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Drug Topics®

Voice of the Pharmacist DrugTopics.com August 2013

PAIN CONTROL IN THE ELDERLY

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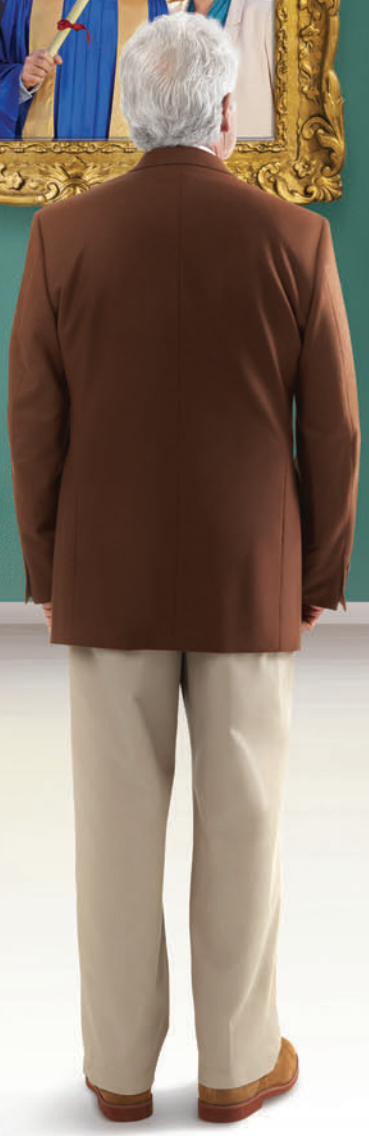
NEW

In moderate to severe Alzheimer's disease

Once-daily Namenda XR™ 28 mg+AChEI* demonstrated



Help slow symptom progression. Because there's so much to lose.

There is no evidence that NAMENDA XR or an AChEI prevents or slows the underlying disease process in patients with Alzheimer's disease.

NAMENDA XR™ (memantine hydrochloride) extended-release capsules are indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

Dosage and Administration

- The recommended starting dose of NAMENDA XR is 7 mg once daily. The recommended target dose is 28 mg once daily. The dose should be increased in 7 mg increments to 28 mg once daily. The minimum recommended interval between dose increases is one week, and only if the previous dose has been well tolerated. The maximum recommended dose is 28 mg once daily.
- It is recommended that a patient who is on a regimen of 10 mg twice daily of NAMENDA tablets be switched to NAMENDA XR 28 mg once-daily capsules the day following the last dose of a 10 mg NAMENDA tablet. There is no study addressing the comparative efficacy of these 2 regimens.
- It is recommended that a patient with severe renal impairment who is on a regimen of 5 mg twice daily of NAMENDA tablets be switched to NAMENDA XR 14 mg once-daily capsules the day following the last dose of a 5 mg NAMENDA tablet.

Special Populations

- NAMENDA XR should be administered with caution to patients with severe hepatic impairment.
- A target dose of 14 mg/day is recommended in patients with severe renal impairment (creatinine clearance of 5-29 mL/min, based on the Cockcroft-Gault equation).

FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

063-14000090 04/13

improvements in cognition and global function[1]

- **In a 24-week study of 677 outpatients with moderate to severe AD on stable AChEI therapy, adding NAMENDA XR 28 mg was statistically significantly superior to placebo+AChEI (using an LOCF† analysis) in the co-primary endpoints of[1]:**
  - **Cognition as measured by the Severe Impairment Battery (2.6 unit mean difference)[1]**
  - **Global function as measured by the Clinician's Interview-Based Impression of Change (0.3 unit mean difference)[1]**
- **Studied in combination with leading AChEIs (donepezil, galantamine, or rivastigmine)[1]**
- **No titration required when switching from NAMENDA® (memantine HCl) to NAMENDA XR[1]**
- **The most commonly observed adverse reactions occurring at a frequency of at least 5% in NAMENDA XR-treated patients and at a higher frequency than placebo, respectively, were headache (6%, 5%), diarrhea (5%, 4%), and dizziness (5%, 1%)[1]**

Important Safety Information

Contraindications

- NAMENDA XR is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

Warnings and Precautions

- NAMENDA XR should be used with caution under conditions that raise urine pH (including alterations by diet, drugs and the clinical state of the patient). Alkaline urine conditions may decrease the urinary elimination of memantine, resulting in increased plasma levels and a possible increase in adverse effects.
- NAMENDA XR has not been systematically evaluated in patients with a seizure disorder.

Adverse Reactions

- The most commonly observed adverse reactions seen in patients administered NAMENDA XR (28 mg/day) in a controlled clinical trial, defined as those occurring at a frequency of at least 5% in the NAMENDA XR group and at a higher frequency than placebo were headache (6% vs 5%), diarrhea (5% vs 4%), and dizziness (5% vs 1%).

Drug Interactions

- No drug-drug interaction studies have been conducted with NAMENDA XR, specifically. The combined use of NAMENDA XR with other NMDA antagonists (amantadine, ketamine, or dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

*AChEI=acetylcholinesterase inhibitor.

†LOCF=last observation carried forward.

For more details, please visit **www.NamendaXRHCP.com**.

Please see brief summary of Prescribing Information on the following page.

Reference: 1. NAMENDA XR™ (memantine HCl) Prescribing Information. Forest Pharmaceuticals, Inc., St Louis, MO.

NEW
Once-Daily

Namenda XR™
(memantine HCl) extended release capsules
7 mg, 14 mg, 21 mg, 28 mg

NAMENDA XR (memantine hydrochloride) extended release capsules
Brief Summary of full Prescribing Information
Initial U.S. Approval: 2003

INDICATIONS AND USAGE: NAMENDA XR (memantine hydrochloride) extended-release capsules are indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS: Hypersensitivity - NAMENDA XR is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation *[*See *Description in the full Prescribing Information].*

WARNINGS AND PRECAUTIONS: Genitourinary Conditions - Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine. **Seizures -** NAMENDA XR has not been systematically evaluated in patients with a seizure disorder. In clinical trials of memantine, seizures occurred in 0.3% of patients treated with memantine and 0.6% of patients treated with placebo.

ADVERSE REACTIONS: Clinical Trial Data Sources - NAMENDA XR was evaluated in a double-blind placebo-controlled trial treating a total of 676 patients with moderate to severe dementia of the Alzheimer's type (341 patients treated with NAMENDA XR 28 mg/day dose and 335 patients treated with placebo) for a treatment period up to 24 weeks. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Adverse Reactions Leading to Discontinuation -** In the placebo-controlled clinical trial of NAMENDA XR [See *Clinical Studies in the full Prescribing Information*], which treated a total of 676 patients, the proportion of patients in the NAMENDA XR 28 mg/day dose and placebo groups who discontinued treatment due to adverse events were 10.0% and 6.3%, respectively. The most common adverse reaction in the NAMENDA XR treated group that led to treatment discontinuation in this study was dizziness at a rate of 1.5%. **Most Common Adverse Reactions -** The most commonly observed adverse reactions seen in patients administered NAMENDA XR in the controlled clinical trial, defined as those occurring at a frequency of at least 5% in the NAMENDA XR group and at a higher frequency than placebo were headache, diarrhea and dizziness. Table 1 in the full Prescribing Information lists treatment-emergent adverse reactions that were observed at an incidence of ≥ 2% in the NAMENDA XR treated group and occurred at a rate greater than placebo. The first value displays the percentage of patients in the placebo group (N=335) and the second shows the percentage in the group receiving 28 mg of NAMENDA XR (N=341). **Gastrointestinal Disorders:** Diarrhea (4%, 5%), Constipation (1%, 3%), Abdominal pain (1%, 2%), Vomiting (1%, 2%); **Infections and infestations:** Influenza (3%, 4%); **Investigations:** Weight, increased (1%, 3%); **Musculoskeletal and connective tissue disorders:** Back pain (1%, 3%); **Nervous system disorders:** Headache (5%, 6%), Dizziness (1%, 5%), Somnolence (1%, 3%); **Psychiatric disorders:** Anxiety (3%, 4%), Depression (1%, 3%), Aggression (1%, 2%); **Renal and urinary disorders:** Urinary incontinence (1%, 2%); **Vascular disorders:** Hypertension (2%, 4%), Hypotension (1%, 2%). **Vital Sign Changes -** NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with NAMENDA XR. A comparison of supine and standing vital sign measures for NAMENDA XR and placebo in Alzheimer's patients indicated that NAMENDA XR treatment is not associated with orthostatic changes. **Laboratory Changes -** NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with NAMENDA XR treatment. **ECG Changes -** NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with NAMENDA XR treatment. **Other Adverse Reactions Observed During Clinical Trials of NAMENDA XR -** Following is a list of treatment-emergent adverse reactions reported from 750 patients treated with NAMENDA XR for periods up to 52 weeks in double-blind or open-label clinical trials. The listing does not include those events already listed in Table 1, those events for which a drug cause was remote, those events for which descriptive terms were so lacking in specificity as to be uninformative, and those events reported only once which did not have a substantial probability of being immediately life threatening. Events are categorized by body system. **Blood and Lymphatic System Disorders:** anemia. **Cardiac Disorders:** bradycardia, myocardial infarction. **Gastrointestinal Disorders:** fecal incontinence, nausea. **General Disorders:** asthenia, fatigue, gait disturbance, irritability, peripheral edema, pyrexia. **Infections and Infestations:** bronchitis, nasopharyngitis, pneumonia, upper respiratory tract infection, urinary tract infection. **Injury, Poisoning and Procedural Complications:** fall. **Investigations:** weight decreased. **Metabolism and Nutrition Disorders:** anorexia, dehydration, decreased appetite, hyperglycemia. **Musculoskeletal and Connective Tissue Disorders:** arthralgia, pain in extremity. **Nervous System Disorders:** convulsion, dementia Alzheimer's type, syncope, tremor. **Psychiatric Disorders:** agitation, confusional state, delirium, delusion, disorientation, hallucination, insomnia, restlessness. **Respiratory, Thoracic and Mediastinal Disorders:** cough, dyspnea. **Memantine Immediate Release Clinical Trial and Post Marketing Spontaneous Reports -** The following additional adverse reactions have been identified from previous worldwide experience with memantine (immediate release) use. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to memantine and have not been listed elsewhere in labeling. However, because some of these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship between their occurrence and the administration of memantine. These events include: **Blood and Lymphatic System Disorders:** agranulocytosis, leukopenia (including neutropenia), pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura. **Cardiac Disorders:** atrial fibrillation, atrioventricular block (including 2nd and 3rd degree block), cardiac failure, orthostatic hypotension, and torsades de pointes. **Endocrine Disorders:** inappropriate antidiuretic hormone secretion. **Gastrointestinal disorders:** colitis, pancreatitis. **General disorders and administration site conditions:** malaise, sudden death. **Hepatobiliary Disorders:** hepatitis (including abnormal hepatic function test, cytolytic and cholestatic hepatitis), hepatic failure. **Infections and infestations:** sepsis. **Investigations:** electrocardiogram QT prolonged, international normalized ratio increased. **Metabolism and Nutrition Disorders:** hypoglycaemia, hyponatraemia. **Nervous System Disorders:** convulsions (including grand mal), cerebrovascular accident, dyskinesia, extrapyramidal disorder, hypertonia, loss of consciousness, neuroleptic malignant syndrome, Parkinsonism, tardive dyskinesia, transient ischemic attack. **Psychiatric Disorders:** hallucinations (both visual and auditory), restlessness, suicidal ideation. **Renal and Urinary Disorders:** acute renal failure (including abnormal renal function test), urinary retention. **Skin Disorders:** rash, Stevens Johnson syndrome. **Vascular Disorders:** pulmonary embolism, thrombophlebitis, deep venous thrombosis. The following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in the product labeling: aspiration pneumonia, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, depressed level of consciousness (including rare reports of coma), dysphagia, encephalopathy, gastritis, gastroesophageal reflux, intracranial hemorrhage, hyperglycemia, hyperlipidemia, ileus, impotence, lethargy, myoclonus, supraventricular tachycardia, and tachycardia. However, there is again no evidence that any of these additional adverse events are caused by memantine.

DRUG INTERACTIONS: No drug-drug interaction studies have been conducted with NAMENDA XR, specifically. **Use with other N-methyl-D-aspartate (NMDA) Antagonists -** The combined use of NAMENDA XR with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution. **Effect of Memantine on the Metabolism of Other Drugs -** *In vitro* studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isozymes CYP1A2, -2C9, -2E1 and -3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected. Pharmacokinetic studies evaluated the potential of memantine for interaction with donepezil (See *Use with Cholinesterase Inhibitors*) and bupropion. Coadministration of memantine with the AChE inhibitor donepezil HCl does not affect the pharmacokinetics of either compound. Memantine did not affect the pharmacokinetics of the CYP2B6 substrate bupropion or its metabolite hydroxybupropion. **Effect of Other Drugs on Memantine -** Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the pharmacokinetics of memantine. A clinical drug-drug interaction study indicated that bupropion did not affect the pharmacokinetics of memantine. **Drugs Eliminated via Renal Mechanisms -** Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of memantine and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the antihyperglycemic drug Glucovance® (glyburide and metformin HCl) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance®, indicating the absence of a pharmacodynamic interaction. **Drugs That Make the Urine Alkaline -** The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions. **Drugs Highly Bound to Plasma Proteins -** Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely [See *Drug Interactions*]. **Use with Cholinesterase Inhibitors -** Coadministration of memantine with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine immediate-release and donepezil was similar to that of donepezil alone.

USE IN SPECIFIC POPULATIONS: Pregnancy - Pregnancy Category B: There are no adequate and well-controlled studies of NAMENDA XR in pregnant women. NAMENDA XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 6 and 21 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 2 times the MRHD on a mg/m^2 basis. **Nursing Mothers -** It is not known whether memantine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother. **Pediatric Use -** The safety and effectiveness of memantine in pediatric patients have not been established.

DRUG ABUSE AND DEPENDENCE: Memantine is not a controlled substance. Memantine is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 3,254 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE: Signs and symptoms most often accompanying overdosage with other formulations of memantine in clinical trials and from worldwide marketing experience, alone or in combination with other drugs and/or alcohol, include agitation, asthenia, bradycardia, confusion, coma, dizziness, ECG changes, increased blood pressure, lethargy, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2 grams in an individual who took memantine in conjunction with unspecified antidiabetic medications. This person experienced coma, diplopia, and agitation, but subsequently recovered. One patient participating in a NAMENDA XR clinical trial unintentionally took 112 mg of NAMENDA XR daily for 31 days and experienced an elevated serum uric acid, elevated serum alkaline phosphatase, and low platelet count. No fatalities have been noted with overdoses of memantine alone. A fatal outcome has very rarely been reported when memantine has been ingested as part of overdosing with multiple drugs; in those instances, the relationship between memantine and a fatal outcome has been unclear. Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

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St. Louis, MO 63045

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Please also see full Prescribing Information at www.namendaxr.com

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Drug Topics®
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Pain control in the elderly

More than 50% of the elderly have reported pain lasting more than a year. With chronic conditions so prevalent in this growing demographic, pharmacists can play a crucial role in the management of opioid therapy for seniors. PAGE 42

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CPE CONTINUING EDUCATION

Common pain conditions

Osteoarthritis, low back pain, fibromyalgia, sprains, and generalized headaches: Spot the signs and symptoms, and know when patients need more than OTC relief. PAGE 48

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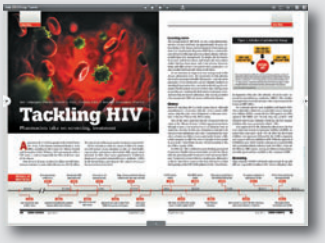

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Voices

Merritt's "classless attack"

PCMA CEO Mark Merritt's letter ["A word from PCMA," Voices, June 2013] was a sad and classless attack on every pharmacist who serves his clients. We work very hard to ensure that patients receive the best care possible. Comparing us to fast food was a real low blow.

Mr. Merritt, your organization is much like the Mafia. You skim off your take of the healthcare budget while providing no actual benefit. You then force pharmacies to accept horrible take-it-or-leave-it proposals. When you mandate mail order and it fails to deliver as promised, we are the ones who take care of your sick customers. But unless it's a spreadsheet number, you couldn't care less.

Your letter shows how little you think of pharmacists. I sleep well because I know I have made a positive difference to my customers. How can you sleep at night?

Tim Melin, RPh
VERONA, WIS.

Pharmacy tobacco bans don't work

Regarding Jim Ober's article ["Why do drugstores sell products that kill?" Student Corner, May 2013]:

First of all, I do not condone tobacco use. My mother died of throat and lung cancer from a smoking habit. She chose to smoke, so she suffered the consequences.

I am the owner of an independent pharmacy located in Boston, where the sale of tobacco products in pharmacies has been banned. This ban only makes customers cross the street to buy tobacco at the liquor store. The ban is totally ineffective in stopping people from smoking.

People will smoke no matter where they have to go to get tobacco. If the city of Boston really wanted to be serious about the smoking issue, they would ban it from all stores, not just pharmacies. The city still gets its tax dollars. It is all about the money, not the feigned rhetoric of helping people to stop using tobacco products.

We should be wary of any government that can ban legal products.

Gary Einsidler
BOSTON, MASS.

Why Rx prices keep going up

On March 31, 2010, at the age of 80, I closed my independent pharmacy. My professional life coincided with the growth of Medicaid, employer-provided

Continued on pg. 12

DISPENSED AS WRITTEN James "Goose" Rawlings, RPh

Can we make PBMs obsolete?

Last fall, as one of several speakers to address a group of pharmacy students, I presented my thoughts on the future of pharmacy. I have strong feelings about where pharmacy is going and where we need to go. And I don't think it's all doom and gloom, either. Yes, we have problems, but kids today are really smart, and I'm confident they'll figure things out. My theory is that there is always an opportunity, even in the worst times. I had a great time talking to the students, both during my presentation and after.

All the other presentations were good, but one caught my attention. The speaker was a self-employed pharmacist. Where the future of pharmacy was concerned, she truly was a visionary, at least in my eyes. I don't think the students realized it, but they were listening to a revolutionary plan to take back our profession. Her idea was simple and within the reach of every pharmacist. This woman was making a difference while she performed rewarding work and paid the bills. And she was not dispensing or actually working in a pharmacy.

The angle

What this pharmacist was doing was showing up the pharmacy benefit managers (PBMs) by actually doing what they claim to do, but don't.

Working with small-to-medium-sized companies, she performs drug utilization review (DUR) on their employees and makes recommendations. Unlike a PBM, which bases its recommendations on the rebates it can collect, she bases hers on improving patient outcomes through drug therapy management. From a drug standpoint, she is an advocate for the employees of these companies. She is paid on a capitated rate for each employee, and she is profitable. Similar to employee nurses, common in many companies, she is an employee pharmacist.

The difference

I asked her what results she had seen, and she said that the patients she served were healthier and the companies spent less on healthcare per patient, even after her fee was factored in.

She also let me know that the PBMs did not like what she was doing. I asked her why the companies she represented even needed a PBM, and she replied, "Well, they do have good computers."

She went on to say that while the PBM has good patient data, it is somewhat flawed. For example, PBM's tout compliance through refill programs on prescriptions, but they cannot verify whether the patients actually take the medication. By monitoring patient medical records and lab results, she can.

PBMs don't really do anything with the data they collect to improve patient care; it is used simply as leverage to squeeze rebates out of manufacturers. The PBMs then pass on a small portion of each rebate to the companies they "manage."

The question

I have long wondered why the hospital where I work doesn't ditch our PBM and do its own employee DUR. After all, the pharmacists here already perform DUR every day for our patients. Why not continue the practice with our own employees?

The bean-counters just can't see past the rebates. They can't see that the PBM is making a dollar using your data and giving you a dime.

They can't see that if they handled everything in-house, with resources they already have or could easily obtain, they would come out ahead, with healthier employees. The rebates are like a drug they can't kick, a really powerful, addictive drug.

If you are working with a program like this as part of your practice, I would like to hear from you. We could take back the profession from short-sighted middle management unable to see the value of clinical pharmacy. Or we could replace the greatest danger to pharmacy in general: the PBM.

Ideally, we can do both. The potential to change our profession is there. We have the skills to do it. It's time to get started. DT

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

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BAYER

Voices

Continued from pg. 9

prescription insurance, and PBMs. I also witnessed the introduction of computers and their constant modifications. All these innovations were supposed to lower the cost of pharmacy operation and improve patient care.

Coincidental with these developments was a meteoric rise in prescription costs. Surely, I am not the only person to connect these two phenomena. Computers do indeed contribute to efficiency, but they are not without cost. Hardware and maintenance are expensive. Then there is the monthly cost of software service. Employee training adds more cost.

Government agencies, insurance companies, and PBMs routinely discover the need for another report, which must be incorporated into the program. These items are not free. They are costs borne by the pharmacy and must be added to the cost of each prescription. Add to all these expenses the time required of the pharmacy staff to satisfy these requirements and one can gain some understanding of the exponential rise in prescription costs.

Insurance companies do not operate at a loss. They never pay out more in benefits than they take in through premiums. And PBMs do not offer their services free of charge.

If the revenues of insurance companies, PBMs, and other agencies involved in processing pharmacy claims were combined, and that amount were subtracted from the total cost of prescriptions, one would see the reason for the increases in prescription cost.

Patient health and welfare are no longer the primary focus. The goal now is how to squeeze more revenue out of the patient and more profit out of the process.

Martin E. Cloessner, Jr.
JONESVILLE, LA.

BOPs don't protect pharmacists


Voices

In Jill Sande's letter ["Been there, left that," Voices, May 2013], she remarked how the collective state boards of pharmacy have allowed us to be treated as nonprofessionals. Sande may be misinformed as to the function of the various pharmacy state boards. In my experience, which now spans 49 years, the functions of the boards are twofold. The main function is to protect the public from us, the pharmacists, with the related function of extracting money from us to accomplish this.

I have never known of a board of pharmacy acting as a protector. In fact, I have actually known boards to turn pharmacists over to other authorities for punitive measures (after they had extracted their own pound of flesh).

Sande should stay away from chain pharmacies unless she wants to work as a highly paid automaton in some of the most unpleasant conditions existing today. No chain pharmacists that I've ever talked to believe that they control anything in their practice, from taking orders from a high-school-educated store manager to being castigated for not meeting the prescription numbers quota for their shifts.

Drury H. Bynum, RPh, MBA, FASCP
MONROE, LA.

Nothing wrong with rewarding success

In "To each according to his needs" [Voices, May 2013], Mike Saija wrote: "I have a very wealthy customer who owns a large business. His copays are ZERO because he owns the company, but his employees have regular copays. Is this right or fair?"

The response is yes, it is entirely right and fair. The employer has taken risks to build a profitable business and is entitled to the fruits of his success, which in this case include no copay on his prescriptions.

His employees [should] be grateful to have a job with a prescription plan with regular copays. Without the employer, the employees would not have any work and, thus, no prescription plan at all. If the employees are unhappy, they can always seek employment elsewhere or start their own businesses so that they too could have no copay.

Yes, it is entirely right and fair to reward success.

Kenneth W. Dietel, RPh, MBA
LEWES, DEL.

The value of sunscreen sprays YTD

I think it is negligent that "Here comes the sun" [OTC, June 2013] states that

"While at the beach or the pool, parents can ensure their children's safety from the harmful effects with SPF 70 for Kids Continuous Mist Sunscreen."

As a pharmacy journal, you should be aware that the FDA has made recommendations to avoid sunscreen sprays.

FDA has requested additional data to establish effectiveness of sunscreen spray products and to determine whether they present a safety concern if inhaled unintentionally. These requests arose because sprays are applied differently from other sunscreen dosage forms, such as lotions and sticks.

As a pediatric pharmacist, I urge all pharmacists to be aware that this product WILL NOT ensure children's safety.

Beth Deen, PharmD, BCNSP
COOK CHILDRENS MEDICAL CENTER
FORT WORTH, TEXAS

Independents are a dying breed

"Put your money where your mouth is," by David Stanley [View from the Zoo, June 2013], resonated with me! I worked in the corporate pharmacy world off and on all through my career, but I was never happier than when I was doing relief work for independent pharmacies through my own agency.

About 14 years ago, I moved from northern California to Washington state. The job with Long's in California was more than tolerable, but the mindset in the same (recently purchased) chain in Washington was ridiculous. The manager went out of his way to make my day harder, and when I sought help higher up, it was more of the same. I hated going to work and just decided one day, as David did, that enough was enough.

I started looking for a full-time job working relief at the independents in the area. Much to my surprise, there were VERY few independents left. It took me a long time to put together a schedule for myself, but I did.

But then the stores I was working for started dropping like flies. Through the unfair insurance reimbursements and loss leader competition, they just couldn't make it. It is so sad to see that happening to the entrepreneurial part of pharmacy that I love so much.

I became a realtor several years ago and I love it, even though I still work in pharmacy a couple of days a week.

I wish David SO much luck in his new venture! I hope it works out well.

Nothing compares to the relationships that one can develop while working in an independent pharmacy.

In the end, it's all about helping people, isn't it?

Laura Fletcher, RPh
MOUNT VERNON, WA.

We want to hear from you

Printed and e-mailed letters should be brief and include the writer's name, address, daytime phone number, and date of the issue you are referencing: Editor, ***Drug Topics***, 24950 Country Club Blvd., Suite 200, North Olmsted, OH 44070-5351. E-mail address: drugtopics@advanstar.com. Letters may be edited for length, style, content, and clarity at our discretion.

STUDENT CORNER Kevin Cowart, PharmD Candidate

An update on insulin resistance and the use of U-500 insulin

Insulin resistance can be described as a decrease in sensitivity, or as a decreased biological response to insulin.[1] Because of its unique associations with cardiovascular risk, obesity, hypertension, and dyslipidemia, no single etiological explanation has been described for insulin resistance. Research has shown that the pathogenesis of insulin resistance results from either lipid accumulation or the contribution of systemic inflammation, or through genetic mutations involving autoantibodies to the insulin receptor.[2]

There is considerable variation in opinions on how to identify and clinically measure insulin resistance in humans, according to researchers.

Clinicians have used between 100-200 units per day as a cutpoint for diagnosing insulin resistance.[3] A more direct tool for measurement, known as the "gold standard" for measuring insulin resistance, is the euglycemic hyperinsulinemic clamp.[1]

Similar direct measurements have been accepted as estimates of insulin resistance, including the frequently sampled intravenous glucose tolerance test, the steady-state plasma-glucose method, the oral glucose tolerance test, and the homeostatic model assessment (HOMA)[1].

Described in recent literature, the HOMA attempts to measure beta-cell function and to quantify insulin resistance through mathematical formulas.[1] A unique advantage of the HOMA over the methods mentioned previously is that it does not require invasive, time-consuming procedures. However, none of the direct measurements of insulin resistance cited above has demonstrated superiority in comparison to fasting insulin levels.[1] Overall, there continues to be a lack of standardization among methods and measurements to define and quantify insulin resistance in human beings.

Challenges for pharmacists

According to recent surveillance data from the Centers for Disease Control and Prevention (CDC), the prevalence of diabetes among U.S. adults has grown by 45% over the past 20 years, with the greatest increase seen among seniors over age 65.[4] As the diabetes epidemic grows, clinicians can expect to encounter more insulin-resistant patients who present with challenging medication regimens.

For these patients, reaching target goals of therapy in connection with low-density lipoprotein cholesterol (LDL-C), hemoglobin A1c (HbA1c), blood pressure, fasting and postprandial glucose levels, and body mass index (BMI) continues to be a challenge. The combination of these metabolic disorders has led to a need for higher total daily insulin requirements and to the use of U-500 insulin in insulin-resistant patients in an attempt to optimize pharmacologic therapy and achieve glycemic goals.

Current use of U-500 insulin

In order to ensure the safe and effective use of insulin therapy, pharmacists should familiarize themselves with the use of U-500 insulin, as its use is expected to rise with the diabetes epidemic.

In comparison to the insulin response shown by types 1 and 2 diabetes patients, the dose-response curve in insulin-resistant patients is significantly diminished at doses greater than 100 units.[3] However, it has been shown that insulin-resistant patients eventually achieve therapeutic goals at high doses of insulin.[3] For this reason, the use of U-500 insulin should be considered for patients who are insulin-resistant.

Current evidence for the use of U-500 insulin is limited to retrospective case series reports, which have demonstrated the effectiveness of either multiple daily injections or a continuous subcutaneous insulin infusion in improving glycemic control.[3] U-500 insulin is five times more potent than U-100 insulin, with a pharmacokinetic profile most closely related to that of NPH insulin.[3]

In light of the increased potency of U-500 insulin, it is important for pharmacists to counsel patients on the proper use of U-500 insulin. All other forms of insulin should be discontinued, the proper (i.e., tuberculin) syringe should be employed, and the pharmacist should instruct the patient on when and how to inject U-500 insulin.

A pharmacoeconomic analysis demonstrated that U-500 insulin provides a potential cost advantage over U-100

Continued on pg. 45

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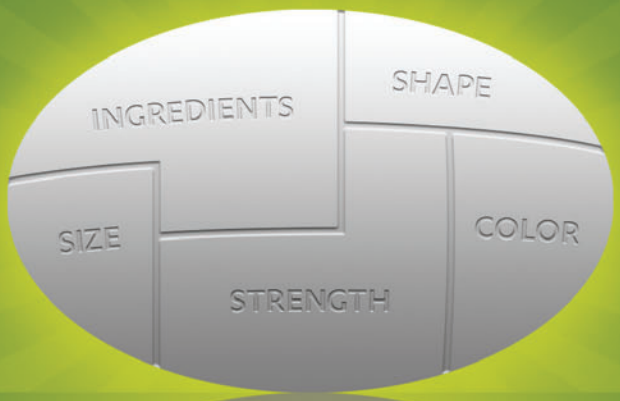

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May 2013

VIEW FROM THE ZOO David Stanley, RPh

Time to reconsider the penalties for filling bogus prescriptions

The man at my counter was young, with the chiseled body of an athlete. His prescription for 360 oxycodone tablets was the first red flag. His willingness to pay for it with a fistful of cash was the second. A few questions to my technicians gave rise to a mountain of other questions, and I soon explained to the young man that we wouldn't be filling his prescription.

As helpful as a fistful of cash can be in getting a new business off the ground, I, like most of you, know the devastation caused by the opiates flooding across our country, the lives ended prematurely and the anguish endured by survivors and loved ones. I wasn't committing an extraordinary act in turning away that prescription. Most people would have done the same thing.

Unfortunately, people don't control our profession anymore. Our livelihood, like so many parts of the modern economy, is run by that artificial paper entity, the corporation. Considered a "person" for legal purposes, the corporation, with no body to imprison or soul to damn, has proven itself a wonderful vehicle for maximizing business efficiency and revenue.

An artificial person doesn't concern itself, however, with the ethical implications of turning loose a wave of narcotics in our cities. It is concerned only with the risks of whatever penalty it might incur if caught vs. the benefit of getting away with it. The artificial person looks at that fistful of cash and its first conclusion is how it will help the balance sheet.

If you think I'm wrong, you need look no further than to the state of Florida, where Walgreens, the country's second-largest pharmacy corporation by revenue, just paid an $80 million fine for what the Drug Enforcement Agency called a "systematic practice" of turning a blind eye to those red flags pharmacists know so well. The result was "tens of thousands of violations" of drug laws. One of this corporation's pharmacies went from ordering 95,800 oxycodone pills in 2009 to 2.2 million in 2011. Six of its Florida stores ordered over a million pills each in 2011, whereas the average pharmacy uses just 73,000.

Whatever you think about the modern corporate structure, you can't argue that its efficiency, whether putting oxycodone into the hands of criminals or dollars onto the bottom line, is unparalleled.

A speeding ticket

You would also be hard-pressed to deny that the corporation excels in minimizing risk in the event that it gets caught doing things it shouldn't.

I did the math. According to last year's tax returns, that $80 million penalty would have been the equivalent of my paying a fine of $452. Actions that would have resulted in the death penalty for my small business or any other end up being the equivalent of a speeding ticket for the artificial person that fills almost 20% of the nation's prescriptions.

Other pharmacy chains have also found themselves in trouble for similar actions, and I can tell you that I myself was pressured to fill inappropriate controlled substance prescriptions while toiling away at one of the chains. Regarding its obligation to keep narcotics out of the hands of criminals and addicts, the artificial person appears to have analyzed the risk-versus-reward ratio and far too often come to a conclusion different from the one people with bodies and souls would have arrived at.

That is why, I gathered, that the young man at my — not the shareholders' — counter wasn't all that upset when I turned him away. Instead of the shock you would expect from someone in serious pain who was being denied access to relief, his reaction was courteous and almost . . . professional. His tone was that of mild disappointment that we couldn't do business together, as opposed to that of someone looking squarely in the face of physical agony.

There's no way to be sure, of course, but I'm willing to bet that eventually he did find a business partner — one with a listing on a major stock exchange and policies that make it maximally efficient and minimally accountable.

Call me a pessimist, but I doubt that a 4-cent-per-share penalty will make much of a lasting impact on corporate actions. After all, I know how effective speeding tickets are at slowing traffic. DT

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

Walgreens to offer community care on Johns Hopkins campus

Walgreens is partnering with Johns Hopkins Medicine to build a store adjacent to the hospital's East Baltimore campus that will target students and staff as well as the surrounding community.

The new store, which will be located at Science and Technology Park, is scheduled to open in November. It will feature a Take Care Clinic staffed by board-certified nurse practitioners. In addition to offering a full selection of daily living products, it will also offer healthy food options.

"This is a significant next step in our relationship, leveraging the clinical expertise of Johns Hopkins Medicine and Walgreens' expansive healthcare resources to create a retail hub for community-based care," said Kermit Crawford, president of pharmacy, health, and wellness for Walgreens.

"Our pharmacy and Take Care Clinic will provide an environment for collaborative healthcare innovation, while also providing greater access to healthcare services for the Johns Hopkins community, students, employees, and patients. This new venture is another way in which we're advancing community pharmacy to help more people get, stay, and live well," he said.

In collaboration with Johns Hopkins the store will offer a number of services, including student health services, chronic disease education and awareness programs, smoking cessation programs, HIV testing, and immunizations.

"These programs will provide a novel approach to population health and medical services," said Patricia M.C. Brown, JD, president of Johns Hopkins HealthCare. "They will benefit not only Johns Hopkins employees and the surrounding community, but also form the level of healthcare collaboration that could serve as a national model."

Johns Hopkins officials believe the collaboration with Walgreens will enable the institution to reach even further into the community, as its physicians will work with nurse practitioners at the Take Care Clinic and will be available during clinic hours for consultation.

"We will also use the lessons learned from this collaboration beyond our community, as Johns Hopkins Medicine continues to set the standard for medical education, research, and patient care on a national scale and around the world," said Paul Rothman, MD, dean of the Johns Hopkins University School of Medicine and CEO of Johns Hopkins Medicine.

Walgreens' new store will offer student health services, immunizations, chronic diabetes education, and HIV testing.

A NEW DATABASE

NIH website lists supplement ingredients

About half the adults in the United States regularly take dietary supplements to add nutrients or other ingredients to their diets. But how many know what's actually in those supplements?

The National Institutes of Health (NIH) now provides some of those answers to researchers, healthcare professionals, and consumers through a new website, *www.dsld.nlm.nih.gov,* that lists the label ingredients of about 17,000 dietary supplements.

"This database will be of great value to many diverse groups of people, including nutrition researchers, healthcare providers, consumers, and others," said Paul M. Coates, PhD, director of the NIH Office of Dietary Supplements (ODS). "For example, research scientists might use the Dietary Supplement Label Database to determine total nutrient intakes from food and supplements in populations they study."

ODS already provides a mobile app that helps consumers keep track of vitamins, minerals, herbs, and other products they take. The app also has science-based, reliable information on dietary supplements.

Using the website/database, consumers can quickly search for specific ingredient or label text, search for dietary ingredients and specific products, and search by supplement manufacturer. They can also combine options to make advanced searches.

"The Dietary Supplement Label Database will be updated regularly to incorporate most of the more than 55,000 dietary supplement products in the U.S. marketplace," said Steven Phillips, MD, director of the National Library of Medicine's Division of Specialized Information Services.

Phillips noted that hundreds of new dietary supplements are added to the marketplace each year, some are removed, and product formulations and label information are adjusted frequently.

The website/database is a collaboration between ODS and NLM. It receives input from a federal working group on dietary supplements that includes representatives from most NIH institutes and centers, FDA, Agency for Healthcare Research and Quality, Administration for Community Living, Centers for Disease Control and Prevention, Office of Disease Prevention and Health Promotion, Consumer Product Safety Commission, Department of Defense, and many others.

FIRST WOMAN DEAN AT UF

Johnson named dean of University of Florida College of Pharmacy

With her appointment as dean of the University of Florida College of Pharmacy, Julie A. Johnson, PharmD, became the seventh dean in the school's 90-year history and its first woman dean.


Julie Johnson

Johnson, a faculty member of the UF College of Pharmacy since 1998, previously chaired the department of pharmacotherapy and translational research. Before coming to UF, Johnson was a faculty member at the University of Tennessee College of Pharmacy.

"Through a rigorous national search and a field of superb finalists, Dr. Johnson emerged as uniquely qualified and well suited for this position," said David S. Guzick, MD, PhD, senior vice president for health affairs and president of UF Health. "Her extraordinary record of research that translates into improved patient care, her demonstrated ability to mentor faculty into successful research careers, her history of excellence in teaching and outreach at the University of Florida, and her ambitious vision for the College of Pharmacy's future, made her the ideal candidate for dean."

Johnson is a well-known leader and researcher in pharmacogenomics and personalized medicine. She leads the International Warfarin Pharmacogenetics Consortium. Pharmacy-board-certified in pharmacotherapy and cardiology, she has focused her research efforts on individualizing medicine for patients based on their genetic makeup, particularly those with high blood pressure and other heart diseases.

"It is my great honor to be selected to serve as the next dean of the UF College of Pharmacy," Johnson said. "I look forward to working with our faculty, staff, and students to elevate our research productivity, enhance our educational programs, and extend our relationships with practicing pharmacists across the state."

Among her many accolades, Johnson was named the V. Ravi Chandran professor of pharmaceutical sciences in 2004. She currently directs the UF Center for Pharmacogenomics and the UF Health Personalized Medicine Program, and she has published more than 200 journal articles, editorials, and book chapters.

In June, she was awarded $3.7 million to continue the UF Health Personalized Medicine Program at the UF Clinical and Translational Science Institute (CTSI).

"Julie has shown a unique ability to develop partnerships across the Health Science Center and help the CTSI build an innovative and nationally recognized program," said David R. Nelson, MD, UF assistant vice president for collaborative research in the life sciences and director of the CTSI. "She is the ideal person to help leverage the extensive strengths of

NCPA REPORT CARD

Medication adherence challenging for Americans, survey reveals

Both bad and good news resulted from the national medication adherence survey conducted by the National Community Pharmacists Association (NCPA) and released in June.

The survey, titled "Medication Adherence in America: A National Report Card," found that Americans earn a C+ on medication adherence, with one-third receiving a D or an F.

Langer Research Associates interviewed more than 1,000 Americans who are 40 years of age and older with at least one chronic condition. The most prevalent chronic conditions were high blood pressure and high cholesterol, which patients had for two years or more.

"Anything less than an 'A' on medication adherence is very concerning," said B. Douglas Hoey, RPh, CEO of NCPA, in a media call that launched the report. Complications from nonadherence cost the U.S. healthcare system $500 billion in annual costs, he said, citing a recent IMS Health report.

The good news is the important role pharmacists play in improving medication adherence. Langer Research found that the biggest predictor of medication adherence is patients' personal connection (or lack thereof) with a pharmacist or pharmacy staff.

VIDEOS

The survey "Medication Adherence in America: A National Report Card," released by NCPA, found average to poor med adherence among Americans. NCPA CEO Douglas Hoey, RPh, shares the results. **http://drugtopics.com/Medadhere**

Patrons of independent community pharmacies reported the highest level of personal connection (89%), followed by large chains (67%) and mail order (36%). "They [survey respondents] were more than 200% more likely to say their pharmacist knows them better than their mail-order pharmacy," Hoey said.

To improve adherence, Hoey and NCPA are urging Congress to implement H.R. 1024, the Medication Therapy Management Empowerment Act. "This legislation would expand seniors' access to medication in the Medicare Part D program without costing the government a dime," Hoey said. In addition, states should adopt legislation that gives patients a choice in pharmacy services, instead of mandating mail-order plans.

Payers should also encourage greater adoption of medication synchronization services, in which consumers can schedule a time to pick up all their medications at once.

"Payment policies that restrict pharmacy medication synchronization services are short-sighted," Hoey said.

–Christine Blank, Contributing Editor

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INDICATIONS

LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults.

IMPORTANT SAFETY INFORMATION FOR LATUDA

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for use in patients with dementia-related psychosis.**
- **Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. LATUDA is not approved for use in patients under the age of 18 years.**

Please see additional Important Safety Information, including **Boxed Warnings**, and Brief Summary of Prescribing Information on adjacent pages.

SUNOVION

IMPORTANT SAFETY INFORMATION AND INDICATIONS FOR LATUDA

WARNINGS:

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS

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CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Strong CYP3A4 inducers (e.g., rifampin)

WARNINGS AND PRECAUTIONS

Cerebrovascular Adverse Reactions, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Tardive Dyskinesia (TD): TD is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients with antipsychotic drugs. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

Metabolic Changes

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Patients with a preexisting low white blood cell count (WBC) or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: LATUDA may cause orthostatic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension and in patients with known cardiovascular disease or cerebrovascular disease.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer's dementia).

Potential for Cognitive and Motor Impairment: Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Suicide: The possibility of suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo) for LATUDA:

- Adult patients with bipolar depression: akathisia, extrapyramidal symptoms, and somnolence
- Adult patients with schizophrenia: somnolence, akathisia, extrapyramidal symptoms, and nausea

INDICATIONS

LATUDA is indicated for:

- Treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults
- Treatment of schizophrenia in adults

Please see Brief Summary of Prescribing Information, including **Boxed Warnings**, on adjacent pages.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

WARNINGS:

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death *[see Warnings and Precautions (5.1)]*.**
- **LATUDA is not approved for use in patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.**
- **Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.2)]*.**
- **In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.2]*.**

1 INDICATIONS AND USAGE

1.1 Schizophrenia

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia *[see Clinical Studies (14.1)]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2)]*.

1.2 Depressive Episodes Associated with Bipolar I Disorder

Monotherapy: LATUDA is indicated as monotherapy for the treatment of patients with major depressive episodes associated with bipolar I disorder (bipolar depression). The efficacy of LATUDA was established in a 6-week monotherapy study in adult patients with bipolar depression *[see Clinical Studies (14.2)]*.

Adjunctive Therapy with Lithium or Valproate: LATUDA is indicated as adjunctive therapy with either lithium or valproate for the treatment of patients with major depressive episodes associated with bipolar I disorder (bipolar depression). The efficacy of LATUDA was established in a 6-week study in adult patients with bipolar depression who were treated adjunctively with lithium or valproate *[see Clinical Studies (14.2)]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2.2)]*.

The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

4 CONTRAINDICATIONS

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone *[see Adverse Reactions (6.1)]*.
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) *[see Drug Interactions (7.1)]*.
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6- to 1.7-times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

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

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

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

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

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

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

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

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

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

5.3 Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.4 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include

elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

5.5 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 2.

Table 2: Change in Fasting Glucose in Schizophrenia Studies

		LATUDA				
	Placebo	20 mg/day	40 mg/day	80 mg/day	120 mg/day	160 mg/day
Mean Change from Baseline (mg/dL)						
	n=680	n=71	n=478	n=508	n=283	n=113
Serum Glucose	-0.0	-0.6	+2.6	-0.4	+2.5	+2.5
Proportion of Patients with Shifts to ≥ 126 mg/dL						
Serum Glucose (≥ 126 mg/dL)	8.3% (52/628)	11.7% (7/60)	12.7% (57/449)	6.8% (32/472)	10.0% (26/260)	5.6% (6/108)

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.8 mg/dL at week 24 (n=355), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307).

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study are presented in Table 3.

Table 3: Change in Fasting Glucose in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	20 to 60 mg/day	80 to 120 mg/day
	n=148	n=140	n=143
Mean Change from Baseline (mg/dL)			
Serum Glucose	+1.8	-0.8	+1.8
Proportion of Patients with Shifts to ≥ 126 mg/dL			
Serum Glucose (≥ 126 mg/dL)	4.3% (6/141)	2.2% (3/138)	6.4% (9/141)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.2 mg/dL at week 24 (n=129).

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 4.

Table 4: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo	20 to 120 mg/day
Mean Change from Baseline (mg/dL)		
	n=302	n=319
Serum Glucose	-0.9	+1.2
Proportion of Patients with Shifts to ≥ 126 mg/dL		
Serum Glucose (≥ 126 mg/dL)	1.0% (3/290)	1.3% (4/316)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 5.

Table 5: Change in Fasting Lipids in Schizophrenia Studies

		LATUDA				
	Placebo	20 mg/day	40 mg/day	80 mg/day	120 mg/day	160 mg/day
Mean Change from Baseline (mg/dL)						
	n=660	n=71	n=466	n=499	n=268	n=115
Total Cholesterol	-5.8	-12.3	-5.7	-6.2	-3.8	-6.9
Triglycerides	-13.4	-29.1	-5.1	-13.0	-3.1	-10.6
Proportion of Patients with Shifts						
Total Cholesterol (≥ 240 mg/dL)	5.3% (30/571)	13.8% (8/58)	6.2% (25/402)	5.3% (23/434)	3.8% (9/238)	4.0% (4/101)
Triglycerides (≥ 200 mg/dL)	10.1% (53/526)	14.3% (7/49)	10.8% (41/379)	6.3% (25/400)	10.5% (22/209)	7.0% (7/100)

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol

and triglycerides of -3.8 (n=356) and -15.1 (n=357) mg/dL at week 24, -3.1 (n=303) and -4.8 (n=303) mg/dL at week 36 and -2.5 (n=307) and -6.9 (n=307) mg/dL at week 52, respectively.

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in Table 6.

Table 6: Change in Fasting Lipids in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	20 to 60 mg/day	80 to 120 mg/day
Mean Change from Baseline (mg/dL)			
	n=147	n=140	n=144
Total cholesterol	-3.2	+1.2	-4.6
Triglycerides	+6.0	+5.6	+0.4
Proportion of Patients with Shifts			
Total cholesterol (≥ 240 mg/dL)	4.2% (5/118)	4.4% (5/113)	4.4% (5/114)
Triglycerides (≥ 200 mg/dL)	4.8% (6/126)	10.1% (12/119)	9.8% (12/122)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 (n=130) and -1.0 (n=130) mg/dL at week 24, respectively.

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled, adjunctive therapy bipolar depression studies are presented in Table 7.

Table 7: Change in Fasting Lipids in the Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo	20 to 120 mg/day
Mean Change from Baseline (mg/dL)		
	n=303	n=321
Total cholesterol	-2.9	-3.1
Triglycerides	-4.6	+4.6
Proportion of Patients with Shifts		
Total cholesterol (≥ 240 mg/dL)	5.7% (15/263)	5.4% (15/276)
Triglycerides (≥ 200 mg/dL)	8.6% (21/243)	10.8% (28/260)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA, as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in total cholesterol and triglycerides of -0.9 (n=88) and 5.3 (n=88) mg/dL at week 24, respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 8. The mean weight gain was 0.43 kg for LATUDA-treated patients compared to -0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5 *[see Clinical Studies (14.1)]*, respectively. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

Table 8: Mean Change in Weight (kg) from Baseline in Schizophrenia Studies

		LATUDA				
	Placebo (n=696)	20 mg/day (n=71)	40 mg/day (n=484)	80 mg/day (n=526)	120 mg/day (n=291)	160 mg/day (n=114)
All Patients	-0.02	-0.15	+0.22	+0.54	+0.68	+0.60

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at week 24 (n=755), -0.59 kg at week 36 (n=443) and -0.73 kg at week 52 (n=377).

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study are presented in Table 9. The mean weight gain was 0.29 kg for LATUDA-treated patients compared to -0.04 kg for placebo-treated patients. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 2.4% for LATUDA-treated patients versus 0.7% for placebo-treated patients.

Table 9: Mean Change in Weight (kg) from Baseline in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo (n=151)	20 to 60 mg/day (n=143)	80 to 120 mg/day (n=147)
All Patients	0.0	+0.56	+0.02

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in weight of -0.02 kg at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 10. The mean weight gain was 0.11 kg for LATUDA-treated patients compared to 0.16 kg for placebo-treated patients. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 3.1% for LATUDA-treated patients versus 0.3% for placebo-treated patients.

Table 10: Mean Change in Weight (kg) from Baseline in the Adjunctive Therapy Bipolar Depression Studies

	Placebo (n=334)	LATUDA 20 to 120 mg/day (n=327)
All Patients	+0.16	+0.11

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate in the short-term and continued in the longer-term study, had a mean change in weight of +1.28 kg at week 24 (n=86).

5.7 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male patients *[see Adverse Reactions (6)]*.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice *[see Nonclinical Toxicology (13)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 11.

Table 11: Median Change in Prolactin (ng/mL) from Baseline in Schizophrenia Studies

		LATUDA				
	Placebo	20 mg/day	40 mg/day	80 mg/day	120 mg/day	160 mg/day
All Patients	-1.9 (n=672)	-1.1 (n=70)	-1.4 (n=476)	-0.2 (n=495)	+3.3 (n=284)	+3.3 (n=115)
Females	-5.1 (n=200)	-0.7 (n=19)	-4.0 (n=149)	-0.2 (n=150)	+6.7 (n=70)	+7.1 (n=36)
Males	-1.3 (n=472)	-1.2 (n=51)	-0.7 (n=327)	-0.2 (n=345)	+3.1 (n=214)	+2.4 (n=79)

The proportion of patients with prolactin elevations ≥ 5× upper limit of normal (ULN) was 2.8% for LATUDA-treated patients versus 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 1.6% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -0.9 ng/mL at week 24 (n=357), -5.3 ng/mL at week 36 (n=190) and -2.2 ng/mL at week 52 (n=307).

Bipolar Depression

Monotherapy

The median change from baseline to endpoint in prolactin levels, in the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, was +1.7 ng/mL and +3.5 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin by dose range are shown in Table 12.

Table 12: Median Change in Prolactin (ng/mL) from Baseline in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	**20 to 60 mg/day**	**80 to 120 mg/day**
All Patients	+0.3 (n=147)	+1.7 (n=140)	+3.5 (n=144)
Females	0.0 (n=82)	+1.8 (n=78)	+5.3 (n=88)
Males	0.4 (n=65)	+1.2 (n=62)	+1.9 (n=56)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

The proportion of patients with prolactin elevations ≥ 5x upper limit of normal (ULN) was 0.4% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 0% versus 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA in the short-term and continued in the longer-term study, had a median change in prolactin of -1.15 ng/mL at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

The median change from baseline to endpoint in prolactin levels, in the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies was +2.8 ng/mL with LATUDA 20 to 120 mg/day compared to 0.0 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL. Median changes for prolactin across the dose range are shown in Table 13.

Table 13: Median Change in Prolactin (ng/mL) from Baseline in the Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo	**20 to 120 mg/day**
All Patients	0.0 (n=301)	+2.8 (n=321)
Females	+0.4 (n=156)	+3.2 (n=162)
Males	-0.1 (n=145)	+2.4 (n=159)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

The proportion of patients with prolactin elevations ≥ 5x upper limit of normal (ULN) was 0.0% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 0% versus 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate, in the short-term and continued in the longer-term study, had a median change in prolactin of -2.9 ng/mL at week 24 (n=88).

5.8 Leukopenia, Neutropenia and Agranulocytosis

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm^3) should discontinue LATUDA and have their WBC followed until recovery.

5.9 Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension and syncope, perhaps due to its α1-adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and bradycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

Orthostatic hypotension, as assessed by vital sign measurement, was defined by the following vital sign changes: ≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing position.

Schizophrenia

The incidence of orthostatic hypotension and syncope reported as adverse events from short-term, placebo-controlled schizophrenia studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0% (0/708)].

In short-term schizophrenia clinical studies, orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.8% with LATUDA 40 mg, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg and 0.8% with LATUDA 160 mg compared to 0.7% with placebo.

Bipolar Depression

Monotherapy

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, there were no reported adverse events of orthostatic hypotension and syncope.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 20 to 60 mg and 0.6% with LATUDA 80 to 120 mg compared to 0% with placebo.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression therapy studies, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 1.1% with LATUDA 20 to 120 mg compared to 0.9% with placebo.

5.10 Seizures

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, seizures/convulsions occurred in 0.1% (2/1508) of patients treated with LATUDA compared to 0.1% (1/708) placebo-treated patients.

Bipolar Depression

Monotherapy

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, no patient experienced seizures/convulsions.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, no patient experienced seizures/convulsions.

5.11 Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

In clinical studies with LATUDA, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, somnolence was reported by 17.0% (256/1508) of patients treated with LATUDA (15.5% LATUDA 20 mg, 15.6% LATUDA 40 mg, 15.2% LATUDA 80 mg, 26.5% LATUDA 120 mg and 8.3% LATUDA 160 mg/day) compared to 7.1% (50/708) of placebo patients.

Bipolar Depression

Monotherapy

In the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, somnolence was reported by 7.3% (12/164) and 13.8% (23/167) with LATUDA 20 to 60 mg and 80 to120 mg, respectively compared to 6.5% (11/168) of placebo patients.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies, somnolence was reported by 11.4% (41/360) of patients treated with LATUDA 20-120 mg compared to 5.1% (17/334) of placebo patients.

5.12 Body Temperature Dysregulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration *[see Patient Counseling Information (17.9)]*.

5.13 Suicide

The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the incidence of treatment-emergent suicidal ideation was 0.4% (6/1508) for LATUDA-treated patients compared to 0.8% (6/708) on placebo. No suicide attempts or completed suicides were reported in these studies.

Bipolar Depression

Monotherapy

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the incidence of treatment-emergent suicidal ideation was 0.0% (0/331) with LATUDA-treated patients compared to 0.0% (0/168) with placebo-treated patients. No suicide attempts or completed suicides were reported in this study.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, the incidence of treatment-emergent suicidal ideation was 1.1% (4/360) for LATUDA-treated patients compared to 0.3% (1/334) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.14 Activation of Mania/Hypomania

Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes.

In the bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

5.15 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.16 Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

6 ADVERSE REACTIONS

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain) *[see Warnings and Precautions (5.6)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.8)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.11)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.12)]*
- Suicide *[see Warnings and Precautions (5.13)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.14)]*
- Dysphagia *[see Warnings and Precautions (5.15)]*
- Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies *[see Warnings and Precautions (5.16)]*

6.1 Clinical Trials Experience

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

The information below is derived from an integrated clinical study database for LATUDA consisting of 3799 patients exposed to one or more doses of LATUDA for the treatment of schizophrenia and bipolar depression in placebo-controlled studies. This experience corresponds with a total experience of 1250.9 patient-years. A total of 1106 LATUDA-treated patients had at least 24 weeks and 371 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Schizophrenia

The following findings are based on the short-term, placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in Table 14.

Table 14: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

	Percentage of Patients Reporting Reaction						
		LATUDA					
Body System or Organ Class	**Placebo (N=708) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**	**All LATUDA (N=1508) (%)**
Gastrointestinal Disorders							
Nausea	5	11	10	9	13	7	10
Vomiting	6	7	6	9	9	7	8
Dyspepsia	5	11	6	5	8	6	6
Salivary Hypersecretion	<1	1	1	2	4	2	2
Musculoskeletal and Connective Tissue Disorders							
Back Pain	2	0	4	3	4	0	3
Nervous System Disorders							
Akathisia	3	6	11	12	22	7	13
Extrapyramidal Disorder*	6	6	11	12	22	13	14
Dizziness	2	6	4	4	5	6	4
Somnolence**	7	15	16	15	26	8	17
Psychiatric Disorders							
Insomnia	8	8	10	11	9	7	10
Agitation	4	10	7	3	6	5	5
Anxiety	4	3	6	4	7	3	5
Restlessness	1	1	3	1	3	2	2

Note: Figures rounded to the nearest integer

*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus

**Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Dose-Related Adverse Reactions in the Schizophrenia Studies

Akathisia and extrapyramidal symptoms were dose-related. The frequency of akathisia increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 10.7% for LATUDA 40 mg, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg). Akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

Bipolar Depression (Monotherapy)

The following findings are based on the short-term, placebo-controlled premarketing study for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n=331).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5%, in either dose group, and at least twice the rate of placebo) in patients treated with LATUDA were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 6.0% (20/331) LATUDA-treated patients and 5.4% (9/168) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 15.

Table 15: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in a Short-term Monotherapy Bipolar Depression Study

	Percentage of Patients Reporting Reaction			
Body System or Organ Class Dictionary-derived Term	**Placebo (N=168) (%)**	**LATUDA 20-60 mg/day (N=164) (%)**	**LATUDA 80-120 mg/day (N=167) (%)**	**All LATUDA (N=331) (%)**
Gastrointestinal Disorders				
Nausea	8	10	17	14
Dry Mouth	4	6	4	5
Vomiting	2	2	6	4
Diarrhea	2	5	3	4
Infections and Infestations				
Nasopharyngitis	1	4	4	4
Influenza	1	<1	2	2
Urinary Tract Infection	<1	2	2	2
Musculoskeletal and Connective Tissue Disorders				
Back Pain	<1	3	<1	2
Nervous System Disorders				
Extrapyramidal Symptoms*	2	5	9	7
Somnolence**	7	7	14	11
Akathisia	2	8	11	9
Psychiatric Disorders				
Anxiety	1	4	5	4

Note: Figures rounded to the nearest integer
*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus
**Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Dose-Related Adverse Reactions in the Monotherapy Study:
In the short-term, placebo-controlled study (involving lower and higher LATUDA dose ranges) [see Clinical Studies (14.2)] the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA in any dose group and greater than placebo in both groups were nausea (10.4%, 17.4%), somnolence (7.3%, 13.8%), akathisia (7.9%, 10.8%), and extrapyramidal symptoms (4.9%, 9.0%) for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively.

Bipolar Depression

Adjunctive Therapy with Lithium or Valproate
The following findings are based on two short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in subjects treated with LATUDA were akathisia and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 16.

Table 16: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Short-term Adjunctive Therapy Bipolar Depression Studies

	Percentage of Patients Reporting Reaction	
Body System or Organ Class Dictionary-derived Term	**Placebo (N=334) (%)**	**LATUDA 20 to 120 mg/day (N=360) (%)**
Gastrointestinal Disorders		
Nausea	10	14
Vomiting	1	4
General Disorders		
Fatigue	2	3
Infections and Infestations		
Nasopharyngitis	2	4
Investigations		
Weight Increased	1	3
Metabolism and Nutrition Disorders		
Increased Appetite	2	3
Nervous System Disorders		
Extrapyramidal Symptoms*	9	14
Somnolence**	5	11
Akathisia	5	11
Psychiatric Disorders		
Restlessness	1	

Note: Figures rounded to the nearest integer
*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus
**Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Extrapyramidal Symptoms

Schizophrenia
In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 17.

Table 17: Incidence of EPS Compared to Placebo in Schizophrenia Studies

		LATUDA				
Adverse Event Term	**Placebo (N=708) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**
All EPS events	**9**	**10**	**21**	**23**	**39**	**20**
All EPS events, excluding Akathisia/ Restlessness	**6**	**6**	**11**	**12**	**22**	**13**
Akathisia	3	6	11	12	22	7
Dystonia*	<1	0	4	5	7	2
Parkinsonism**	5	6	9	8	17	11
Restlessness	1	1	3	1	3	2

Note: Figures rounded to the nearest integer
*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Bipolar Depression

Monotherapy
In the short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% versus 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% versus 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in Table 18.

Table 18: Incidence of EPS Compared to Placebo in the Monotherapy Bipolar Depression Study

		LATUDA	
Adverse Event Term	**Placebo (N=168) (%)**	**20 to 60 mg/day (N=164) (%)**	**80 to 120 mg/day (N=167) (%)**
All EPS events	5	12	20
All EPS events, excluding Akathisia/ Restlessness	2	5	9
Akathisia	2	8	11
Dystonia*	0	0	2
Parkinsonism**	2	5	8
Restlessness	<1	0	3

Note: Figures rounded to the nearest integer
*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Adjunctive Therapy with Lithium or Valproate
In the short-term, placebo-controlled adjunctive therapy bipolar depression studies, for LATUDA-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 15.3% versus 9.8% for placebo. The incidence of akathisia for LATUDA-treated patients was 7.7% versus 4.3% for placebo-treated patients. Incidence of EPS is provided in Table 19.

Table 19: Incidence of EPS Compared to Placebo in the Adjunctive Therapy Bipolar Depression Studies

Adverse Event Term	**Placebo (N=334) (%)**	**LATUDA 20 to 120 mg/day (N=360) (%)**
All EPS events	**13**	**24**
All EPS events, excluding Akathisia/ Restlessness	**9**	**14**
Akathisia	5	11
Dystonia*	1	1
Parkinsonism**	8	13
Restlessness	1	4

Note: Figures rounded to the nearest integer
*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (BAS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesias.

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%), the SAS (LATUDA, 5.0%; placebo, 2.3%) and the AIMS (LATUDA, 7.4%; placebo, 5.8%).

Bipolar Depression

Monotherapy
The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.4%; placebo, 5.6%), the SAS (LATUDA, 3.7%; placebo, 1.9%) and the AIMS (LATUDA, 3.4%; placebo, 1.2%).

Adjunctive Therapy with Lithium or Valproate
The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.7%; placebo, 2.1%), the SAS (LATUDA, 2.8%; placebo, 2.1%) and the AIMS (LATUDA, 2.8%; placebo, 0.6%).

Dystonia
Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Schizophrenia
In the short-term, placebo-controlled schizophrenia clinical studies, dystonia occurred in 4.2% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 3.5% LATUDA 40 mg, 4.5% LATUDA 80 mg, 6.5% LATUDA 120 mg and 2.5% LATUDA 160 mg) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

Bipolar Depression

Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.8% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.0% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 1.1% of LATUDA-treated subjects (20 to 120 mg) compared to 0.6% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA
Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily within the premarketing database of 2905 patients with schizophrenia. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 14 or those that appear elsewhere in the LATUDA label are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: ***Infrequent:*** *anemia*

Cardiac Disorders: ***Frequent:*** *tachycardia;* ***Infrequent:*** *AV block 1st degree, angina pectoris, bradycardia*

Ear and Labyrinth Disorders: ***Infrequent:*** *vertigo*

Eye Disorders: ***Frequent:*** *blurred vision*

Gastrointestinal Disorders: ***Frequent:*** *abdominal pain, diarrhea;* ***Infrequent:*** *gastritis*

General Disorders and Administrative Site Conditions: ***Rare:*** *sudden death*

Investigations: ***Frequent:*** *CPK increased*

Metabolism and Nutritional System Disorders: ***Frequent:*** *decreased appetite*

Musculoskeletal and Connective Tissue Disorders: ***Rare:*** *rhabdomyolysis*

Nervous System Disorders: ***Infrequent:*** *cerebrovascular accident, dysarthria*

Psychiatric Disorders: ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder*

Renal and Urinary Disorders: ***Infrequent:*** *dysuria;* ***Rare:*** *renal failure*

Reproductive System and Breast Disorders: ***Infrequent:*** *amenorrhea, dysmenorrhea;* ***Rare:*** *breast enlargement, breast pain, galactorrhea, erectile dysfunction*

Skin and Subcutaneous Tissue Disorders: ***Frequent:*** *rash, pruritus;* ***Rare:*** *angioedema*

Vascular Disorders: ***Frequent:*** *hypertension*

Clinical Laboratory Changes
Schizophrenia

Serum Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from > 0.79 to > 1.3 mg/dL based on the centralized laboratory definition for each study (Table 20).

Table 20: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Schizophrenia Studies

Laboratory Parameter	**Placebo (N=708)**	**LATUDA 20 mg/day (N=71)**	**LATUDA 40 mg/day (N=487)**	**LATUDA 80 mg/day (N=538)**	**LATUDA 120 mg/day (N=291)**	**LATUDA 160 mg/day (N=121)**
Serum Creatinine Elevated	2%	1%	2%	2%	5%	7%

Bipolar Depression

Monotherapy

Serum Creatinine: In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.01 mg/dL for LATUDA-treated patients compared to -0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.8% (9/322) of LATUDA-treated patients and 0.6% (1/162) on placebo (Table 21).

Table 21: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in a Monotherapy Bipolar Depression Study

Laboratory Parameter	Placebo (N=168)	LATUDA 20 to 60 mg/day (N=164)	LATUDA 80 to 120 mg/day (N=167)
Serum Creatinine Elevated	<1%	2%	4%

Adjunctive Therapy with Lithium or Valproate

Serum Creatinine: In short-term, placebo-controlled premarketing adjunctive studies for bipolar depression, the mean change from Baseline in serum creatinine was +0.04 mg/dL for LATUDA-treated patients compared to -0.01 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 4.3% (15/360) of LATUDA-treated patients and 1.6% (5/334) on placebo (Table 22).

Table 22: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adjunctive Therapy Bipolar Depression Studies

Laboratory Parameter	Placebo (N=334)	LATUDA 20 to 120 mg/day (N=360)
Serum Creatinine Elevated	2%	4%

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect LATUDA

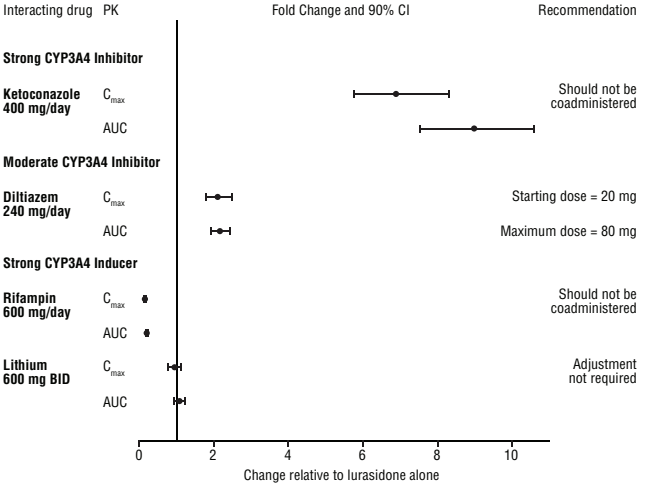
LATUDA is predominantly metabolized by CYP3A4. LATUDA should not be used concomitantly with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) or strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) *[see Contraindications (4)]*. The LATUDA dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4 (e.g., diltiazem, atazanavir, erythromycin, fluconazole, verapamil, etc.). If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose *[see Dosage and Administration (2.5)]*.

Lithium: It is not necessary to adjust the LATUDA dose when used concomitantly with lithium (Figure 1).

Valproate: It is not necessary to adjust the LATUDA dose when used concomitantly with valproate. A dedicated drug-drug interaction study has not been conducted with valproate and LATUDA. Based on pharmacokinetic data from the bipolar depression studies valproate levels were not affected by lurasidone, and lurasidone concentrations were not affected by valproate.

Grapefruit: Grapefruit and grapefruit juice should be avoided in patients taking LATUDA *[see Dosage and Administration (2.5)]*.

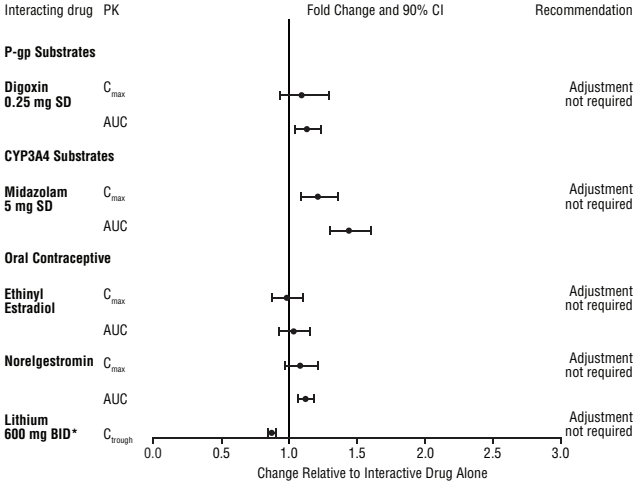
Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics



7.2 Potential for LATUDA to Affect Other Drugs

No adjustment is needed on the dose of lithium, valproate, or substrates of P-gp or CYP3A4 when coadministered with LATUDA (Figure 2).

Figure 2: Impact of LATUDA on Other Drugs



*Steady state lithium Ctrough on Day 4 vs Day 8 when lithium was coadministered with lurasidone at steady state

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well controlled studies of LATUDA use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Safe use of LATUDA during pregnancy or lactation has not been established; therefore, use of LATUDA in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

Animal Data

No adverse developmental effects were observed in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day, which is approximately half of the maximum recommended human dose (MRHD) of 160 mg/day, based on mg/m^2 body surface area.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 1.5- and 6-times, in rats and rabbits, respectively, the MRHD of 160 mg/day based on mg/m^2 body surface area.

8.3 Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk of drug discontinuation to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

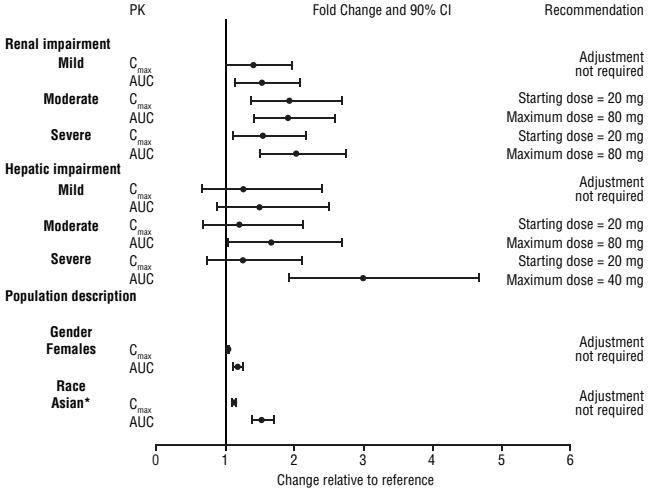
Clinical studies with LATUDA did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects. It is unknown whether dose adjustment is necessary on the basis of age alone.

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

8.6 Other Patient Factors

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 3.

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics



*Compare to Caucasian

10 OVERDOSAGE

10.1 Human Experience

In premarketing clinical studies, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2 Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consider the possibility of multiple-drug overdose.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly, the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

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INDICATIONS

LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults.

IMPORTANT SAFETY INFORMATION FOR LATUDA

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for use in patients with dementia-related psychosis.**
- **Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. LATUDA is not approved for use in patients under the age of 18 years.**

Please see additional Important Safety Information, including **Boxed Warnings**, and Brief Summary of Prescribing Information on adjacent pages.

SUNOVION

Up front » In Depth

Julie Miller

Unauthorized prescribers bilk Part D out of $5.4 million

Estimates of the cost of Medicare fraud range broadly from $17 billion to $90 billion. However, there are no estimates of — or methods to detect — how much of the waste results from human error and not blatant crime.

A recent study from the Office of the Inspector General (OIG) found that in 2009 Medicare Part D paid for $5.4 million worth of Rx drugs ordered by individuals who clearly had no authority to prescribe, such as massage therapists and dieticians. The report raises concerns about both Medicare waste and patient safety.

However, OIG does not further explore how the inappropriate prescriptions were generated, which individuals or practices were involved, or why pharmacies filled the orders, said Lee Lasris, founding partner of South Florida's Health Law Center.

"It's too complicated a set of relationships to simply say there's a lot of inappropriate prescribing," Lasris said. "Are we talking about criminal conspiracy, or are we talking about mistakes?"

More than 29,000 of the improper Rxs were for controlled substances and came from nearly 5,000 different individuals with no prescribing authority. Drugs most often prescribed include simvastatin, lisinopril, hydrocodone-acetaminophen, amlodipine besylate, and levothyroxine sodium.

Possible explanations

Even with today's electronic prescribing systems, logistical mistakes still occur in prescribing practice. Most electronic systems employ drop-down menus designed to help users quickly fill data fields. It seems plausible that medical office staff could accidentally choose the wrong name from a menu, or that a pharmacy technician might enter a legitimate prescriber's information incorrectly, resulting in a mistaken reference to a provider not authorized to prescribe.

"All kinds of people are connected to medical doctors who think they might be doing something the right way, and they're part of a process that can break down," Lasris said. "If I operate under the authority or personal supervision of a doctor and he instructs me to write down the order, and an office clerk doesn't attach the physician's name to it and it just goes out, then it's not as evil a situation as it seems to be in the OIG report."

For drugs that have street value, such as hydrocodone, the second most-prescribed drug in the report, the obvious explanation would be fraud, Lasris said.

"If the pharmacy fills a controlled-substance prescription and the Drug Enforcement Administration number is not on there, the pharmacy is supposed to inquire, at least. Otherwise the pharmacy violates the law," he said. "But that's up to the states to jerk the license or put the pharmacy out of business."

Plan responsibility

The Centers for Medicare and Medicaid Services (CMS) noted that the Part D database used to create the OIG report might contain incorrect information. In a time when Medicare spending is under close scrutiny, OIG recommends that Part D plan sponsors be responsible for verifying providers before prescription claims are paid. CMS agreed.

In fact, New Jersey Congressman Frank Pallone Jr. indicated last month that he wants to introduce legislation requiring Part D plans to verify the prescribers of controlled substance prescriptions before the claim is paid. While Congress does have regulatory authority over Part D sponsors, it does not regulate the pharmacies that fill the orders. Pharmacy regulation is done at state level.

Under OIG's recommendation and Pallone's proposal, a drug claim originating from an inappropriate prescriber could be rejected and payment denied, although the initial fill would still be completed.

Worst offenders

In all, OIG studied 14 provider types that have no authority to prescribe and found 72,552 inappropriate prescriptions at a cost of $5.4 million. Nutritionists topped the list with more than 700 individuals writing 20,044 prescriptions inappropriately.

The report also singled out certain states. California had 25% of the inappropriate Rx claims and Florida had 20%.

"Florida ranks high on every bad deed that they find involving improper Medicare payments," Lasris said. "Florida is a laughingstock when it comes to Medicare fraud and healthcare fraud in general. There's a lot of 'smoke' here, and typically when there's smoke, there's fire. We do get our share of criminal convictions."

It could be argued that report is simply a way for Medicare to deny certain payments, he said, but the analysis does not go far enough to identify the real problem.

In March, FDA proposed that certain prescription drugs be moved to a new category that would allow pharmacists to have some authority to prescribe for patients with chronic conditions and regular drug regimens. Not surprisingly, delegates of the American Medical Association reviewed and opposed the idea last month. DT

Julie Miller *is Editor-in-Chief of* Managed Healthcare Executive. *This article appears in its August 2013 issue.*

Up front
In Depth

Johanna Sierra, BS, PharmD candidate, and
Vaiyapuri Subramaniam, PharmD, MS, FCP, FASHP, FASCP

The impact of pharmacists on public health

Closing gaps in healthcare disparities

It is much more cost-effective to prevent chronic diseases than to treat them after they occur. Most chronic diseases could be prevented through lifestyle and environmental changes, according to the U.S. Centers for Disease Control and Prevention (CDC).[1]

Reducing adult smoking rates by 1% could result in at least 30,000 fewer heart attacks, 16,000 fewer strokes, and $1.5 billion saving over five years, according to the CDC.[1] Also, if one-tenth of all Americans began a walking program, $5.6 billion could be saved in the treatment of heart disease.[1] In addition, routine childhood vaccinations result in $50 billion saved annually in direct and indirect costs.[1]

Public health interventions have significant economic ramifications at both the societal and individual levels. A community's financial investment in the well-being of its members will be reflected in fewer health disparities, greater universal access to health care, and an emphasis on early health education and promotion.

As the most accessible healthcare professionals in the community, pharmacists can take the initiative to bridge the gap in these health disparities by effectively communicating with their patients and community on the topics of health literacy, smoking cessation, diabetes, lifestyle changes, and the importance of vaccinations.

Health literacy

Independent risk factors for low health literacy include ethnicity, socioeconomic status, older age, and limited education, according to the National Assessment of Adult Literacy.[2] Pharmacists who are trained to recognize and properly communicate with a patient who has low health literacy will positively impact public health through improved population health outcomes and, ultimately, decreases in mortality and healthcare costs.

Pharmacists can help bridge the health-disparities gap by addressing medication adherence and lifestyle modification in chronic disease cases.

When patients come into the pharmacy to pick up their medications, the pharmacist is the most appropriate healthcare provider to ensure proper understanding of medication use and to reinforce the benefits of adherence. Pharmacists can bridge communication gaps that exist as a result of cultural differences and health literacy disparities among patients.

Pharmacists have the training and knowledge to assess and address a patient's health needs. They have an obligation to focus on the patient and to maintain impeccable standards of quality and safety within their pharmacy practice. Pharmacists can help bridge the health-disparities gap by addressing medication adherence and lifestyle modifications, specifically for patients with chronic diseases.

Causes of nonadherence to medication regimens include side effects, patients' inability to understand the benefits of the medication, and pill burden. Pharmacists have the opportunity to expand their clinical roles beyond the perceived scope of practice and engage patients through services targeting improved adherence and reduced healthcare costs. They can model these methods by taking an active role in public health through primary, secondary, and tertiary prevention.

Health promotion/education

Primary prevention includes measures taken to either eliminate patients' risk factors or increase their resistance to disease. Pharmacists can educate their patients about interventions that require no treatment, such as changes in lifestyle, nutrition, and their environment. Encouraging people to protect themselves from the sun's ultraviolet rays is one example.

Health education about specific disease states will empower patients to take a more proactive approach to their healthcare. To prepare to educate patients, pharmacists can take local cultural literacy courses relevant to the populations they serve. Culturally relevant educational materials provided in specific languages or with graphic representations will reinforce key concepts and messages that the pharmacist seeks to convey.

An equally important primary prevention service is vaccination education. More than 50,000 U.S. adults and 300 children die annually from vaccine-

Indication

Osphena™ (ospemifene) is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Select Important Safety Information

Boxed WARNING: Endometrial Cancer and Cardiovascular Disorders

Osphena is an estrogen agonist/antagonist with tissue selective effects. In the endometrium Osphena has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen therapy. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

The Women's Health Initiative (WHI) estrogen-alone substudy reported an increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg], relative to placebo. Osphena 60 mg had thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women vs. 1.04 and 0 per thousand women for placebo and a DVT incidence rate of 1.45 vs. 1.04 per thousand women for placebo. Osphena should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

Please see additional Important Safety Information and Brief Summary of the Full Prescribing Information, including Boxed WARNING, on the following pages.

Select Important Safety Information

Contraindications

- Osphena should not be used in patients with undiagnosed abnormal genital bleeding, known or suspected estrogen-dependent neoplasia, active deep vein thrombosis (DVT), pulmonary embolism (PE) or active arterial thromboembolic disease or a history of these conditions
- Women who are or may become pregnant. Osphena may cause fetal harm when administered to a pregnant woman. Ospemifene was embryo-fetal lethal with labor difficulties and increased pup deaths in rats at doses below clinical exposures, and embryo-fetal lethal in rabbits at 10 times the clinical exposure based on mg/m^2. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to a fetus

Warnings and Precautions

Osphena has not been adequately studied in women with breast cancer; therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.

Osphena should not be used in women with severe hepatic impairment as it has not been studied.

In clinical trials the more commonly reported adverse reactions in ≥1 percent of patients treated with Osphena 60 mg compared to placebo were: hot flush (7.5% vs. 2.6%), vaginal discharge (3.8% vs. 0.3%), muscle spasms (3.2% vs. 0.9%), hyperhidrosis (1.6% vs. 0.6%), and genital discharge (1.3% vs. 0.1%).

Do not use estrogens or estrogen agonists/antagonists, fluconazole, or rifampin concomitantly with Osphena.

Please see Brief Summary of the Full Prescribing Information, including Boxed WARNING, on the following page.

The first and only NON-ESTROGEN ORAL treatment for moderate to severe dyspareunia, due to menopause

- **REVERSES** key physiological signs of vulvar and vaginal atrophy (VVA), which include increasing superficial cells, decreasing parabasal cells, and decreasing vaginal pH
- Significantly **IMPROVED** the most bothersome symptom (MBS)* of VVA, which was moderate to severe dyspareunia
- Available in a 60-mg **ORAL** tablet taken once daily with food
- Most common adverse reactions include hot flush, vaginal discharge, muscle spasms, hyperhidrosis, and genital discharge

NLY The **FIRST** FDA-approved estrogen agonist/antagonist for moderate to severe dyspareunia, due to menopause.

New Osphena™
(ospemifene) tablets
60 mg

STUDY DESIGN: Two 12-week, randomized, double-blind, placebo-controlled, parallel-group efficacy studies in 1745 generally healthy postmenopausal women. The first clinical study included 3 treatment groups: Osphena 30 mg (n=282), Osphena 60 mg (n=276), and placebo (n=268). The second clinical study included 2 treatment groups: Osphena 60 mg (n=463) and placebo (n=456). Clinical endpoints for both clinical studies included: a mean change from baseline to Week 12 for percentage of superficial cells on a vaginal smear, percentage of parabasal cells on a vaginal smear, vaginal pH, and most bothersome symptom of VVA (dyspareunia) self-reported by the patient.* A 52-week, randomized, double-blind, placebo-controlled, long-term safety study was also conducted with 2 treatment groups: Osphena 60 mg (n=363) and placebo (n=63).

*MBS was defined as the most bothersome moderate to severe symptom at baseline.

osphena.com

OSPHENA™ (ospemifene) 60 mg tablets
BRIEF SUMMARY – See Package Insert for Complete Prescribing Information.

WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS

Endometrial Cancer

OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed and random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see *Warnings and Precautions (5.2)*].

Cardiovascular Disorders

There is a reported increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) who received daily oral conjugated estrogens (CE) [0.625 mg]-alone therapy over 7.1 years as part of the Women's Health Initiative (WHI) [see *Warnings and Precautions (5.1)*].

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 0.72 and 1.45 per thousand women, respectively in OSPHENA 60 mg treatment group and 1.04 and 0 in placebo [see *Warnings and Precautions (5.1)*]. The incidence of DVT was 1.45 per thousand women in OSPHENA 60 mg treatment group and 1.04 per thousand women in placebo [see *Warnings and Precautions (5.1)*]. OSPHENA should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE: OSPHENA is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

CONTRAINDICATIONS: OSPHENA is contraindicated in women with any of the following conditions:
- Undiagnosed abnormal genital bleeding
- Known or suspected estrogen-dependent neoplasia
- Active DVT, pulmonary embolism (PE), or a history of these conditions
- Active arterial thromboembolic disease [for example, stroke and myocardial infarction (MI)], or a history of these conditions
- OSPHENA is contraindicated in women who are or may become pregnant. OSPHENA may cause fetal harm when administered to a pregnant woman. Ospemifene was embryo-fetal lethal with labor difficulties and increased pup deaths in rats at doses below clinical exposures, and embryo-fetal lethal in rabbits at 10 times the clinical exposure based on mg/m^2. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Cardiovascular Disorders

Risk factors for cardiovascular disorders, arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus), should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per ten thousand women-years). The increase in risk was demonstrated in year 1 and persisted.

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 0.72 and 1.45 per thousand women, respectively in OSPHENA 60 mg treatment group and 1.04 and 0 per thousand women in placebo.

Should thromboembolic or hemorrhagic stroke occur or be suspected, OSPHENA should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo. In the OSPHENA clinical trials, a single MI occurred in a woman receiving 60 mg of ospemifene.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE), was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per ten thousand women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per ten thousand women-years). The increase in VTE risk was demonstrated during the first 2 years.

In the OSPHENA clinical trials, the incidence of DVT was 1.45 per thousand women in OSPHENA 60 mg treatment group and 1.04 per thousand women in placebo. Should a VTE occur or be suspected, OSPHENA should be discontinued immediately.

If feasible, OSPHENA should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant Neoplasms

Endometrial Cancer

OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has agonistic effects. In the OSPHENA clinical trials (60 mg treatment group), no cases of endometrial cancer were seen with exposure up to 52 weeks. There was a single case of simple hyperplasia without atypia. Endometrial thickening equal to 5 mm or greater was seen in the OSPHENA treatment groups at a rate of 60.1 per thousand women vs 21.2 per thousand women for placebo. The incidence of any type of proliferative (weakly plus active plus disordered) endometrium was 86.1 per thousand women in OSPHENA vs 13.3 per thousand women for placebo. Uterine polyps occurred at an incidence of 5.9 per thousand women vs 1.8 per thousand women for placebo.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. The use of progestins with OSPHENA therapy was not evaluated in the clinical trials.

Clinical surveillance of all women using OSPHENA is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Breast Cancer

OSPHENA 60 mg has not been adequately studied in women with breast cancer; therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.

Severe Hepatic Impairment

OSPHENA should not be used in women with severe hepatic impairment [see Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)].

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:
- Cardiovascular Disorders [see *Boxed Warnings, Warnings and Precautions (5.1)*]
- Malignant Neoplasms [see *Boxed Warnings, Warnings and Precautions (5.2)*]

Clinical Trial Experience

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

The safety of OSPHENA has been assessed in nine phase 2/3 trials (N=1892) with doses ranging from 5 to 90 mg per day. The duration of treatment in these studies ranged from 6 weeks to 15 months. Most women (N=1370) had a treatment period of at least 12 weeks, 409 had at least 52 weeks (1 year) of exposure.

The incidence rates of thromboembolic and hemorrhagic stroke were 0.72 per thousand women (1 reported case of thromboembolic stroke) and 1.45 per thousand women (2 reported cases of hemorrhagic stroke), respectively in OSPHENA 60 mg treatment group and 1.04 and 0 per thousand women, respectively in placebo. The incidence of deep vein thrombosis (DVT) was 1.45 per thousand women in OSPHENA 60 mg treatment group (2 reported cases of DVT) and 1.04 (1 case of DVT) in placebo.

In clinical trials the more commonly reported adverse reactions in ≥1 percent of patients treated with Osphena 60 mg compared to placebo were: hot flush (7.5% vs. 2.6%), vaginal discharge (3.8% vs. 0.3%), muscle spasms (3.2% vs. 0.9%), hyperhidrosis (1.6% vs. 0.6%), and genital discharge (1.3% vs. 0.1%).

DRUG INTERACTIONS

OSPHENA is primarily metabolized by CYP3A4 and CYP2C9. CYP2C19 and other pathways contribute to the metabolism of ospemifene.

Estrogens and estrogen agonist/antagonist

OSPHENA should not be used concomitantly with estrogens and estrogen agonists/antagonists. The safety of concomitant use of OSPHENA with estrogens and estrogen agonists/antagonists has not been studied.

Fluconazole

Fluconazole, a moderate CYP3A/strong CYP2C9/moderate CYP2C19 inhibitor, should not be used with OSPHENA. Fluconazole increases the systemic exposure of ospemifene by 2.7-fold. Administration of fluconazole with ospemifene may increase the risk of OSPHENA-related adverse reactions [see *Clinical Pharmacology (12.3)*].

Rifampin

Rifampin, a strong CYP3A4/moderate CYP2C9/moderate CYP2C19 inducer, decreases the systemic exposure of ospemifene by 58%. Therefore, coadministration of OSPHENA with drugs such as rifampin which induce CYP3A4, CYP2C9 and/or CYP2C19 activity would be expected to decrease the systemic exposure of ospemifene, which may decrease the clinical effect [see *Clinical Pharmacology (12.3)*].

Ketoconazole

Ketoconazole, a strong CYP3A4 inhibitor increases the systemic exposure of ospemifene by 1.4-fold. Administration of ketoconazole chronically with ospemifene may increase the risk of OSPHENA-related adverse reactions [see *Clinical Pharmacology (12.3)*].

Warfarin

Repeated administration of ospemifene had no effect on the pharmacokinetics of a single 10 mg dose of warfarin. No study was conducted with multiple doses of warfarin. The effect of ospemifene on clotting time such as the International Normalized Ratio (INR) or prothrombin time (PT) was not studied [see *Clinical Pharmacology (12.3)*].

Highly Protein-Bound Drugs

Ospemifene is more than 99% bound to serum proteins and might affect the protein binding of other drugs. Use of OSPHENA with other drug products that are highly protein bound may lead to increased exposure of either that drug or ospemifene [see *Clinical Pharmacology (12.3)*].

Multiple Enzyme Inhibition

Coadministration of OSPHENA with a drug known to inhibit CYP3A4 and CYP2C9 isoenzymes may increase the risk of OSPHENA-related adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic effects: Pregnancy Category X [see *Contraindications (4)*].

Nursing Mothers

It is not known whether OSPHENA is excreted in human breast milk. In a nonclinical study, ospemifene was excreted in rat milk and detected at concentrations higher than that in maternal plasma.

Pediatric Use

OSPHENA is not indicated in children. Clinical studies have not been conducted in the pediatric population.

Geriatric Use

Of the 1892 OSPHENA-treated women enrolled in the nine phase 2/3 trials of OSPHENA, >19 percent were 65 years of age or older. No clinically meaningful differences in safety or effectiveness were observed between these women and younger women less than 65 years of age.

Renal Impairment

The pharmacokinetics of ospemifene in women with severe renal impairment (CrCL<30 mL/min) was similar to those in women with normal renal function [see *Clinical Pharmacology (12.3)*].

No dose adjustment of OSPHENA is required in women with renal impairment.

Hepatic Impairment

The pharmacokinetics of ospemifene has not been studied in women with severe hepatic impairment (Child-Pugh Class C); therefore, OSPHENA should not be used in women with severe hepatic impairment [see *Warnings and Precautions (5.3)*, and *Clinical Pharmacology (12.3)*].

No clinically important pharmacokinetic differences with OSPHENA were observed between women with mild to moderate hepatic impairment and healthy women [see *Clinical Pharmacology (12.3)*].

No dose adjustment of OSPHENA is required in women with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

OVERDOSAGE

There is no specific antidote for OSPHENA.

Based on OSPHENA (ospemifene) 60 mg tablets, Prescribing Information 02/2013.

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preventable diseases or their complications. Immunizations, including those administered by pharmacists, help prevent an estimated 14 million cases of vaccine-preventable diseases and 33,000 cases of death.[3]

One of the major objectives for the U.S. Department of Health and Human Services Healthy People 2010 initiative, a nationwide health-promotion and disease-prevention program, is to improve immunization rates among individuals in the United States.[4] Pharmacists are capable of identifying at-risk populations and encouraging such patients to consider the advantages of receiving vaccinations in the pharmacy. The most relevant vaccinations are patients' yearly flu shot as well as pneumococcal and zoster vaccine for shingles. Currently, all 50 states allow pharmacists to administer vaccinations.[5]

Clinical care

The goal of secondary prevention is to find and treat disease early, before it becomes symptomatic or before it can be transmitted to others.[6]

Patients see their pharmacists more regularly than they do most other healthcare providers. Therefore, pharmacists can follow the progress of patients during the 10-minute interactions they have at least once every month, and using information that arises during the visit, they can suggest the next steps for patients to take.

Well-established clinical testing or screenings will detect risk factors such as elevated blood pressure, which helps in the prevention of strokes and heart attacks; finger sticks reveal elevated blood sugar levels in patients with prediabetes; and PPD skin tests detect cases of asymptomatic tuberculosis.[6]

By explaining the consequences associated with refusal to seek medical assistance or to adhere to medication or suggested lifestyle changes, a pharmacist can influence patients.

Rehabilitative care

Tertiary prevention targets the person who already has symptoms of the disease. The goal is to prevent damage and pain from the disease and slow down the disease progression, or even when possible to prevent the disease from causing other complications.[6]

Tertiary prevention may slow the course of some progressive diseases and prevent or delay many complications associated with chronic diseases such as arthritis, asthma, and diabetes. A pharmacist who knows the complications connected with each disease state can make appropriate interventions.

When a pharmacist urges a patient to pay attention to HbA1c levels and blood-sugar readings, the pharmacist is practicing tertiary prevention.

National Eye Institute research has shown that patients who maintain tight control of their blood-sugar levels have a better chance to delay or prevent the devastating complications of diabetic retinopathy.[7] When a pharmacist urges a patient to pay closer attention to hemoglobin A1c levels and blood-sugar readings, the pharmacist is practicing tertiary prevention.

With smoking cessation, pharmacists are ethically obligated to offer information and assistance to any patient currently smoking. Pharmacists should recognize the patients who would most benefit from quitting and focus their efforts on these individuals. Patients who fit this description have diabetes, chronic obstructive pulmonary disease, asthma, and cancer.

By taking the time to speak to and educate these populations, pharmacists can play a role that from a public health perspective can have a significant impact on the course of their diseases. DT

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Mark P. Walberg, PharmD, PhD

Give it your best shot: Four simple tips for vaccinators

As a faculty trainer for the American Pharmacists Association's Pharmacy-Based Immunization Delivery certification program and as a pharmacist who offers immunizations, I have trained hundreds and vaccinated thousands of individuals. Here are some tips and observations that will, hopefully, be beneficial to pharmacists in any setting who want to immunize patients.

Talk to your patients

It is easy to get into the habit of giving the patient's questionnaire a quick glance, noting no issues, and proceeding to vaccination. Instead, stop and ask your patient a few questions that may not be on your screening questionnaire. Even a "How are you doing today?" can go a long way.

Consider that the patient may only have glanced at the questions and not taken the time to carefully read them. Ask your patient, "Do you have any questions? Have you had this vaccine before? Are you allergic to anything?" If the patient asks why you are asking *again*, respond simply that you want to be sure there is nothing to prevent the patient from receiving the vaccine in question. Safety first.

If the person has received the vaccine previously, the patient has the opportunity to tell you about any previous reactions or to comment about any sickness vaccination may have caused. You now have another opportunity to:

- Verify that the vaccine is not contraindicated
- Determine that based on current recommendations[1], the patient does need another dose of the vaccine
- Correct any vaccine misconceptions that were expressed, and/or
- Educate the patient about common vaccine-related reactions and what to do if they occur.

What most people don't realize is that this brief question-and-answer period is more than just fact-checking. Listening to *how* your patient speaks and watching body language will give you a good indication of how nervous your patient is. A tight-lipped patient who won't look at you when you are conversing is a dead giveaway. Many patients will take this time to ask questions about the vaccine or tell you about their fear of needles.

Trust a patient who tells you about passing out during inoculations or blood draws. I have had patients (and students) who will pass out at the very sight of a needle. At least once a year I give a flu shot to a patient lying on the ground to avoid any injury from falling out of a chair. I have a good deal of empathy for patients with a heightened vasovagal reflex or fear of needles. I used to be one of them, and I know how reluctant I was to get vaccinated because of it. Staying calm and confident throughout the process will alleviate, or at least diminish, a patient's jitters.

If you have a concerned patient who presents you with a litany of allergies, take the time to get the package insert (PI) for the vaccine in question. Show the patient the ingredients listed in the "DESCRIPTION" section of the PI (section 11 of any PI).Also, check for latex allergies if the vaccine container has a latex stopper, typical of prefilled syringes (noted in PI section 16, "How Supplied/Storage and Handling"). Some patients will even react to latex gloves or bandages.

The last thing anyone would want is redness caused by a latex bandage near the injection site and to misinterpret the appearance as an injection-site reaction or, worse yet, the beginning of an allergic reaction to the vaccine. I stock only latex-free supplies for this very reason.

Sit back and relax

Ask your patients to "sit back, relax, and enjoy the show." If you don't get a reaction, go back three paragraphs.

Ask your patient to sit back in the chair and relax as much as possible. For intramuscular injections in the deltoid, have the patient rest the arm you will be injecting at the side and place the hand palm up on his or her lap. This will disengage the deltoid muscle more than resting the arm on an armrest, dangling it at the side, or in some cases trying to flex the muscle to "help" you see where the muscle is.

The deltoid can be hard to find in some patients. In this situation, place your hand on the outer side of the pa-

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Four simple tips for vaccinators

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tient's elbow and ask him or her to laterally raise the arm, thus pushing against your hand. With your other hand, you can easily palpate the deltoid muscle.

I mention this because I have seen many patients who received injections in the middle of the arm, in line with their triceps muscle, who claim to have received an intramuscularly administered vaccine (e.g., influenza).

Incorrect administration may decrease vaccine effectiveness, so make sure you know that you are administering it into the right tissue/location. Vaccines administered incorrectly may have to be readministered by the correct route.

If you are unsure about revaccination, go to the Advisory Committee on Immunization Practices (ACIP) Recommendations page on the website of the Centers for Disease Control and Prevention (CDC).[1]

Good positioning should be practiced by the vaccinator as well. Before you unsheathe the syringe, make sure that your patient is in a convenient position for you to deliver the injection and dispose of the syringe once the inoculation is completed (in addition to activating the safety device).

Failure to have your supplies and sharps container in a convenient location can result in your fumbling for a bandage, scrambling for a cotton ball to stop a bleed, or even sticking yourself with a used syringe before its disposal.

Don't go off course

Follow what is generally taught in connection with all injections: After the injection is performed, activate the safety device and dispose of the syringe in a sharps container.

Nothing else should occur before needle disposal. Your eyes should not leave the needle until it is disposed of properly.

I have watched vaccinators activate the safety device and place the syringe in a prescription tote, on the ground, or on a countertop prior to disposal. I have also seen safety devices fail to activate. The combination of the two could lead to a life-altering needle-stick injury.

Are you watching the patient in case he or she passes out after the shot is given? Proper injection technique includes having a hand on your patient while you are injecting and disposing of the syringe. If the patient faints, you have a hand on the arm or shoulder and can keep the patient in the seat.

I don't worry about patients fainting. I worry about what they will hit on the way down or that the floor will catch them if I have not correctly positioned myself and held them in the seat.

I recommend creating a small supply kit that is always within reach of the vaccinator. This kit should include general injection supplies (e.g., bandages, alcohol swabs, etc.), a sharps container, and emergency supplies.

If the patient starts to bleed, activate the safety device, dispose of the syringe, *and then* deal with the blood dripping down the patient's arm. Most patients will not bleed when a vaccine is administered correctly. If bleeding doe occur, the source is just a superficial capillary.

The chances of bleeding are increased if your patient is warm or flushed (increased blood flow to the peripheral capillaries in the skin), or if the patient's sleeve has been tightly rolled up on the arm. Your cotton ball should be ready for this contingency … to be used after your syringe is disposed of properly.

Be prepared

All immunization protocols should contain a section about adverse reactions that follow administration of a vaccination.

If your protocol has no such section, it is time for a new protocol. This and other helpful information is available free on the website of the Immunization Action Coalition (*http://www.immunize.org/clinic/administering-vaccines.asp*[2]).

Have you read your protocol? Do you have it posted somewhere convenient, or is it readily available should you need it? Do you have all the medications that it enumerates?

The first medication included in the emergency protocol is epinephrine, many times in the form of an Epi-pen. Most pharmacies have this in stock, but has your pharmacy provided a separate supply for your emergency kit? Recommendations suggest that the kit include at least three adult Epi-pens.[2]

I recommend creating a small supply kit that is always within reach of the vaccinator. This kit should include the general injection supplies (e.g., bandages, alcohol swabs, etc.), a sharps container, and emergency supplies.

If you are in a community pharmacy and must vaccinate in the waiting area, the kit should be with you. You don't want to leave the patient while you search for an emergency medication, nor do you want to call out to other pharmacy personnel for assistance. Leaving the patient, even for a forgotten bandage, makes an amateur and unprofessional impression.

Be prepared and be professional. DT

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Fred Gebhart, Contributing Editor

New HIPAA requirements coming

Is your pharmacy ready for the new Health Insurance Portability and Accountability Act (HIPAA) Omnibus Rules? New privacy rules took effect in March, 2013, and enforcement begins in September.

"All of the familiar rules surrounding health information and individual patient information have changed," said HIPAA consultant Jeff Hedges, CDME, president and CEO of RJ Hedges & Associates. "Every pharmacy in the country is subject to new requirements for protected health information, network and password security, law enforcement, patient rights and protections, policies and protocols, the handling of information breaches, new business associate agreements, and more. Enforcement begins on September 23."


Jeff Hedges

Hedges outlined the new HIPAA rules during a webinar sponsored by Pharmacy Development Services.

Privacy practices posted

All pharmacies must have a new and revised Notice of Privacy Practices (NOPP) posted in a public area and on websites no later than September 23, he said. All patients must be given a copy of the new NOPP and asked to sign the new notice, although signature is not required.

All the basic definitions used in privacy regulations have changed. So have the rules that govern access to records, restrictions on protected health information, confidential communications of protected health information, and accounting for disclosures of protected health information.

Requirements to safeguard health information have been strengthened. So have reporting requirements for breaches that compromise the security or privacy of protected health information.

"A breach is anyone getting patient information who is not authorized to get it," Hedges said. "It doesn't matter if the information is stolen, if your computer is hacked, or if a patient discards packaging that has their name or other protected health information on it. If there is a breach, you have a duty to notify the patients affected, the federal government, and maybe your local media."

Report privacy breaches

Every breach must be reported directly to the patient or patients involved, he said. The Department of Health and Human Services (DHHS) must also be notified of every breach and there must be an action plan to prevent similar breaches in the future. Fewer than 500 breaches can be reported in a batch, not later than the end of February of the year after the breaches become known.

If more than 500 patients are involved, immediate notification must be given to DHHS and major local media outlets, including newspapers, radio, and television.

"It is not going to help your image to be on the 6:00 news explaining why you lost patient data," Hedges said. "Giving the wrong script to the wrong patient is a breach. Your clerks have to be aware that they are responsible. Personally responsible."

Many of the new HIPAA rules are designed to prevent breaches. Computer networks must be secured and protected by passwords. Every user must have an individual password, and all passwords must be changed at least every 180 days.

Wireless routers and network access points are a weak link in many networks, he added. Every router and access point must be password-protected. USB devices are another potential danger because they can be used to download and store health information that should be protected. Point-of-sale electronics and credit-card devices that capture and store patient names, Rx numbers, and sales data can also be the source of unintended breaches. Disgruntled or former employees can also disclose protected information. The person who causes the breach can be held personally responsible, Hedges said.

The federal government is interested primarily in what steps are taken to minimize risks. That means that when a breach is reported, the pharmacy must also report steps taken to prevent future risks. If officials are satisfied, there may be no fines involved. But not acting on a breach brings a $1.5 million fine for each occurrence.

"The consequences of breaching health information are a real threat to all healthcare providers," Hedges said. "Your liability insurance does not cover these fines, and bankruptcy does not relieve you of the debt." DT

Fred Gebhart *is a healthcare writer based in Gold Hill, Ore.*

While all albuterol may be the same

ONE QUICK-RELIEF INHALER IS DIFFERENT

ProAir® HFA (albuterol sulfate) offers a complete package of helpful features including a built-in dose counter[1]

- Patients know how many puffs are left[1] and when to refill
- A longer-duration, less forceful, warmer plume[2] may give patients more time to inhale
- Storage flexibility and portability[1,3,4] means no need to reprime if dropped

ProAir HFA (albuterol sulfate) Inhalation Aerosol is indicated in patients 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

Important Safety Information

- Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life-threatening. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister
- Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma
- ProAir HFA, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders (especially coronary insufficiency, cardiac arrhythmias, and hypertension), convulsive disorders, hyperthyroidism, and diabetes
- Potential drug interactions can occur with beta-blockers, diuretics, digoxin, or monoamine oxidase inhibitors, and tricyclic antidepressants
- Do not exceed the recommended dose
- Adverse events, which occurred at an incidence rate of at least 3% with ProAir HFA, include headache, tachycardia, pain, dizziness, pharyngitis, and rhinitis

Please see Brief Summary of Prescribing Information on next 2 pages.

To learn more about ProAir HFA, visit
ProAirHFA.com/hcp

PROAIR® HFA
(albuterol sulfate) Inhalation Aerosol

The difference is in the design

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TEVA Respiratory

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR PROAIR® HFA (ALBUTEROL SULFATE) INHALATION AEROSOL
For Oral Inhalation Only

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bronchospasm

PROAIR HFA Inhalation Aerosol is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

1.2 Exercise-Induced Bronchospasm

PROAIR HFA Inhalation Aerosol is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

4 CONTRAINDICATIONS

PROAIR HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol components. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate *[see **Warnings and Precautions (5.6)**]*.

5 WARNINGS & PRECAUTIONS

5.1 Paradoxical Bronchospasm

PROAIR HFA Inhalation Aerosol can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROAIR HFA Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

5.2 Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROAIR HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

5.3 Use of Anti-inflammatory Agents

The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

5.4 Cardiovascular Effects

PROAIR HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROAIR HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.6 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving PROAIR HFA Inhalation Aerosol.

5.7 Coexisting Conditions

PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.8 Hypokalemia

As with other beta-agonists, PROAIR HFA Inhalation Aerosol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

6 ADVERSE REACTIONS

Use of PROAIR HFA may be associated with the following:

- Paradoxical bronchospasm *[see **Warnings and Precautions (5.1)**]*
- Cardiovascular Effects *[see **Warnings and Precautions (5.4)**]*
- Immediate hypersensitivity reactions *[see **Warnings and Precautions (5.6)**]*
- Hypokalemia *[see **Warnings and Precautions (5.8)**]*

6.1 Clinical Trials Experience

A total of 1090 subjects were treated with PROAIR HFA Inhalation Aerosol, or with the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol, during the worldwide clinical development program.

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

Adult and Adolescents 12 Years of Age and Older: The adverse reaction information presented in the table below concerning PROAIR HFA Inhalation Aerosol is derived from a 6-week, blinded study which compared PROAIR HFA Inhalation Aerosol (180 mcg four times daily) with a double-blinded matched placebo HFA-Inhalation Aerosol and an evaluator-blinded marketed active comparator HFA-134a albuterol inhaler in 172 asthmatic patients 12 to 76 years of age. The table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROAIR HFA Inhalation Aerosol treatment group and more frequently in the PROAIR HFA Inhalation Aerosol treatment group than in the matched placebo group. Overall, the incidence and nature of the adverse events reported for PROAIR HFA Inhalation Aerosol and the marketed active comparator HFA-134a albuterol inhaler were comparable.

Adverse Experience Incidences (% of Patients) in a Six-Week Clinical Trial*

Body System/Adverse Event (as Preferred Term)		PROAIR HFA Inhalation Aerosol (N = 58)	Marketed active comparator HFA-134a albuterol inhaler (N = 56)	Matched Placebo HFA-134a Inhalation Aerosol (N = 58)
Body as a Whole	Headache	7	5	2
Cardiovascular	Tachycardia	3	2	0
Musculoskeletal	Pain	3	0	0
Nervous System	Dizziness	3	0	0
Respiratory System	Pharyngitis	14	7	9
	Rhinitis	5	4	2

* This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROAIR HFA Inhalation Aerosol group and more frequently in the PROAIR HFA Inhalation Aerosol group than in the placebo HFA Inhalation Aerosol group.

Adverse events reported by less than 3% of the patients receiving PROAIR HFA Inhalation Aerosol but by a greater proportion of PROAIR HFA Inhalation Aerosol patients than the matched placebo patients, which have the potential to be related to PROAIR HFA Inhalation Aerosol, included chest pain, infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea, ear disorder, ear pain, and urinary tract infection.

In small cumulative dose studies, tremor, nervousness, and headache were the most frequently occurring adverse events.

Pediatric Patients 4 to 11 Years of Age: Adverse events reported in a 3-week pediatric clinical trial comparing the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol (180 mcg albuterol four times daily) to a matching placebo HFA inhalation aerosol occurred at a low incidence rate (no greater than 2% in the active treatment group) and were similar to those seen in adult and adolescent trials.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of PROAIR HFA. 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. Reports have included rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (reported fatal in one case), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging.

The following adverse events have been observed in postapproval use of inhaled albuterol: urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles). In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypertension or hypotension, palpitations, central nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

7 DRUG INTERACTIONS

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with PROAIR HFA Inhalation Aerosol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

7.1 Beta-Blockers

Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROAIR HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, consider cardioselective beta-blockers, although they should be administered with caution.

7.2 Diuretics

The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics. Consider monitoring potassium levels.

7.3 Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and PROAIR HFA Inhalation Aerosol.

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

PROAIR HFA Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C:

There are no adequate and well-controlled studies of PROAIR HFA Inhalation Aerosol or albuterol sulfate in pregnant women. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established. Animal reproduction studies in mice and rabbits revealed evidence of teratogenicity. PROAIR HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure approximately eight-tenths of the maximum recommended human dose (MRHD) for adults on a mg/m^2 basis and in 10 of 108 (9.3%) fetuses at approximately 8 times the MRHD. Similar effects were not observed at approximately one-thirteenth of the MRHD. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 630 times the MRHD.

In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 65 times the MRHD *[see **Nonclinical Toxicology (13.2)**]*.

8.2 Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of PROAIR HFA Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. PROAIR HFA Inhalation Aerosol has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including albuterol.

8.3 Nursing Mothers

Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of PROAIR HFA Inhalation Aerosol are excreted in human milk.

Caution should be exercised when PROAIR HFA Inhalation Aerosol is administered to a nursing woman. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROAIR HFA Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of PROAIR HFA Inhalation Aerosol for the treatment or prevention of bronchospasm in children 12 years of age and older with reversible obstructive airway disease is based on one 6-week clinical trial in 116 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily with placebo, and one single-dose crossover study comparing doses of 90, 180, and 270 mcg with placebo in 58 patients *[see **Clinical Studies (14.1)**]*. The safety and effectiveness of PROAIR HFA Inhalation Aerosol for treatment of exercise-induced bronchospasm in children 12 years of age and older is based on one single-dose crossover study in 24 adults and adolescents with exercise-induced bronchospasm comparing doses of 180 mcg with placebo *[see **Clinical Studies (14.2)**]*.

The safety of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is based on one 3-week clinical trial in 50 patients 4 to 11 years of age with asthma using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol comparing doses of 180 mcg four times daily with placebo. The effectiveness of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of PROAIR HFA 90 mcg and 180 mcg with placebo in 55 patients with asthma and a 3-week clinical trial using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol in 95 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol four times daily with placebo *[see **Clinical Studies (14.1)**]*.

The safety and effectiveness of PROAIR HFA Inhalation Aerosol in pediatric patients below the age of 4 years have not been established.

8.5 Geriatric Use

Clinical studies of PROAIR HFA Inhalation Aerosol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see **Warnings and Precautions (5.4, 5.7)**]*.

All $beta_2$-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROAIR HFA Inhalation Aerosol.

Treatment consists of discontinuation of PROAIR HFA Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROAIR HFA Inhalation Aerosol.

The oral median lethal dose of albuterol sulfate in mice is greater than 2,000 mg/kg (approximately 6,800 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 3,200 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 1,400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In young rats, the subcutaneous median lethal dose is approximately 2,000 mg/kg (approximately 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6,400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

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Julia Talsma, Content Channel Director

Pain control in the elderly

Your role in opioid therapy management of chronic nonmalignant conditions

Chronic nonmalignant pain is a common, costly problem in the United States. In the elderly — adults 65 years and older — more than 50% have reported pain lasting more than one year. In a survey of nursing-home residents, approximately half noted persistent pain.

The cost of treating back pain, the most common nonmalignant pain condition, reached almost $91 billion in the United States in 1998. Despite these expenditures, approximately 25% of nursing-home residents reported inadequate pain control and were receiving no analgesics.

So, in 2000, the U.S. Congress designated 2001-2010 as the "Decade of Pain Control and Research." That same year, the Joint Commission on Accreditation of Healthcare Organizations released standards for pain management that recognized the need for appropriate assessment and management of patients with pain. The judicious use of opioids was recommended in several published guidelines for patients with chronic nonmalignant pain who had not responded to other analgesic agents.

"There remains uncertainty about the optimal use of opioids for chronic noncancer pain. Some patients do not experience significant improvements in pain or function even on high doses of opioids," stated the *APS-AAPM Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain*, published February 10, 2009.

However, prescribers of opioid pain relievers continue to use opioids for Medicare beneficiaries with chronic nonmalignant pain. According to the *2012 Drug Trend Report* from Express Scripts Inc., there was a 4.1% increase in opiate use last year among Medicare recipients in the commercially insured population.

"We did a retrospective analysis and looked at the use of narcotics among the large commercially insured U.S. population with data from 2010. What we found was, in general, patients 65 and older were using more narcotics, and the gender difference is that women were using more than men. Older members tend to fill more opioid prescriptions," said Keith Widmer, a neuroscience specialist pharmacist and senior manager for ESI's neurospecialist practice, overseeing clinical specialists who work with pain medications.

Keith Widmer

The good news is that although there had been a rise in opioid use among the elderly, in 2008 drug over-

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dose death rates in those 65 years and older were among the lowest in age-adjusted rates, with 1.0 death per 100,000 population, age-adjusted to the 2000 U.S. standard population. The lowest risk was among children 0 to 14 years of age, with 0.1 death per 100,000 population. The highest risk was seen among adults 45 to 54 years old, with 10.4 deaths from opioid pain relievers per 100,000 population, according to the *Morbidity and Mortality Weekly Report* of November 4, 2011.

Best candidates for pain relief

The best candidates for treatment of chronic nonmalignant pain with opioid pain relievers, according to Trinh Pham, PharmD, BCOP, are individuals with:

- Chronic back pain of somatic origin that does not respond to nonopioids
- Chronic back pain requiring a third-line adjuvant to help with neuropathic pain
- Osteoarthritis pain that does not respond to acetaminophen or in patients who cannot take nonsteroidal anti-inflammatory drugs
- Neuropathic pain that has not fully responded to first- and second-line antineuropathic therapies.

Pham, associate clinical professor, University of Connecticut School of Pharmacy, Storrs, Conn., discussed these indications for opioids in the management of pain, as well as the pharmacist's role in pain management with opioids, in her article, "Pharmacology and therapeutics of pain medications: Part 2," in the June 2013 issue of *Drug Topics*.

"Pharmacists have a vital role in the management of patients who are receiving opioid analgesics for pain control," Pham wrote. "The active involvement of pharmacists in the assessment, monitoring, and management of response to pain therapy ensures decreased risk of opioid misuse, successful pain control, and minimal development of side effects."


Richard Gannon

Inpatient services

Pharmacists are vital in managing patients with chronic nonmalignant pain. They can help educate patients and prescribers about the appropriate use of opioids as part of a multimodal approach to analgesia, according to Richard Gannon, PharmD, pain management specialist, Department of Pharmacy Services, Hartford Hospital, Hartford, Conn. Hartford Hospital has had a pharmacy pain service since 1979.

Gannon, who is in charge of the service, typically monitors 16 patients daily, assessing their levels of pain and side effects and adjusting pain medication doses as needed. He works from 7:30 a.m. to 5:30 p.m. Monday through Friday for physicians and mid-level practitioners who place orders for a pain consult through the patient's medical record, leaving an electronic note for the physician to review and order the appropriate medication.

"Because the elderly patients tend to be more sensitive both in terms of their responses to pain medications and their development of side effects, we use a multimodal approach to analgesia," Gannon told *Drug Topics*. "If we are considering acetaminophen and the patient is more than 80 years old, we limit the dose to 3 g per day. For the elderly to get a nonsteroidal anti-inflammatory drug, we're worried about their potential for GI bleeding and their potential for having some kidney dysfunction. In the case of neuropathic pain, there are a number of medications — anticonvulsants — that can be considered, yet most of the drugs have side effects of sedation and delirium."

Gannon stresses the need to start with lower doses of the multimodal analgesics in order to provide elderly patients with effective pain control. Patients are assessed every day, and the doses are adjusted on the basis of patient response and patient side effects.

Despite the view of the World Health Organization that use of morphine in adults, including the elderly, is the "gold standard" for chronic malignant and nonmalignant pain control, Hartford Hospital's pain service prefers to use hydromorphone and Fentanyl in the elderly population.

"For the elderly patients, we know they are more susceptible to the accumulation of morphine metabolites, with some of them more potent than morphine itself. Some will tend to cause nausea and delirium," Gannon said. "So if we are using patient-controlled analgesia [PCA] postoperatively, we will use a hydromorphone or Fentanyl PCA, not a morphine PCA."

Some elderly patients cannot swallow medications, so they may receive an epidural infusion or a PCA at Hartford Hospital. These patients are monitored for pain with a pain score, sedation score, and vital signs to ensure good pain control and minimal side effects, he said.

Side effects associated with opioids

Several side effects may affect patients treated with opioid therapy. These include constipation, nausea and vomiting, pruritus, respiratory depression, sedation, confusion and delirium, and some that are less common, such as myoclonus, bladder spasm, urinary retention, hypogonadism, and hypoadrenalism.

One of the biggest problems with opioid therapy is constipation, so all patients at Hartford Hospital receiving this


Mary Inguanti

therapy will also receive a stimulant laxative, Gannon said.

The patient assessment is important before prescribing opioids, said Mary Inguanti, PharmD, a *Drug Topics* editorial advisor.

"You have to know the patient history and what other drugs the patient is taking. Also, there could be other clinical conditions, such as untreated sleep apnea, that have to be considered, which would be more of a drug-disease interaction, not a drug-drug interaction," she said.

In managing elderly patients with nonmalignant pain, it is important for the pharmacist to work with the physician to ascertain what kind of pain needs treatment. "The collaboration of the team — the physician, the pharmacist, the nurse, the physical therapist — is really essential to understand what the problem is and what is the cause of the noncancer pain," Inguanti said.

The role of the pharmacist goes beyond standard drug-drug interactions and redundancy of drugs with the same side-effect profile. "The role of the pharmacist is really that of a case manager, rather than exclusively a medication manager," she said. "I think pharmacists are well positioned for that."

Outpatient services

Community pharmacists also are in a good position to help elderly patients with noncancer pain management. Face-to-face medication therapy management (MTM) is a real niche for this patient population, according to David Stanley, RPh, owner of Three Rivers Pharmacy, Three Rivers, Calif., and a *Drug Topics* contributor.


David Stanley

"Monitoring pain management treatments for the elderly is a challenge," Stanley said. An elderly patient may present a prescription that sets off all the Beers List red flags. "The computer will be beeping and blinking and screaming at you, yet everything's fine. This is a great opportunity to move down the MTM path, sit the patient down, talk with the patient and document that this medication is setting off my Beers List warning, but everything is fine."

Although there are few specific drugs that really should not be prescribed with opiates, some should be carefully monitored. Indomethacin can cause central nervous system (CNS) reactions such as drowsiness and nausea. Oral diclofenac in the elderly may cause stomach/intestinal bleeding and kidney effects. And patients taking benzodiazepines with opioids may be at increased risk for overdose death, Stanley noted.

"With any kind of narcotic in the elderly, you will want to monitor for sedation or any kind of CNS risk, especially if they have any history of poor mental functioning. You also want to monitor liver function and warn about GI motility," he said.

Comorbidities

It is important to assess renal function in the elderly, because every year after age 30, patients' creatinine clearance and renal function decline. In addition, pharmacists should ask about balance and mobility issues, Widmer said.

"Lack of mobility increases the risk of a fall. This is one of the areas that we emphasize in our seniors education program," Widmer said. "If lack of mobility is an issue, our pharmacists will suggest talking it over with the prescriber and seeing a physical therapist to help increase mobility. Pharmacists really play an important role by encouraging the use of durable medical equipment, when needed."

The devices need to be properly fitted and correctly used, because otherwise, for elderly patients, they pose increased risk of falls.

"It is a great niche for someone who does have a durable medical equipment practice. It is a great reason to go into it," Stanley said.

Nonpharmacologic interventions

In addition to physical therapy, pharmacists can suggest other nonpharmacologic interventions for noncancer pain, including rehabilitation, therapeutic exercises, occupational therapy, cognitive behavioral therapy, relaxation techniques, acupuncture, and breathing exercises, Widmer said.

"There are different levels of evidence among these different interventions, and they really differ based on the different type of pain being treated. Some work well for some individuals and some don't, because pain is different in each individual," he said. "When you treat pain with a multimodality approach with nonpharmacological interventions, then it can start to reduce the need for some of the pharmacologic interventions, which have adverse effects associated with them."

Stanley agrees that nonpharmacologic interventions can work. At one point he had bad back pain and couldn't get into his car. Then he started working out and the pain disappeared. "For some pain, a good massage therapist or good workout will probably do you good, depending on what the issue is," he said. DT

Insulin resistance and the use of U-500 insulin

Continued from pg. 14

Overall, there continues to be a lack of standardization among methods and measurements to define and quantify insulin resistance in human beings.

insulin; because the volume per injection is reduced and patients need fewer syringes to inject, it costs less per unit.[3] In addition, because U-500 insulin is used alone, patients no longer require a bolus and basal insulin to achieve glycemic goals.

Future implications for diabetes care

According to the guidelines of the American Diabetes Association (ADA), patients with forms of insulin resistance more extreme than those of patients with type 2 diabetes are classified as having "other specific types of diabetes."[3] It is a challenge for pharmacists and providers to help these patients reach their glycemic goals, not only because of their insulin resistance, but also perhaps because of the presence of the metabolic syndrome.

To date, in order to classify a patient as insulin-resistant, pharmacists and providers have been forced to rely upon an arbitrary number of units required to achieve glycemic goals.

As the diabetes epidemic continues, further research should focus on population-based studies that determine a cutpoint for diagnosing insulin resistance, in addition to providing insulin-resistant patients with evidence-based pharmacotherapy. DT

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NEW DRUG REVIEW Kevin W. Chamberlin, PharmD

FDA approves third oral agent for MS

Dimethyl fumarate (Tecfidera, Biogen Idec) oral delayed-release capsules, formerly called BG-12, were approved by FDA March 27, 2013 for the treatment of relapsing forms of multiple sclerosis (MS). It is the third oral drug to be recently approved for the treatment of these types of MS.

Efficacy

Dimethyl fumarate and its metabolite monomethyl fumarate have been shown to activate an antioxidant response pathway, nuclear factor [erythroid-derived 2]-like 2 (Nrf2), in vitro and in vivo in animals and humans. It is thought that the Nrf2 pathway is involved in cellular defense against oxidative stress.

The CONFIRM study was a phase 3 comparison between dimethyl fumarate and placebo of 1417 patients with relapsing-remitting MS for 2 years. Dimethyl fumarate 240 mg given orally two or three times a day reduced the annual relapse rate (ARR) by 44% and 51%, respectively, versus placebo. Additionally, new or enlarged CNS lesions were significantly reduced with dimethyl fumarate. Glatirimer acetate was included as an active comparator in the study and showed an ARR of 29%. Neither dimethyl fumarate nor glatiramer acetate slowed the progression of disability compared to placebo.

Another phase 3 study comparing dimethyl fumarate with placebo (DEFINE) enrolled 1,234 patients with relapsing-remitting MS and compared two dosages with placebo for 2 years. Dimethyl fumarate showed a significant reduction of 53% in ARR as well as a significant reduction in new CNS lesions and lesion progression. In this study, unlike CONFIRM, dimethyl fumarate did show a decrease in disability progression versus placebo.

The efficacy of dimethyl fumarate appears to be similar to that of fingolimod and slightly better than teriflunomide for reducing ARR.

Safety

Dimethyl fumarate most commonly causes flushing (40% of patients) and gastrointestinal (GI) effects (diarrhea, nausea, vomiting), but these effects tend to lessen with time and can be reduced by administration with food. Dimethyl fumarate can also lower white blood cell counts, and the manufacturer recommends that a complete blood count be performed within six months before the patient starts on the medication and repeating at least once a year while the patient remains on therapy.

While no evidence exists that its effects on white counts is related to any increased risk of opportunistic infections, mean lymphocyte counts decreased by about 30% during the first year of treatment but stabilized thereafter, according to studies. A handful of cases of progressive multifocal leukopenia (PML) have been reported after use of other products containing dimethyl fumarate prescribed to treat psoriasis. To date, no cases of PML have been reported with dimethyl fumarate used for the treatment of MS. Compared with fingolimod and teriflunomide, dimethyl fumarate appears to have better safety data, though no direct head-to-head comparisons have been made.

No appreciable drug-drug interactions have been reported with dimethyl fumarate, especially since it is not metabolized by CYP enzymes. Food reduces flushing, but otherwise has not been associated with pharmacokinetic effects of dimethyl fumarate.

Dosing

The starting dose for dimethyl fumarate is 120 mg twice a day for 7 days, followed by a maintenance dose of 240 mg twice a day. Dimethyl fumarate should be swallowed whole and may be taken with or without food, though taking it with food might reduce flushing.

No dosage adjustments are required for renal or hepatic dysfunction. Patients should be counseled to keep dimethyl fumarate in its original container as it is sensitive to light; unused capsules need to be discarded after 90 days of opening. Dimethyl fumarate is available in 7-day starter packs of 120 mg, 23-day bottles, and 30-day bottles of 240 mg. DT

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ANTICOAGULATION THERAPIES Anna D. Garrett, PharmD, BCPS

Prothrombin complex concentrate approved for acute bleeding

The FDA has approved a new plasma-derived product for the urgent reversal of vitamin-K antagonist (VKA) anticoagulation in adults with acute major bleeding.

The new product, Kcentra, offers an additional option to address the problem of acute bleeding in patients who are receiving chronic anticoagulation therapy with warfarin and other VKA anticoagulants. The current standard of care in the United States for reversal of VKA therapy in patients with acute major bleeding includes withdrawal of VKA therapy, vitamin K administration, and administration of plasma.

Prothrombin complex concentrate (PCC) can be used more quickly than plasma to reverse the effect of VKA anticoagulants. Unlike plasma, it does not require blood-group typing or thawing. In addition, it is administered in a lower volume than plasma is given; this is important for patients who may not be able to tolerate a large volume of plasma. As with plasma, PCC is given together with vitamin K.

Kcentra is the first four-factor PCC in the United States to be approved for the urgent reversal of VKA (e.g., warfarin) therapy in patients who are experiencing acute major bleeding. Other PCCs licensed in the United States are indicated for the treatment of hemophilia B.

PCCs are not approved for reversal of target-specific anticoagulants. There are case reports of use for this purpose, and some success has been noted. However, the data are too limited to determine the efficacy and safety in this situation.

A boxed warning on the Kcentra label states that this product carries a risk of blood clots. Clinicians should monitor patients receiving the product for signs and symptoms of thromboembolic events.

Source: http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM351877.pdf

Dabigatran has new boxed warning

The manufacturer of dabigatran (Janssen Pharmaceuticals) has added a new boxed warning stating that stopping the drug may increase the risk of stroke in patients with nonvalvular atrial fibrillation. This issue is already mentioned in the package labeling; the move is designed to heighten the awareness of prescribers about the potentially serious consequences of leaving patients without anticoagulation during times of transition (e.g. a switch back to warfarin or interruption for procedures).

The warning also spotlights the importance of patient education with target-specific anticoagulants. The consequences of nonadherence to the medications can be devastating, and pharmacists play a critical role in contributing to successful outcomes with new anticoagulants. Patients need a thorough understanding of the consequences of missing doses or stopping the medication without consulting their prescribers.

A number of anticoagulation clinics are adding target-specific anticoagulant consultations to the menu of services they provide. Patients receive extensive education and periodic follow-up calls to ensure tht they are tolerating therapy and adhering to the prescribed regimen.

Source: http://www.xareltohcp.com/important-safety-information.html

Rivaroxaban approved for ACS use in Europe

The European Commission has given its approval to rivaroxaban for secondary prevention in adult patients who have had biomarker-confirmed acute coronary syndrome (ACS). The indication is for 2.5 mg twice daily in combination with standard antiplatelet therapy.

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) had recommended the approval of rivaroxaban for ACS in March, based largely on the ATLAS ACS 2 TIMI 51 trial, which randomized more than 15,000 patients. In the trial, the 2.5-mg twice-daily dose was associated with a reduction in overall and cardiovascular mortality vs. placebo, despite an increased risk of bleeding and intracranial hemorrhage (ICH). The 5-mg dose also tested in the trial, however, was associated with an increased bleeding risk that outweighed the drug's benefits.

For the new generation of oral anticoagulants, approval for the ACS indication has been more of a challenge than has been the case with approval for other indications.

FDA has delayed its ruling on rivaroxaban for ACS secondary prevention pending submission of more safety data.

Source: http://www.medscape.com/viewarticle/804734 DT

Anna D. Garrett *is a clinical pharmacist and president of Dr. Anna Garrett, a health and wellness coaching company in Asheville, N.C.*

CPE CREDIT: 2.0

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EDUCATIONAL OBJECTIVES

Goal: To assist pharmacists in understanding the management of common pain conditions.

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

- **Describe the signs and symptoms of common pain conditions**
- **Discuss pharmacologic and nonpharmacologic treatment options for the common pain conditions**
- **Recognize the signs and symptoms for which a pharmacist should refer the patient to a physician**

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 #0009-9999-13-010-H01-P

Grant Funding: Supported by an educational grant from Purdue Pharma, L.P.

Activity Fee: There is no fee for these activities.

Initial release date: 8/10/2013
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Management of common pain conditions encountered by pharmacists:

Osteoarthritis; low back pain; fibromyalgia; sprains, strains, contusions; and generalized headaches

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Abstract

Many common pain conditions are often first triaged by pharmacists in community and outpatient settings, and pharmacists are often sought out in hospital setting for advice on therapies. The pharmacist plays an important role as a first source of information and intervention for patients, caregivers, and prescribers. Pharmacists can play an integral role in identifying the signs and symptoms of common ailments, such as osteoarthritis, low back pain, fibromyalgia, muscle strains, and generalized headaches. These conditions are often handled initially with nonpharmacologic or over-the-counter pharmacologic means. Understanding when to refer a patient with these common pain conditions for a more extensive review and work-up is critical for patient safety and recovery.

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Faculty Disclosure: Dr. Chamberlin and Dr. Holle have no actual or potential conflict of interest associated with this article.

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IMAGE: THINKSTOCK / ISTOCKPHOTO

Pain Management Considerations in Medication Therapy Management CPE Series

Welcome to the last activity in the CPE series, Pain Managment Considerations in Medication Therapy Management, which has been designed for pharmacists who need to further their clinical and MTM skills in the management of patients with pain. From April 2013 to August 2013, pharmacists can earn up to 10 hours of CPE credit with 5 monthly knowledge-based activities from the University of Connecticut School of Pharmacy and *Drug Topics*.

This last installment focuses on the management of common pain conditions encountered by pharmacists, including osteoarthritis, low back pain, fibromyalgia, sprains, strains, contusions, and generalized headaches.

Common pain conditions encountered by pharmacists include: osteoarthritis; low back pain; fibromyalgia; sprains, strains, and contusions; and generalized headaches. Many of these pain conditions are often treated initially with similar nonpharmacologic and pharmacologic modalities and interventions. Managing these common pain conditions early on can provide patients with a good quality of life while minimizing the development of chronic, long-term disability from pain and loss of function.

Osteoarthritis

The ever-aging population, coupled with the obesity epidemic, has likely caused an uptick in the incidence of osteoarthritis (OA), now considered to occur in 1 in 10 adults and affecting nearly 27 million in the United States.[1,2] Osteoarthritis involves degeneration of cartilage most commonly in the joints of the hands, knees, and hips.[2] Nearly 60% of all patients diagnosed with OA are age 60 or older, with women outpacing men in diagnosis after age 55.[1,2] As the incidence of OA increases with age, so do the risks for adverse effects with commonly employed therapies, including nonsteroidal anti-inflammatory drugs (NSAIDs).[1]

OA is a mechanical abnormality involving the degradation of joints, cartilage, and bones. When bone surfaces become less protected by cartilage, the bones become exposed and subsequently damaged by friction. The distal interphalangeal (DIP) joints—those joints closest to the end of fingers and toes—are commonly the first to show signs of swelling in early OA. The swelling of DIP joints, caused by the formation of osteophytes (calcific spurs) of the articular cartilage, is often a result of repeated trauma (use) at the joint over time. Diagnosis is commonly made by both clinical and radiologic findings, with the identification of joint-space narrowing on radiographs, in addition to pain and function, as primary end points to the diagnosis of OA.[3]

> Every 10 pounds of weight loss will take 30 pounds of weight off the knees.

Exercise is recommended as a primary intervention for patients with hip and knee osteoarthritis as it helps with range of motion, although no preference between land-based and aquatic-based programs is made because each individual will have differing needs and abilities. If the patient is not aerobically conditioned, however, the recommendation is to begin with the less joint-stressing aquatic exercises before moving to land-based exercise.[1] Weight reduction is highly effective, especially with knee OA; recent research has demonstrated that not only does pain reduce, resulting in an improved function, but also that cartilage and bone markers improve.[2,4] Every 10 pounds of weight loss takes 30 pounds of weight off the knees.[2,4] **Table 1** outlines a step-up approach to the medical management of OA.[1,5] Acetaminophen is the first-choice oral analgesic due to its safety and efficacy.[1,2] Acetaminophen must be dosed at its analgesic dosing—equal to or more than 650 mg orally every 6 or 8 hours—for it to achieve analgesic effect. Many times patients fail to self-dose or be prescribed acetaminophen at the appropriate dose for pain to be reduced. Optimal effect while minimizing potential liver damage can be obtained by recommending dosing of 975 mg orally every 8 hours and counseling to avoid alcohol use while using acetaminophen.

Although acetaminophen is still often used first, most agree that NSAIDs are more effective at managing the symptoms of OA.[6] Traditional oral NSAIDs (ibuprofen, naproxen) can provide an excellent option for patients to step up to if acetaminophen offers limited or no effect. Ibuprofen has a maximum daily dose of 1200 mg per day for OA, and naproxen sodium (over-the-counter [OTC] dosing) suggests a 220-mg to 440-mg initial dose followed by a maximum of 440 mg in an 8- to 12-hour period, or 660 mg in 24 hours. Researchers have identified risk factors for NSAID-associated gastrointestinal (GI) complications to include: a previous GI event (especially if complicated), age, concomitant use of anticoagulants, corticosteroids, other NSAIDs (including low-dose aspirin), high-dose NSAID therapy, and chronic debilitating disorders (especially cardiovascular disease).[7] NSAIDs are very effective for the management of OA, but they are not without their risks as outlined in **Table 2**.[1,6,7,9-16]

Topical NSAIDs are considered to be as equally efficacious as their oral counterparts; however, the increased cost does not necessarily outweigh the better adverse-event profile to warrant their consideration ahead of oral NSAID therapy.[1,8] Some of the

TABLE 1

STEP-UP APPROACH TO OSTEOARTHRITIS THERAPY

Step	Intervention
7	Severe disease: Consider joint replacement
6	Severe disease: Consider hyaluronic acid injection to joint
5	Severe disease: Consider corticosteroid injection to joint
4	Severe disease: Consider opioid therapy
3	Moderate disease: Add glucosamine/chondroitin for at least 3 months; discontinue if no change
2	Mild disease: Acetaminophen scheduled around the clock; step-up /add-on NSAID if not completely effective
1	Mild disease: Exercise and weight loss

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

Source: Ref 1, 5

TABLE 2

ORAL NSAID TREATMENT OPTIONS AND THEIR RISKS FOR TREATING OSTEOARTHRITIS

NSAID	Consideration
Nonselectives	• Initial response in few days to 1 week; peak response in 2 weeks • GI ulcer formation in 1%-4% of users (longer use, prior history increase risk) • A proton pump inhibitor should be prescribed if NSAID must be used in patient at increased GI risk • *Helicobacter pylori* infection increases risk of NSAID-related GI complications • Naproxen potentially has lower cardiovascular event rate vs other NSAIDs
Celecoxib	• As effective as nonselective NSAIDs for symptoms of arthritis • Fewer severe GI complications than nonselective NSAIDs • May have increased cardiovascular event rate vs other NSAIDs, especially at doses above 200 mg/day
Meloxicam	• Not a true NSAID, but favors COX-2 over COX-1 • More analgesia offered at higher dose (15 mg) than lower dose (7.5 mg); less selective at higher dose • May have better GI complication profile than nonselective counterparts
Salsalate	• Considered no safer than other NSAIDs
Topical NSAIDs	• Substantially less systemic absorption than oral counterparts (<6%) • Increased risk for localized and dermatologic reactions (itching in 7%) • Avoid direct sunlight exposure to treated area(s)

Abbreviations: COX, cyclo-oxygenase; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug

Source: Ref 1,6,7,9-16

benefit of topical NSAIDs such as diclofenac gel can be attributed to its need to be applied 4 times a day and massaged into the area. The topical diclofenac includes a measuring card for application; the 2-g dose is for OA of the upper body (hands) and the 4-g dose is indicated for OA of the lower body (hips, knees). This dosing card should be folded in half and discarded after each application. Patients need to specifically be counseled to avoid direct sunlight exposure to the treated area(s). Additionally, topical diclofenac users need to wait 10 minutes after applying before covering with clothing or gloves (if applying to hands). Patients should not bathe or shower for at least 1 hour after application.[9]

Duloxetine was approved in 2010 for chronic musculoskeletal pain, including that from osteoarthritis. Doses are initiated at 30 mg once daily and titrated to effect, up to a maximum of 60 mg once daily. Direct comparison between duloxetine and NSAID therapy has not been made; however, it is reported that duloxetine users experienced statistically significant benefit over placebo in 2 studies that gained its OA indication.[17] The American College of Rheumatology (ACR) makes no recommendation for the role of duloxetine in the management of OA.[1]

The use of mid-level analgesics or narcotics (World Health Organization step 2 or 3, including tramadol) should be reserved for failure of or contraindication of acetaminophen or NSAIDs.[1] Although the combination of acetaminophen with opioid analgesics can be synergistic in relieving pain, the age-associated incidence of OA suggests that caution should be exercised in considering these agents for treatment due to the risk profile, including increased fall risk, confusion, sedation, and constipation.[18]

The 2012 recommendations from the ACR recommends against the use of glucosamine with or without chondroitin in the treatment of OA.[1] Recent studies suggest that taking a supplement containing glucosamine and chondroitin might help to reduce moderate-to-severe pain, but that these supplements remain ineffective against mild pain.[19] The most effective form of glucosamine is as sulfate salt, dosed at 1500 mg of glucosamine sulfate and 1200 mg of chondroitin daily, either as a single dose or divided.[20] Caution should be exhibited when these medications are used in those taking warfarin, because both glucosamine and chondroitin are heparinoids and may raise the INR. Continuous therapy lasting 3 to 6 months is needed to determine whether the supplement is effective or not; the tablets are most often large in size and can be expensive for individuals as an OTC purchase.[19] Upset stomach and elevations in blood glucose levels, although reportedly not any worse in diabetics than in nondiabetics, are the most commonly reported adverse effects.[19]

OA-suffering patients will often seek out a pharmacist's advice for therapy initiation. Recommendations for OTC interventions, both traditional and nontraditional, should be made with the patient's full medical and medication profile under review, and in conjunction with the primary care provider. Failure or lack of complete response to the aforementioned interventions would indi-

cate the need for full medical or specialist follow-up.

Low back pain

Nearly 100 million people living in the United States suffer from chronic pain, and much of that is attributable to chronic back pain.[21] Low back pain (LBP) has been found to be the second leading cause of physician visits, the third most common cause for surgeries, and the fifth most common reason for hospitalization.[22] Back pain is the most common reason for work absenteeism and for the filing of workers' compensation claims and outpaces costs associated with workers' compensation claims at a ratio of nearly 2:1.[22,23]

Researchers have broadly classified LBP into categories of mechanical, neuropathic, or secondary to another cause.[24] Such categorization would imply that mechanical back pain originates from the spine or its related structures, whereas neuropathic pain stems from the irritation of a nerve root, enabling provider(s) to utilize therapies that target those mechanisms. Factors that help differentiate mechanical from neuropathic back pain are listed in **Table 3.**[24]

When screening patients, it is imperative to rule out "red flags" (possible indicators of spinal involvement) and "yellow flags" (factors considered indicative of long-term disability) that would indicate need for referral to a specialist.[24,25,26] These flags are listed in **Table 4**.[24,25,26]

Patients who are overweight or obese have a higher risk of having LBP. Systematic reviews of 33 studies evaluating this association showed a statistically significant relation and an increased risk of having LBP in the previous 12 months, seeking care for LBP, or having chronic LBP.[25] Additionally, patients with chronic back pain have a higher association with sleep disturbances than their nonpain counterparts. Chronic LBP has been significantly linked with greater sleep disturbance, reduction in sleep quality, poor daytime functioning, and greater sleep dissatisfaction.[26]

Exercise therapy is modestly effective for improving pain and function in adults with chronic LBP, with aerobic and strengthening programs having been shown to reduce long-term disability. Core strengthening and stabilization exercises for as little as 2 sessions of 30 to 45 minutes each per week have been associated with reduced pain and disability.[27] Treadmill walking sessions of 40 minutes each, 2 times per week, of low-to-moderate intensity, may be as effective as specific low back strengthening exercises for improving pain and function.[28] Physical therapy is an often underused specialty service that can provide great, nonpharmacologic relief of pain symptoms in LBP patients. Of note, the European guidelines for management of chronic nonspecific LBP consider heat and cold therapy as interventions not routinely recommended.[29]

TABLE 3

FACTORS DIFFERENTIATING MECHANICAL FROM NEUROPATHIC BACK PAIN

	Mechanical	Neuropathic
Patient descriptors	Throbbing, aching	Shooting, stabbing, tingling, numb
Radiation	To the upper thigh, buttocks Extension below the knee uncommon	Extension below the knee common
Movement vs rest	Worsened with movement, improved by rest Prolonged sitting aggravates symptoms	Leaning forward or bending down (reaching to toes with knees unbent) offers relief; Little difficulty walking uphill, bicycling
Common causes	Traumatic event (fall, vehicle accident)	Herniated disc, disc protrusion

Source: Ref 24

NSAIDs may reduce pain in chronic LBP, but evidence is lacking to support the role of acetaminophen despite the American College of Physicians and American Pain Society joint guideline for treatment of LBP recommending both NSAIDs and acetaminophen as first-line choices in these patients.[30] Recommended dosing is similar to that used for OA. Patients should be counseled that extended use of NSAIDs can lead to increased risk for GI ulceration, worsening or poor blood-pressure control, fluid retention, and risks for cardiovascular events and renal damage. Renal concerns are especially important in elderly patients who can suffer from the "triple whammy" effect when an NSAID is combined with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a diuretic, resulting in acute kidney injury.[31]

Renal concerns are especially important in elderly patients who can suffer from the "triple whammy" effect when an NSAID is combined with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a diuretic, resulting in acute kidney injury.

Nonbenzodiazepine muscle relaxants (e.g., carisoprodol, cyclobenzaprine) were shown to have insufficient evidence to support their role in treating LBP.[32] Insufficient evidence exists for direct comparison of skeletal muscle relaxants (SMRs) to analgesics. In a systematic review, it was found that cyclobenzaprine is more effective than placebo in the management of back pain, but that the effect is lost after

TABLE 4

"RED FLAG" AND "YELLOW FLAG" SIGNS FOR SPECIALIST REFERRAL

Red flags	Yellow flags
Age <20 or >50	Prior episode(s) of back pain
Fever and unexplained weight loss	Fear avoidance behavior
Bladder or bowel dysfunction	Reduced or low baseline activity levels
History of malignancy	Presence of anxiety, depression, emotional distress, or social withdrawal
Immunosuppression or prolonged use of corticosteroids	Social or financial problems
Disturbed gait	
Persistent, nonresponsive pain	

Source: Ref 24-26

just 4 days of continuous therapy.[33] Cyclobenzaprine's structure closely mimics that of first-generation tricyclic antidepressants, as does its highly anticholinergic side-effect profile. Furthermore, cyclobenzaprine is a substrate of CYP450 3A4, 1A2, and 2D6 warranting careful evaluation of its concomitant use with other medications. Carisoprodol is an SMR that has an active barbiturate metabolite in meprobamate. Its effects as an SMR versus a sedative have long been called into question.[34]

Duloxetine may improve chronic LBP, but the extent of the benefit is not clear.[35] Other antidepressants, including tricyclics and selective serotonin reuptake inhibitors (SSRIs), may not reduce pain in patients with nonspecific LBP, but instead may help with the depression associated with the chronicity of LBP. Target and maximum doses for duloxetine remain the same in LBP as for OA.

Tramadol is a noncontrolled analog of codeine indicated for moderate-to-severe pain. Unlike NSAIDs, tramadol lacks any significant cardiovascular, GI, or renal impairment concerns, although dosing adjustments are recommended for renally impaired patients.[36] Tramadol does require activation via metabolism through CYP450 2D6, an enzyme that is lacking in 7% to 10% of Caucasians.[37] Tramadol's dependence on 2D6 for activation is also a concern in those patients receiving powerful 2D6 inhibitors, such as fluoxetine or paroxetine. Inhibition of the 2D6 pathway can lead to inadequate analgesia while increasing adverse effects 2- to 3-fold.[36,37] Patients should be counseled about the common adverse effects of tramadol, including headaches, nausea, somnolence, constipation, dry mouth, and dizziness.

Transdermal buprenorphine is a partial opioid agonist and antagonist that is associated with a reduction of pain in opioid-naïve patients with moderate-to-severe chronic LBP, but its long-term efficacy data are lacking. For patients who are initiating a buprenorphine transdermal system (BTS) as their first opioid, or for those patients whose prior total daily dose of opioid is less than 30 mg of oral morphine equivalents per day, 5 µg/hr is the recommended patch strength. For patients whose prior total daily dose of opioid is between 30 and 80 mg of oral morphine equivalents per day, it is recommended to titrate down to an equivalent of 30 mg per day before applying the starting dose of the BTS at 10 µg/hr. Short-acting analgesics may be used until the patient achieves adequate analgesia on the BTS. The dose can be titrated in all users at a minimum interval of 72 hours to a maximum recommended dose of 20 µg/hr. The patch should be replaced and the site of application rotated every 7 days. Common adverse effects of the BTS include headache, dizziness, nausea, and itching at the application site. QTc prolongation has been reported at doses exceeding the maximum recommended dose of 20 µg/hr. Concomitant administration with class 1A or class II antiarrhythmics should be avoided due to this effect. Proper disposal of the BTS should be followed via the included disposal unit and in the household trash.[38]

Opioids were shown to have short-term efficacy in chronic back pain, but long-term efficacy data supporting their use are lacking. Studies of moderate-to-high quality compared opioids to nonopioids or placebo; all trials showed that superior analgesia was achieved with opioids, but these studies had a mean duration of 64 days (7-112 days), making long-term efficacy difficult to evaluate.[39] As always, adequate bowel regimens should be costarted with any opioid therapy to prevent constipation.

For acute, nonspecific back pain, patients should be reassured and advised to remain active and working when possible. Patients whose symptoms worsen or persist should be referred for more intensive intervention to rule out serious disease, especially including those patients with major trauma, back pain at rest or at night, loss of sensation or function of limbs/extremities, or loss of bladder or bowel control.

Fibromyalgia

Fibromyalgia is a chronic, debilitating central pain disorder associated with somatic symptoms such as fatigue, insomnia, cognitive/memory problems, and psychologic distress.[40] Many patients, however, experience a multitude of other symptoms, and some suggest that fibromyalgia is part of a much larger continuum of central sensitivity syndromes.[40,41] It is estimated that fibromyalgia affects 2% to 5% of the population in the United States and is 7 times more commonly diagnosed in women than men.[41,42] This disease can develop at any age, but tends to be more common with increasing age.[41] Patients with fibromyalgia often have comorbidities such as depression, insomnia, anxiety, rheumatic diseases, HIV, hepatitis C, or other systemic illnesses (e.g., chronic fatigue, irritable bowel syndrome, hyperprolactinemia), sometimes making it difficult to recognize and diagnose fibromyalgia because of the overlapping symptomology.

The underlying pathophysiology of fibromyalgia is not well understood. The hallmark symptoms of chronic pain and allodynia (tenderness in response to normally nonpainful stimuli) are understood to be defects in the ascending pain

TABLE 5

FDA-APPROVED THERAPIES FOR FIBROMYALGIA

Drug	Available dosages	Dose	Efficacy	Adverse effects	Clinical pearls
Duloxetine (Cymbalta)	Capsules, enteric pellets 20 mg 30 mg 60 mg	30 mg po daily x 7 days, then 60 mg po daily	Improved pain, 50% reduction QOL Sleep disturbances	Nausea (40%) Headache (30%) Insomnia (20%) Dizziness (19%) Constipation (17%) Dry mouth (17%) Somnolence (14%) Diarrhea (13%) Sweating (11%) Fatigue (11%)	• Higher doses (120 mg/d) not more efficacious • Best taken in morning • Most AEs diminish over time • Do not use in ESRD, hepatic impairment, significant alcohol use • Contraindicated in patients within 2 weeks or concurrently taking MAOIs, uncontrolled narrow-angle glaucoma, or hypersensitivity • Gradually decrease when discontinuing to limit AE effects • Metabolized by CYP1A2 and 2D6; avoid use with potent CYP1A2 inhibitors; potent CYP2D6 inhibitors may decrease duloxetine concentrations • Concurrent smokers: decreases concentration by 30%, but dose adjustment not recommended; poor metabolizers may have increased concentrations • May enhance effects of warfarin, antiplatelet effect of NSAIDs • Avoid drugs that may enhance serotonergic or CNS effects • Some herbal medications may increase CNS depression • Avoid valerian, St. John's wort, SAMe, kava kava, gotu kola
Milnacipran (Savella)	Tablets 12.5 mg 25 mg 50 mg 100 mg	12.5 mg po x 1 day 1, 12.5 mg po BID days 2-3, 25 mg po BID days 4-7, then 50 mg po BID (up to 100 mg po BID)	Improved pain fatigue Improved cognition	Nausea (30%) Headaches (18%) Constipation (18%) Flushing (14%) Sweating (13%) Palpitations and increased HR (7-8 bpm) Increased BP (3 mm Hg SBP or DBP, regardless of previous hypertension)	• Available in 4-week blister pack (for tapering dose) and individual strengths • Most AEs diminish over time • Do not use in ESRD, reduce dose in severe renal impairment • Contraindicated in patients within 2 weeks or concurrently taking MAOIs, uncontrolled narrow-angle glaucoma, or hypersensitivity • Gradually decrease when discontinuing to limit AEs • Administer with food to decrease nausea, but absorption not affected by food • No CYP450 interactions • Avoid drugs that may enhance serotonergic or CNS effects • May enhance effects of warfarin, antiplatelet effect of NSAIDs • Some herbal medications may increase CNS depression • Avoid valerian, St. John's wort, SAMe, kava kava, gotu kola
Pregabalin (Lyrica)	Capsules 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg 300 mg Solution 20 mg/mL	75 mg po BID (up to 225 mg po BID)	Improved pain sleep QOL	Dizziness (40%) Somnolence (24%) Headache (15%) Weight gain (13%) Dry mouth (11%)	• Higher doses (600 mg/d) not more efficacious • Increase after 1 week at each dose level • Most AEs diminish over time • Contraindicated with hypersensitivity • Adjust dose for renal impairment • No dose adjustments for hepatic impairment; avoid in significant alcohol use • Gradually decrease when discontinuing to limit AEs • No CYP450 interactions • Avoid drugs that may enhance CNS effects • Some herbal medications may increase CNS depression • Avoid valerian, St. John's wort, SAMe, kava kava, gotu kola

Abbreviations: AEs, adverse effects; CNS, central nervous system; BP, blood pressure; CYP, cytochrome; DBP, diastolic blood pressure; ESRD, end-stage renal disease; HR, heart rate; MAOIs, monoamine oxidase inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; QOL, quality of life; SBP, systolic blood pressure.

Source: Ref 45-48

pathways and the descending inhibitory pathways.[41] In the ascending pathways of patients with fibromyalgia, nociceptive signals become more active through damage to or repeated activation of neurons, facilitating a pathologic "crosstalk" between neurons that results in painful sensations when other neurons are stimulated. With this counter-irritation in fibromyalgia, the descending inhibitory pathways become less active, and rather than inhibiting nociceptive neurons as they normally do, cause diffuse pain when localized neuron activity occurs. Medications for the treatment of fibromyalgia are intended to correct the abnormal pain signaling that occurs in this disorder; however, the pathophysiology of other common symptoms and comorbidities are not explained by these neuronal pathway abnormalities.

The core symptoms of fibromyalgia include pain, fatigue, and sleep disturbances. Pain, often described as burning, contracture, and/or tension, is persistent and chronic with varying intensities and can occur in any part of the body.[43] Typically the pain begins in 1 local area, such as the neck, spine, or shoulders, and then disseminates more widely to other areas over time. Tender points most commonly are positioned at the area of muscle insertion or directly over the muscle itself. Subjectively, patients may complain of swollen joints or limbs even without noticeable physical evidence of swelling or paresthesias—the sensation of burning, tingling, pricking, or numbness—without any objective findings. The pain symptoms may vary in relation to time of day, activity, stress, sleep levels, and weather conditions. Pain and stiffness tend to be worse in the morning and improve throughout the day. Symptoms are most improved with warm, dry weather, moderate physical activity, adequate sleep, and relaxation.

Approximately 90% of patients with fibromyalgia have fatigue, which can often be debilitating.[43] Patients will commonly complain of feeling exhausted even on waking. This may be related to the sleep disturbances, such as nonrestorative sleep and insomnia, that many patients experience.[42,43] For most patients with fibromyalgia, this is the most troubling symptom and often leads them to seek a diagnosis.

A large part of the treatment of fibromyalgia involves nonpharmacologic therapies.

Other key symptoms include tenderness, stiffness, mood disorders (e.g., depression, anxiety), and cognitive difficulties (e.g., trouble concentrating, forgetfulness, disorganized thinking).[42] For example, mood disorders are reported in up to 90% of patients. Comorbid conditions such as irritable bowel syndrome, tension-type headaches or migraines, interstitial cystitis or painful bladder syndrome, chronic prostatitis, temporomandibular disorder, chronic pelvic pain, and vulvodynia may share certain pathophysiologic features of fibromyalgia and be part of the spectrum of symptoms a patient describes. Patients with fibromyalgia who have new onset of acute pain or new systemic symptoms associated with their pain should be referred to a physician for further evaluation to rule out other causes.

Fibromyalgia is a clinical diagnosis primarily based on a focused history and physical examination.[42] No laboratory or radiologic findings can be used to diagnose the disease; however, they may be used to exclude other diagnoses. The ACR defines fibromyalgia as widespread pain (pain above and below the waist and on both sides of body) lasting 3 months or longer and the presence of axial skeletal pain (e.g., cervical spine, anterior chest, thoracic, or lower back). A patient must also have pain (not just tenderness) on digital palpation at 11 of 18 predesignated tender point sites.[44] Currently, 3 medications are FDA-approved for the pharmacologic treatment of fibromyalgia: the serotonin-norepinephrine-reuptake inhibitors duloxetine and milnacipran, and the alpha-2-gaba ligand pregabalin.[45] Results from clinical trials suggest that all 3 of these drugs are effective in reducing pain. Additionally, duloxetine and pregabalin reduce sleep disturbances and improve quality of life, whereas milnacipran significantly reduces fatigue and improves cognition.[46-48] Selecting the best pharmacologic treatment for an individual patient should be based on specific symptoms, comorbidities, adverse effects, and patient preferences. **Table 5** provides information on dosing, efficacy, adverse effects, and clinical pearls for each of these drugs.[46-48]

Several other drugs have been used to treat fibromyalgia, including tricyclic antidepressants, cyclobenzaprine, SSRIs, opioids, and gabapentin, but evidence to support their use is limited.[41] These drugs may cause a reduction in pain and in some cases a reduction in other symptoms; however, many are associated with significant side effects and so are typically reserved for patients who have contraindications, cannot take, or do not respond to the approved therapies.

A large part of the treatment of fibromyalgia involves nonpharmacologic therapies. Cognitive behavioral therapy and moderate aerobic and muscle strengthening exercises are recommended by the American Pain Society and the European League Against Rheumatism guidelines.[49,50] Other therapies, such as acupuncture, balneotherapy (use of therapeutic bathing), biofeedback, hypnotherapy, and structured exercise and patient education/stress reduction are also suggested as helpful in the long-term treatment of fibromyalgia.

Pause&Ponder

A 60-year-old woman without history of cardiovascular or GI disease has tried acetaminophen up to 3 g/d for the arthritis in her hands. What information might you obtain from her before making a recommendation?

TABLE **6**

SYMPTOMS AND MANAGEMENT OF GENERALIZED HEADACHES

Headache type	Symptoms	Precipitating factors	Pharmacologic treatment	Nonpharmacologic treatment
Allergy headache	Generalized headache with nasal congestion and watery eyes	Seasonal allergies, such as pollen, mold; allergies to food usually not a factor	Antihistamines (cetirizine 5-10 mg po daily; fexofenadine 60 mg po BID or 180 mg po daily; loratadine 5 mg po daily) Topical, nasal corticosteroid (beclomethasone 1-2 sprays per nostril BID, fluticasone propionate 2 sprays per nostril daily; triamcinolone 1-2 sprays per nostril daily) Short-term use: decongestants (pseudoephedrine 60 mg po q 4-6 hr or 120 mg po q 12 hr or 240 mg po daily) Desensitization or immunotherapy injections for long-term control	Remove allergens; Humidify air (steam vaporizer, cool-mist humidifier, steam from warm water); alternate hot and cold compresses (1-3 min); nasal irrigation with saline rinse
Exertion headache	Generalized pain of short duration (min to hr) during or following physical exertion (running, sexual activity) or passive exertion (sneezing, passing a bowel movement)	90% related to migraine or cluster headaches 10% caused by organic disease (aneurysms, tumors, blood vessel malformation)	Determine cause: treat organic disease if cause Indomethacin 50 mg or 75 mg po 1-2 hr before activity triggering activity or scheduled as 25-50 mg po TID Propranolol 1-2 mg/kg/d when NSAIDs contraindicated or not tolerated	Avoid exercise and exacerbating activities until symptoms resolve; rest; ice packs
Fever headache	Generalized pain that develops with fever. Caused by inflamed blood vessels from infection	Infections	Treatment of infection Symptomatic relief: acetaminophen 325-650 mg po q 4-6 hr NSAIDs (ibuprofen 200-400 mg po q 4-6 hr; naproxen 500 mg po then 250 mg q 6-8 hr)	Rest; ice packs
Hypertension headache	Generalized or "hairband" type pain, most severe in morning, diminishing throughout day	Severe hypertension, SBP >200 mm Hg and/or DBP >110 mm Hg	BP treatment per JNC-7 guidelines Avoid NSAIDs, may increase BP; may use acetaminophen temporarily but important to get BP stabilized	Rest; ice packs; monitor BP frequently

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; JNC-7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NSAIDs, nonsteroidal anti-inflammatory drugs: SBP, systolic blood pressure

Source: Ref 45,71-74

Reduction in pain is observed in patients who participate in a structured exercise program that includes strengthening, aerobic conditioning, flexibility, and balance.[43] Additionally, many of these patients have reductions in tender points and improvement in physical function and depression or other mood disorders. Patients should always start an exercise regimen slowly and gradually build up at their own pace so as to not exacerbate symptoms. Water exercise, along with balneotherapy, has been shown to be well tolerated and is especially helpful with stiffness and pain reduction.[51] Seeking assistance from a professional is recommended to provide guidance in selecting an appropriate exercise regimen for each individual.

Cognitive behavioral therapy, a psychotherapeutic approach to the physiologic links between chronic pain and depres-

sion, is used to teach patients to understand the effects of their thoughts, beliefs, and expectations on their symptoms.[43] It should always be used in conjunction with other therapies, and is especially useful in patients who have emotional distress. This therapy can help teach patients how to manage stress, anxiety, or other psychologic emotions that may contribute or result from their fibromyalgia symptoms. This nonpharmacologic therapy has been shown to reduce pain severity and mood disorders in small trials, and its benefit usually can be achieved in 10 to 20 sessions.

Sprains, strains, and contusions

Joint sprains are commonplace in today's society, with knee sprains of the medial collateral ligament being among the most common knee injuries from sports participation and ankle sprains being the most common type of ankle injury in sports.[52,53] Pain location, duration, frequency, any characteristics of the injury (sounds heard at the time of trauma), and injury site evaluation (swelling, redness), coupled with aggravating or alleviating factors, will assist in determining the extent of the sprain. Radiographic imaging with or without magnetic resonance imaging is always recommended to visualize the extent of damage.[54] Therapeutic intervention is often supportive to reduce swelling and hasten recovery via the PRICE (Protection, Rest, Ice, Compression, Elevation) method.[55] NSAIDs (oral and topical) and acetaminophen appear to have equally effective outcomes in reducing pain and swelling and improving function in patients with sprains.[56]

Muscle strains are often precipitated by trauma or motion and are aggravated by continued motion or even a simple cough. Physical exam findings will likely identify localized tenderness at or near the site of the involved muscle strain. Rest and movement limitation for a short period of time will likely provide the greatest relief and prevent further aggravation or reaggravation of the muscle strain. Proper posture, appropriate stretching and lifting techniques, and limiting exposure to biomechanical stressors (manual handling, working with hands above shoulder level, working with vibratory tools) can help reduce occurrence and persistence of pain related to shoulder and back muscle strains over the long term.[57,58]

Concomitant neck pain at presentation in individuals with shoulder strains could be indicative of greater shoulder disability.[59] A frozen shoulder, also known as adhesive capsulitis of the shoulder, is a clinical diagnosis with 3 key hallmarks: shoulder stiffness; severe pain, even at night; and near complete loss of shoulder mobility.[60] Patients tend to present in their 50s and complain of the symptoms in their nondominant shoulder, although the dominant shoulder can become involved within 5 years of resolution of the original symptomatology.[60] The initial phase of a frozen shoulder can last 10 to 36 weeks, with pain and stiffness that worsens at night and responds poorly to NSAIDs.[60] As the pain subsides during months 4 to 12, the stiffness can persist and pain is generally only evident at the extremes of motion. Spontaneous improvement in range of motion and resolution of symptoms can take between 12 and 42 months, with the mean resolution occurring at 30 months.[60]

Contusions (hematomas or bruises) are extremely commonplace. More than 20% of emergency department visits for playground equipment injuries over a 2-year period were diagnosed as contusions, and 14% of soccer players in U.S. high schools have also suffered from contusions.[61,62] The RICE (Rest, acutely ice, compression, elevation) method paired with early immobilization was shown to quicken recovery from a contusion.[63] Acetaminophen and oral NSAIDs showed no statistically significant differences in efficacy or adverse events when employed to manage contusions.[64]

There exists no clear evidence to guide therapy of muscle strains. NSAIDs are commonly employed and response can be limited, although no randomized trials have been supportive of this intervention in shoulder or low back strains, and no evidence exists that NSAIDs are any better than acetaminophen alone for strains.[60,65] A topical NSAID, such as a diclofenac epolamine 180-mg patch applied to the painful site twice a day, provided pain relief as compared to placebo in only 2 of 4 randomized, placebo-controlled trials in which it was evaluated.[66] Progressive range-of-motion exercises as tolerated and, if necessary, intra-articular steroid injections have proven to be helpful in patients, with steroids providing faster relief of symptoms. No long-term differences in pain or recovery times, however, were noted between exercises and joint injections.[67] Doses of methylprednisolone 40 mg or triamcinolone 40 mg as joint injections are commonly cited throughout various shoulder strain literature.

Low back strains may respond well to cold and heat therapy. Cold therapy used on day 1, then heat on subsequent days for up to 2 weeks may provide the best relief from this intervention.[68] Icing with direct, static placement or via ice massage for 20-minute intervals every 4 to 6 hours has been recommended for the acute, initial phase of a strain, but this method lacks direct evidence for overall benefit. Conversely, heat therapy via topical heat wraps for 8 hours on the low back strain has demonstrated a reduction in pain intensity at day 2 to day 14 of the treatment.[68] SMRs may provide relief from symptoms of a strain or sprain as shown in a randomized, double-blind study comparing cyclobenzaprine 10 mg and carisoprodol 350 mg with equal outcomes

Pause&Ponder

You are working the evening shift at a local retail pharmacy and a 58-year-old man walks in and asks to speak with the pharmacist. When you come to the counter, he says, "Man, my head is killing me. Can you recommend something?" What questions would you ask this man to obtain the information you would need to make a recommendation?

in both groups of patients.[69] As with any pain syndrome, pharmacists will want to refer the patient for further intervention by their physician or a specialist when symptoms persist or worsen.

Generalized headaches

Headache is among the most common complaints of adults and can exist without other symptoms or be a result of a local or systemic disease. The most common types of headaches, comprising more than 90% of all headaches, are tension-type headaches, migraines, and medication-overuse headaches.[70] Other types of headaches include cluster headaches, vascular headaches, facial pain-related headaches, headaches of organic origin (e.g., sinus disease, ocular disease, brain tumor), and generalized headaches. Many guidelines and articles exist describing the more common headaches, but most often pharmacists are asked about how to treat generalized headaches. This section focuses on the precipitating factors, accompanying signs and symptoms, and treatment of generalized headaches.

Unlike migraine headaches, which are usually unilateral and pulsating or throbbing in nature, and tension headaches, which are often described as tightness and pressure bilaterally in a band-like area, generalized headaches are typically diffuse pain.[70] These may be located in the frontal portion of the head or throughout the head. Typically the pain is described as mild and self-resolving depending on the etiology. Accompanying neurologic or other symptoms (e.g., nausea, vomiting, photophobia) that often occur with tension or migraine headaches are typically not present.

The types of headaches that are associated with generalized headache pain include headaches related to exertion, fever, allergy, and hypertension (**Table 6**).[45,71-74] Accompanying symptoms may be related to the cause of the headache. For example, allergy-related headaches will often be accompanied by nasal congestion and watery eyes.

Although many patients will describe generalized headaches as being painful and disruptive, most are not life-threatening. Occasionally, however, a headache will be a symptom of a serious underlying infection, cerebral hemorrhage, or brain mass.[70] Worrisome factors that should raise concern are sometimes coined **SNOOP: S**ystemic symptoms (fever, weight loss) or **S**econdary headache risk factors (HIV, systemic cancer), **N**eurologic symptoms or abnormal signs (confusion, impaired alertness, or consciousness), **O**nset (sudden, abrupt, or split-second), **O**lder (new onset and progressive headache, especially in those >50 years), and **P**revious headache history or headache progression (first headache or different change in attack frequency, severity, or clinical features).[73] If any of these symptoms are identified, the patient should be referred to a medical provider for evaluation. Additionally, if a patient describes any recent head trauma, a full evaluation is warranted to rule out a cerebral hematoma.

The pharmacologic and nonpharmacologic treatment of generalized headaches is dependent on the precipitating cause of the headache. **Table 6** describes the pharmacologic and nonpharmacologic treatment of these common generalized headaches.[45,71-74] Nonpharmacologic treatment is aimed at symptom relief and avoiding triggering factors. Before recommending an OTC product, it is important to determine if any worrisome factors are present (see previous discussion) that would require evaluation by a physician. Additionally, it is important to recognize potential contraindications (concurrent disease states), allergies, or drug interactions that may prevent use of a recommended therapy.

Pharmacist's role

Pharmacists are in the first position to triage many patients with common pain conditions discussed herein. Often, pharmacists can be a source of education and reassurance to patients who suffer from acute but minor injuries and advise them of nonpharmacologic interventions and pharmacologic options available to enable the patient to remain active and functional to the greatest extent possible. Pharmacists can work to screen patients with persistent pain that may require further medical or psychosocial intervention. It is the pharmacist's responsibility to minimize untoward adverse effects, such as those risks posed from prolonged use of NSAIDs or the combination of medications with serious risks. This and earlier articles in this continuing education pain management series summarize a number of common recommendations and side-effect management interventions that pharmacists can make to have a profound impact on the care and quality of life for patients in pain.

Pharmacists are often the front-line, first-access healthcare providers to patients with common ailments, including common pain conditions.

Conclusion

Pharmacists are often the front-line, first-access healthcare providers to patients with common ailments, including common pain conditions. Pharmacists have the unique ability to counsel patients and caregivers on effective nonpharmacologic and OTC pharmacologic interventions for such pain syndromes in the initial, acute phase. The ability to recognize when symptoms persist or worsen and to refer these patients for further medical intervention is paramount to patient safety. •

References posted online: www.drugtopics.com/cpe.

TEST QUESTIONS

1. Weight loss of 10 pounds contributes to a ___ pound reduction off the knees.

- **a.** 10
- **b.** 20
- **c.** 30
- **d.** 40

2. Effective acetaminophen dosing for patients with osteoarthritis is:

- **a.** 650 mg orally every 6 to 8 hours, scheduled
- **b.** 325 mg orally every 8 hours as needed
- **c.** 325 mg orally every 4 to 6 hours, scheduled
- **d.** 160 mg orally every 4 hours as needed

3. Topical diclofenac gel:

- **a.** Has substantially less systemic absorption compared to its oral counterparts
- **b.** Has increased risks for localized and dermatologic reactions
- **c.** Has requirements to avoid direct sun exposure to treated area(s)
- **d.** All of the above

4. Glucosamine and chondroitin for osteoarthritis is:

- **a.** Recommended for use by the American College of Rheumatology
- **b.** Most effective as the glucosamine sulfate salt
- **c.** Should be used continuously for 3 to 6 months to determine its effectiveness
- **d.** B and C only

5. Chronic low back pain has been linked with:

- **a.** Sleep disturbance
- **b.** Work absenteeism
- **c.** Poor daytime functioning
- **d.** All of the above

6. Considerations with cyclobenzaprine in the management of low back pain include:

- **a.** CYP450 drug interactions
- **b.** Low anticholinergic profile
- **c.** Sustained effect after 4 days
- **d.** Barbiturate metabolite derivative

7. Considerations with tramadol in the management of low back pain include its:

- **a.** GI ulcer formation potential
- **b.** CYP450 2D6 dependence for activation
- **c.** Cardiovascular event risk
- **d.** Potential to cause renal impairment

8. For patients initiating therapy with the buprenorphine transdermal system whose prior total daily dose of opioid is between 30 and 80 mg oral morphine equivalents per day, the starting dose is:

- **a.** 5 µg/hr
- **b.** 10 µg/hr
- **c.** 20 µg/hr
- **d.** 40 µg/hr

9. The core symptoms of fibromyalgia include which of the following?

- **a.** Pain, headache, and fatigue
- **b.** Pain, fatigue, and sleep disturbances
- **c.** Pain, mood disorders, and sleep disturbances
- **d.** Pain, mood disorders, and headache

10. Which of the following FDA-approved drugs for treatment of fibromyalgia has been shown to significantly improve cognitive function?

- **a.** Amitriptyline
- **b.** Duloxetine
- **c.** Milnacipran
- **d.** Pregabalin

11. Selecting the best pharmacologic therapy for treatment of fibromyalgia should be based on:

- **a.** Specific symptoms, comorbidities, adverse effects, and patient preferences
- **b.** Length of diagnosis
- **c.** FDA approval
- **d.** Impact of disease on quality of life

12. Which of the following exercise regimens is most helpful with stiffness and pain reduction?

- **a.** Water exercise with balneotherapy
- **b.** Aerobic conditioning
- **c.** Structured exercise
- **d.** Weight-bearing exercise

13. The PRICE method is defined as:

- **a.** Rest, acutely ice, compression, elevation
- **b.** Protection, rest, ice, compression, elevation
- **c.** Proper posture, appropriate stretching and lifting techniques, limiting exposure to stressors
- **d.** Posture, relaxation, ice, compression, elevation

14. A frozen shoulder is a clinical diagnosis consisting of:

- **a.** Shoulder stiffness
- **b.** Severe pain, even at night
- **c.** Near complete loss of shoulder mobility
- **d.** All of the above

15. Heat and cold therapy are recommended for:

- **a.** Muscle strains
- **b.** Low back pain
- **c.** Osteoarthritis
- **d.** A and B

16. Which of the following therapies may be effective for patients with muscle strains?

- **a.** Intra-articular steroid injections
- **b.** Diclofenac epolamine
- **c.** NSAIDs
- **d.** All of the above

17. Generalized headaches are often described as:

- **a.** Bilateral pressure
- **b.** Diffuse pain
- **c.** Tightness
- **d.** Unilateral and throbbing

18. Which of the following is an example of a worrisome symptom that should cause a patient to be referred to a physician?

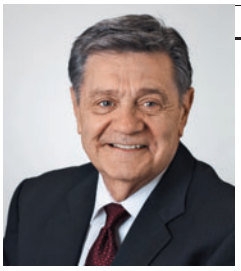
- **a.** Confusion
- **b.** Nausea
- **c.** Gradual onset of pain
- **d.** Unilateral pain

19. First-line pharmacologic treatment of a fever-induced headache is:

- **a.** Acetaminophen
- **b.** Ibuprofen
- **c.** Indomethacin
- **d.** Treatment of infection

20. Which of the following is true of hypertension headaches?

- **a.** Temporary use of nonsteroidal anti-inflammatories is appropriate for symptom relief
- **b.** Headaches are worse in the evening
- **c.** Nonpharmacologic treatment may include nasal saline irrigation
- **d.** None of the above



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

The ethics of a "just culture"

The primary ethical obligation of a pharmacist is to avoid harm by filling each prescription correctly. For this reason, pharmacies, pharmacy organizations, and boards of pharmacy have adopted and espoused the principles of continuous quality improvement.

Regardless of the effort and time a pharmacy puts into developing and implementing its continuous quality improvement (CQI) program, one truth remains — there will still be mistakes and medication errors. No system will eliminate all errors. Any time a medication error reaches a patient, there is a chance that a patient will be injured by the mistake. Risk is in the nature of the profession of pharmacy. It is an imperfect science and an awesome responsibility.

When a mistake is made, the first reaction of those in authority is to blame someone.There must be someone to punish. We look for the last person who worked on the prescription and we heap shame on that person. It is easy to lapse into the 17th century mentality of "burn the witch." Boards of pharmacy often find themselves placed in this position — they must find and punish the culprit.

CQI, however, teaches that the way to reduce medication errors is to improve the process and the workflow. The CQI theory is to look for the root cause of the error and then change the system to eliminate that cause. If all we do is "burn the witch" and fire the pharmacist, then the next time the same sequences of events lines up, we must find a new witch. Eventually there is no one left to fire, no one reports mistakes, and there is no improvement.

Most mistakes in the pharmacy are the result of simple human errors, which any pharmacist and technician can make. As long as human beings play any part in the practice of pharmacy, there will be human errors. We could no more eliminate all mistakes than we could stop being human. CQI systems are necessary because pharmacists and technicians are human beings. The root cause of a pharmacy error, therefore, is the thing that failed to prevent our act of human frailty.

For perhaps 90% of all the medication errors that pharmacists and pharmacy technicians make, the CQI theory of eliminating the "blame and shame" of being human works. We eliminate fear of reporting, and with each reported error there is a search for the root cause and the system is improved. The risk of the next error is reduced.

At-risk behavior

There are a few medication errors, however, for which blame must be assessed and for which punishment is appropriate.

Very occasionally, the root cause of error is not a process flaw or a workflow difficulty. Sometimes the root cause is the at-risk behavior of the pharmacist or pharmacy technician. Examples of possible at-risk behavior include multitasking or trying to fill too many prescriptions at one time.

Still less common, there are times when the person's behavior is not just at-risk, but reckless, times when the individual has shown a reckless disregard for the safety of his or her patients. An example of recklessness is the person who arrives at work drunk or high. Sometimes we say that this person has demonstrated that he or she just doesn't care.

If ethics includes justice, then it is incumbent upon managers, supervisors, and boards of pharmacy members to understand the differences in each of these types of action.

When a medication error is the result of simple human error, then the system needs improvement. When the pharmacist or pharmacy technician exhibits at-risk behavior, education is appropriate.

Actual discipline, however, should be reserved for those individuals who show a reckless disregard for the safety of patients and the system. Punishment cannot be meted out according to the harm that results, but according to the actions that caused it. It is easy to punish — it is hard to determine which person to punish and why.

For a discussion of the concept of a "just culture," I suggest you read Sidney Decker's book, *Just Culture, Balancing Safety and Accountability*, from Ashgate Publishing. Also, visit *www.ISMP.org* and search for "just culture." DT

This article is 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.

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LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

Emergency contraceptive's curious path to OTC status

In June 2013, the Department of Justice (DOJ) under the Obama administration announced an end to its lawsuits over age restrictions on Plan B One-Step (levonorgestrel), the morning-after pill. The DOJ decided not to appeal the ruling made by Judge Edward Korman of the District Court of Eastern New York.

Judge Korman had overturned the decision made by Secretary Kathleen Sebelius of the Department of Health and Human Services (DHHS) to keep the limit of a minimum of 17 years of age for young women seeking to obtain Plan B One-Step without a prescription.

As a result of these latest developments, women of all ages will have access to this morning-after pill, over-the-counter (OTC) and without a prescription.

This marks the latest outcome of the continuing tension between those advocates arguing for greater availability of Plan B One-Step and opponents arguing to restrict its access for underage girls.

The timeline

In light of these most recent developments, the following timeline for *Drug Topics* readers marks key dates leading up to Plan B One-Step's current OTC status for females of all ages. The timeline is not an exhaustive detailing of events, but is intended to highlight the key points that led to the availability of Plan B One-Step to all females OTC and without a prescription.

1999: The U.S. Food and Drug Administration (FDA) approves the emergency contraceptive drug levonorgestrel, known as Plan B, as a prescription-only drug. It is manufactured at this time in a two-tablet format.

2001: Seeking to make Plan B available OTC, the Center for Reproductive Rights, along with countless other activist groups, files a citizen petition with FDA.

2003: Teva (the maker of Plan B) files an application with FDA to make the drug available OTC.

2005: In an attempt to force FDA to respond to its citizen petition, the Center for Reproductive Rights files a lawsuit in a New York federal court.

2006: The citizen petition of the Center for Reproductive Rights is denied. Nonetheless, FDA begins allowing Plan B to be made available without a prescription to women who are at least 18 years of age.

2009: In Brooklyn, U.S. District Judge Edward Korman rules that FDA acted without good faith in denying the citizen petition and orders that Plan B be made available to women 17 and older.

August 2009: FDA approves a generic version of Plan B that is also available OTC for women ages 17 years and older.

February 2011: Teva files an FDA application to move Plan B One-Step from a limited OTC status to an unfettered OTC status without age limits.

December 2011: FDA decides that Plan B One-Step and generic versions of Plan B are safe for females of all ages and that they are able to understand the risks of the emergency contraceptive without prescriber help. Nevertheless, FDA is overruled by DHHS Secretary Sebelius, who states that there is inadequate evidence demonstrating safe drug use by underage girls.

February 2012: The Center for Reproductive Rights reopens its lawsuit against FDA. Secretary Sebelius is now named as a defendant for overruling FDA's decision to make the emergency contraceptive available OTC.

April 2013: Judge Korman overturns Sebelius' decision to set age limits on the nonprescription availability of the emergency contraceptive, stating that the DHHS decision "was arbitrary, capricious, and unreasonable," among other things.

May 2013: The DOJ under the Obama administration announces that it is appealing Judge Korman's order to lift all age limits on buying the emergency contraceptive without a prescription.

June 2013: The 2nd U.S. Circuit Court of Appeals in New York permits girls of all ages to purchase morning-after drugs without a prescription.

June 2013: The DOJ makes an about-face, announcing that it is abandoning all further efforts to appeal Judge Korman's decision. 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.

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New-Skin creates a protective barrier to keep cuts and scrapes clean and safe.

Tecnu First Aid Gel offers antiseptic pain relief without antibiotics for treatment of minor wounds.

Muscle Jel uses menthol and camphor first to cool and then warm aches and sprains.

PHOTOS COURTESY OF PRESTIGE BRANDS/TECNU LABS/WATER-JEL TECHNOLOGIES

OTC

Filling a first aid kit: Some new options for cuts, pain, and itch relief

JULIA TALSMA, CONTENT CHANNEL DIRECTOR

August is a great time for many families to enjoy the outdoors before school starts. Anyone preparing for a camping trip, a hike, a boating adventure, biking, or just swimming should prepare a first aid kit for any unexpected mishaps. Some new items that can be added to the kit are described below.

Minor wound care

New-Skin Liquid Spray Bandage by Prestige Brands Inc. offers good coverage for large cuts and scrapes, protecting against bacterial contamination with its active ingredient of benzethonium chloride 0.2%. This first-aid antiseptic dries rapidly and forms a protective covering that is both flexible and waterproof. Hikers and runners can apply before exercise to prevent blisters. It is available in one-ounce bottles. For smaller cuts and scrapes, **New-Skin Liquid Bandage** offers a brush-on applicator and is available in 0.3- and 1.0-ounce bottles. These products should not be used on infected skin or wounds that are draining, near eyes, or for deep, puncture wounds, and should not be used for longer than one week.

Tecnu First Aid Gel by Tec Labs is an antibiotic-free formula for the prevention of skin infections in minor wounds. For patients who are allergic to topical antibiotics, Tecnu First Aid Gel includes an antiseptic, benzethonium chloride 0.2%, and a pain-relieving agent, lidocaine hydrochloride 2.5%. Because the gel is water-based, it can be easily absorbed by the skin. The product is available in a 2-ounce tube or in single-use packets, and can be used by adults and children.

Pain relief

For fast-acting pain relief, patients can try **Bengay Cold Therapy**, a menthol pain-relieving gel from Johnson & Johnson Consumer Companies Inc. The gel's cooling active ingredients help to ease sprains and muscle and joint pain, and offer long-lasting relief. The scent will disappear soon after application. The manufacturer notes that the gel's intensity of cold equals the professional-grade analgesic used by chiropractors and physical therapists. The gel should not be used on wounds or damaged skin, and should not be used with other products on the same body area. Patients are advised not to use a heating pad in combination with Bengay gels or creams, as topical analgesics affect pain perception.

Water-Jel Technologies offers **Muscle Jel** for relief of minor aches and muscle and joint pain. The light, greaseless formula contains menthol and camphor that first cools and soothes backache, strains, and sprains, and then warms and penetrates deeply to alleviate pain. The therapeutic analgesic is the same as that used by physical therapists, chiropractors, and other health profession-

Continued on pg. 62

Filling a first aid kit

Continued from pg. 61

Cortizone 10 offers itch relief without the mess to adults and children over the age of 2.

Thera-PED and **Thera-TOES** are approved by the American Podiatric Medical Association to soothe those tired tootsies.

als. Muscle Jel is available in a 2-ounce spray bottle, 4-ounce tube, 16- and 32-ounce pump bottle, 128-ounce pump gallon, and in a 24-pack dispenser for first-aid kits. The product has a shelf life of 3 years.

Requiring no refrigeration, **Nexcare Instant Cold Pack** by 3M is ideal for the first-aid kit. The cold pack, activated by squeezing, has both a comfortable outer layer and a foam-insulated layer to help it stay cold longer. The product is recommended for minor muscle aches, sprains, tension headaches, minor burns, and insect bites. It is available as one pack measuring 5" by 9". The Instant Cold Pack should not be chilled or frozen before use as this can cause skin damage, including frostbite.

Itch relief

Patients seeking itch relief without the mess can consider **Cortizone 10 Poison Ivy Relief Pads** by Chattem, formulated for adults and children two years of age and older. The active ingredient, hydrocortisone 1%, is applied with a "touch-free applicator." Snapping the applicator releases the product from the top of the pad; it is then rubbed into the skin until it is absorbed. The pads provide temporary relief to itchy skin resulting from poison ivy, poison oak, and poison sumac, and are also recommended for insect bites, allergies, eczema, psoriasis, and dermatitis. The product should not be used more than 3 to 4 times daily and not beyond 7 days.

Tecnu Rash Relief spray by Tec Labs is a homeopathic medicated anti-itch spray that helps alleviate painful itching, helps prevent scarring, and dries oozing that occurs after exposure to poison ivy, poison oak, and poison sumac. The area can first be cleaned with **Tecnu Extreme Poison Ivy Scrub** or **Tecnu Outdoor Skin Cleanser** to remove the urushiol that is the source of the rash, keeping the rash from spreading. Tecnu Rash Relief spray is available in a 6-ounce nonaerosol spray bottle.

Foot relief

To soothe sore feet and toes, Health Enterprises has developed **TheraPED** and **TheraTOES**, two products that offer hot or cold spa therapy after a long day on those tired feet. TheraPED has a "therma" gel designed to relieve cramped, achy feet and spacers to realign cramped toes. TheraTOES also has a therma gel to help pamper and refresh the feet. Both products have received the seal of acceptance from the American Podiatric Medical Association. DT

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Advertiser Index

*Indicates a demographic advertisement.

RX & OTC

New products

PHOTOS COURTESY OF VIVUS

RX CARE

New Rx

Nearly a year after gaining FDA approval, prescriptions for **Qsymia** [1], once-daily phentermine and topiramate extended-release tablets from Vivus, can now be filled at about 8,000 pharmacies nationwide. Qsymia is FDA-approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related medical condition such as high blood pressure, type 2 diabetes, or high cholesterol. Until recently, the drug was available only through mail-order pharmacies. FDA required extra regulation because Qsymia can cause birth defects if taken by pregnant women. However, FDA has eased the requirements for dispensing Qsymia and now allows certified retail pharmacies to fill the prescriptions. The drug is now available at certified Walgreens, Costco, and Duane Reade pharmacies. **(www.qsymia.com)**

FDA has approved Orexo's **Zubsolv,** a once-daily sublingual tablet CIII, containing both buprenorphine and naloxone for use as maintenance treatment for opioid dependence. According to the manufacturer, it should be used as part of a complete treatment plan that includes counseling and psychosocial support. Compared with other buprenorphine/naloxone treatments, Zubsolv is said to have a higher bioavailability, faster dissolve time, and smaller tablet size with a new menthol taste. The company's subsidiary Orexo US and partner Publicis Touchpoint Solutions will launch the product in September. **(www.orexo.com)**

Brisdelle low-dose paroxetine capsules, 7.5 mg/day, from Noven Therapeutics, received FDA approval for the treatment of moderate-to-severe menopause-related vasomotor symptoms (VMS) such as hot flashes and night sweats. Prior to this approval, hormone therapy was the only FDA-approved treatment for VMS. Hot flashes associated with menopause occur in up to 75% of women and can persist for up to 5 years, or even longer for some women. Brisdelle is dosed once daily at bedtime. Other medications such as Paxil and Pexeva contain higher doses of paroxetine and are approved for treating conditions such as major depressive disorder, obsessive-compulsive disorder, panic disorder, and generalized anxiety disorder. Brisdelle will be available in U.S. pharmacies in November. **(www.brisdelle.com)**

In mid-July, FDA granted approval to **Gilotrif** (afatinib) for patients with metastatic non-small-cell lung cancer whose tumors express specific types of epidermal growth factor receptor (EGFR) gene mutations, as detected by an FDA-approved test. Gilotrif, marketed by Boehringer Ingelheim Pharmaceuticals, is a tyrosine kinase inhibitor that blocks proteins that promote the development of cancerous cells. Gilotrif can be used for patients whose tumors express the EGFR exon 19 deletions or exon 21 L858 substitution gene mutations. FDA gave its approval to the drug con-

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New products

Continued from pg. 63

currently with approval of its companion diagnostic, the Therascreen EGFR RGQ PCR Kit, which helps determine whether a patient's lung-cancer cells express the EGFR mutations. **(http://us.boehringer-ingelheim.com)**

New indications

FDA has expanded the approved use of the antibiotic **Vibativ** (telavancin) to treat patients who have contracted hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by *Staphylococcus aureus*. Vibativ should be used for the treatment of HABP/VABP only when alternative treatments are not suitable. Vibativ was approved in 2009 to treat complicated skin and skin-structure infections. The product is marketed by Theravance Inc. **(www.vibativ.com)**

FDA has approved two new indications for **Latuda** (lurasidone HCl), from Sunovion, a U.S. subsidiary of Dainippon Sumitomo Pharma. Latuda can be used as monotherapy and as adjunctive therapy with either lithium or valproate to treat adult patients with major depressive episodes that are associated with bipolar I disorder. This is the first atypical antipsychotic to receive FDA approval as both monotherapy and adjunctive therapy with lithium or valproate for the treatment of bipolar depression. **(http://www.latuda.com)**

FDA has approved Astellas Pharma's **Astagraf XL** (tacrolimus extended-release capsules) for the prophylaxis of organ rejection in patients who are receiving a kidney transplant with mycophenolate mofetil and corticosteroids, with or without basiliximab induction. This is the first once-daily oral tacrolimus formulation available in the United States for kidney transplant recipients. Astellas' Prograf (tacrolimus) is available in the United States in the form of IV infusion to prevent organ rejection in patients who have had a kidney, liver, or heart transplant. **(http://www.us.astellas.com)**

New generics

In mid-July, FDA approved Lupin's ANDA for **metformin hydrochloride extended-release tablets** in the 500-mg and 1,000-mg strengths. The drug is the generic equivalent to Santarus' Glumetza. Lupin received 180-day exclusivity for products in these dosage amounts. **(www.lupinpharmaceuticals.com)**

Also in mid-July, FDA approved Actavis' **oxymorphone hydrochloride extended-release tablets**, the generic version of Endo Health Solutions' Opana ER, in the 5-mg, 10-mg, 20-mg, 30-mg, and 40-mg strengths. The product is based on a non-crush-resistant version that was withdrawn from the market last year. Actavis already markets the 7.5-mg and 15-mg versions. An FDA rule that was finalized earlier in the year allows for generic versions of the earlier formulation of Opana ER, although Endo produces only the crush-resistant formulation. Actavis also received FDA approval for its generic version of GlaxoSmithKline's Lamictal orally disintegrating tablets. The company plans to launch **lamotrigine orally disintegrating tablets** immediately. They will be available in the following doses: 25 mg, 50 mg, 100 mg, and 200 mg. **(http://ir.actavis.com)**

At the end of June, Dr. Reddy's launched its **lamotrigine extended-release tablets,** a generic therapeutic equivalent to Lamictal XR, following FDA approval of its ANDA for lamotrigine XR tablets. The tablets are available in the following doses: 25 mg, 50 mg, 100 mg, 200 mg, and 300 mg. **(www.drreddys.com)**

In mid-July, Par Pharmaceuticals received FDA approval for its ANDA for **fenofibric acid delayed-release (DR) capsules** in 45-mg and 135-mg dosage strengths. The product is the generic equivalent of Trilipix, from AbbVie. **(www.parpharm.com/generics)**

New OTC

In June, the emergency contraceptive **Plan B One-Step [2]** (levonorgestrel), from Teva Women's Health, received FDA approval for over-the-counter sale to all consumers in the United States. The product, a 1.5-mg tablet, is the first one-tablet emergency contraceptive without age or point-of-sale restrictions to become available in store aisles. **(www.planbonestep.com)**

Nordic Naturals' Professional Division has introduced **Pro EPA with Concentrated GLA** (gamma-linolenic acid), a product that offers a high concentration of omega-3 eicosapentaenoic acid (EPA) and omega-6 gamma-linolenic acid (GLA), as well as omega-3 docosahexaenoic acid (DHA), for comprehensive essential fatty acid support. According to the company's chief medical officer, EPA, DHA, and GLA are essential for optimal health. The EPA and DHA in the product are derived from sardines and anchovies that are wild-caught. The GLA comes from borage seed. **(www.nordicnaturals.com/professionals.php)** DT

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Products & Services

Brokers

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Products & Services

Brokers

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JP AT LARGE Jim Plagakis, RPh

Reflections on chain pharmacy evolution

Life was simpler before computers, wasn't it? Many years ago, I was a dispenser. That is what pharmacists did after Durham-Humphrey. We proudly filled prescriptions.

We still compounded occasionally. Real compounding involves more than just handing a spatula, Aquaphor, and hydrocortisone powder to a technician.

No computer. Life was slower. We kept Rx records on paper. We used a manual typewriter to type labels. There was a thick pad of paper and a pencil to calculate prices. Life *was* simpler.

Chipping away

Right from the beginning, I wanted to make a difference in the business of retail pharmacy in a big way. After all, it was my life.

My dream was shattered in 1970, and I wasn't even 30 years old. An 8 a.m. to 10 p.m. day was what did it.

Then there was the time an older, well-dressed man, slim and bejeweled, came into the pharmacy as if he owned the place. I didn't like it. I knew from the frenetic nervousness of store management that the place was being inspected by upper-level executives.

I extended my hand and told him my name. *He did own the place.* Thrifty in California, with 250+ stores.

The first thing he did was ask whether there was anything he could do for me. I half-seriously told him he could get me a sandwich. He smiled.

"I like to talk with the pharmacists alone," he said. "You're more likely to tell me the truth." He sketched a half-circle in the air with his hand. "These people only tell me what they think I want to hear."

I went into full JP-mode, and that was before there was a JP. I told Mr. Borun what I thought was needed. It still is.

Safety first

He gave me a look and smiled broadly. "I like it," he said. "But, Jim, it is never going to happen."

He swept his arm in a circle again. "It won't happen because it is not their idea, and they won't make it theirs because they won't take chances. They want to keep their jobs."

I must have looked dejected. "You have a good union job," he said. "Pharmacists are in short supply. You can't miss."

An hour later, the store manager gave me a look and put a hot meatball sandwich on the counter.

Two months later, I was the manager of an All-Med Drug Store. I could do anything I wanted. I continued in management at chains for a career (with a couple of three-year hiatuses to keep sane). As long as I used a typewriter, it was all good.

Gave away the store

Then the computer ripped my juju away.

Some guy at headquarters was always watching, spying on me. Some pharmacy-ignorant MBA guys at headquarters crunched numbers and told me how much help I could have. They told me how fast I should work. They abandoned the proven retail model. They came up with a variety-store-based system. They got an anemic variety-store ROI. Funny, before that, pharmacists did it all and we made a lot of money for our companies.

The nonpharmacist MBAs gave away the store. They continually made horrible business deals with the pharmacy benefit managers. Remember when you believed that a $25 gift card for a transferred prescription was just a fad?

It seems that their strategy is to do the same old things, such as $4 or free Rxs, and better. Give Sally a new red dress and she will rock you. Same old Sally, though. A gift card is just a gift card. It ain't pharmacy.

"But," they argue, "it must work, *because they have been doing it for so long."*

It's a good job. Take no risks. Job preservation: A tune that spineless modern pharmacists are good at dancing to.

I confess. I did it. I knew I had to stay within the lines. Boring and dumb when the company's programs did more damage than good. I was an employee pharmacist/manager with a chain drugstore.

I couldn't even override the price on a cash prescription without being dinged for it. The first time I realized that any move outside the cage was noticed was when I got a call from the vice president in charge of pharmacy.

The conversation was friendly until he said, "I see that you overrode the price four times last month."

"How do you know?"

"I get reports." He laughed. "I know everything."

I am as guilty of manning an oar in a galley ship as any of you. I don't brag about it, but they paid me well and my life was pretty good. So sue me. DT

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