance for its insulin device **NovoPen Echo [4]**, the first and only pen device in the United States with half-unit dosing and a memory function that records both dose and time passed since the last injection. The company expects the pen to be particularly attractive to parents and caregivers of children with diabetes, as half-unit dose increments allow for finer adjustments, which can be particularly important for children. In addition, the company is offering removable skins of different colors to enable kids to customize their pens. The pen is made for use with NovoLog (insulin aspart [rDNA origin] injection) PenFill cartridges and will become available in the United States early in 2014. **(www.novonordisk-us.com / www.novolog.com)** DT

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JP AT LARGE Jim Plagakis, RPh

Mismanagers I have known

A CVS intern complained in an e-mail that her nonpharmacist store manager embarrassed her when she was trying to help a patient choose the appropriate solutions for use with his contact lenses. They were looking for a decongestant eye drop he could use when he was wearing his lenses.

She said, "The manager just came up to me and asked, 'What are you doing?'

"I told him and he answered, 'Not for 10 minutes, you're not. You get back in the pharmacy where you belong.' Then he told the customer that he would get Brenda to help him. Brenda is the clerk who works in OTC. She puts up the orders and dusts the shelves. What should I do? I hate pharmacy."

They're everywhere

I believe that incidents like this one, of interference with pharmacists, are more common than many of us want to admit. My career has been bedeviled by nonpharmacist store managers whose specialties were pharmacy micromanagement and pharmacist abuse.

I can't figure it out. Don't they want better bonuses? Their jobs would be easier if they trusted the pharmacists to manage the pharmacy.

My only conclusion is that they're jealous. Pharmacists make more money. To these managers, it looks as if we don't work as hard as they do. We have a regular five-day-a-week schedule, while they can be found at the store six days a week, seven days at Christmas. My advice to them is *Stop bullying the staff and go get a degree.*

Then there was Bill

One guy fought me, it seemed like every day. He would actually stutter when he tried to warn me against *wasting time* on counseling young mothers about lice.

I can't even guess how many times I looked up to find a terrified young mother standing before me, saying, "My child was sent home from school with head lice," while her body language and facial expression said,"I am a horrible mother. My child is filthy and it's my fault."

My first job was to tell her that that wasn't true. Second, I would tell her all about lice, get a package of Nix, and counsel her on its use. Third, I would offer to check her head for lice. With her permission, I ran my fingers through the hair at the nape of her neck. It was a huge relief when I found no nits. The mother would leave tear-free and smiling, and I knew I had done my job.

Bill hated this. His jaw clenched when he saw me counseling, the box of product in hand. He knew this took time when there were Rxs to process. But something else made him go ballistic. "You're going to get us hit with a sexual harassment complaint. Why the hell can't you keep your hands out of their hair?"

"Bill, you're wasting your time. I won't stop counseling my patients, and I'll always do it the way I think I should."

Take a chill pill

Bill also hated it when I helped customers with supplements and herbals. I had invested in *Tyler's Honest Herbal* by Varro Tyler, PhD, and I read it for pleasure. Tyler was a pharmacognosy professor at a time when our profession was marginalizing some really good natural medicines. Bill only relaxed when he realized that sales were often more than $100, at a gross profit of around 50%.

Still, he tried to control me. When I was advising a teenage girl about condoms rather than contraceptive creams, I thought he was going to blow a gasket. The girl had a note from her mother. Very good parenting, I think.

After a few years, lice, Plagakis, and young mothers became his poster children for rotten pharmacy practice. He didn't even know what the practice of pharmacy is really about.

Count, pour, lick and stick? Hardly. Pharmacy practice is defined by counseling. Patients can harm themselves with OTC medicines, not to mention their prescription meds.

Triage also defines our practice. When a patient (often poor) comes for help, we triage. At least we should. We ask questions and then determine whether we can help. We may have to send patients to a doctor. In rare cases, we advise them to head straight for the trauma center. That's triage, and pharmacists save the system millions of dollars a day with it.

We still haven't figured out how to get paid, but that's our own fault.

I told the intern to bide her time and always pick her battles carefully. For her manager, I suggested three easy words: *Leave me alone!* DT

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