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Opioid pain management PAGE 46
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Indications

EpiPen® and EpiPen Jr Auto-Injectors (0.3/0.15 mg) are indicated in the emergency treatment of type 1 allergic reactions, including anaphylaxis, to allergens, idiopathic and exercise-induced anaphylaxis, and in patients with a history or increased risk of anaphylactic reactions. Selection of the appropriate dosage strength is determined according to body weight.

Important Safety Information

EpiPen® Auto-Injectors should only be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK, OR INTRAVENOUSLY.

Epinephrine should be used with caution in patients with certain heart diseases, and in patients who are on drugs that may sensitize the heart to arrhythmias, because it may precipitate or aggravate angina pectoris and produce ventricular arrhythmias. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or taking cardiac glycosides or diuretics. Patients with certain medical conditions or who take certain medications for allergies, depression, thyroid disorders, diabetes, and hypertension, may be at greater risk for adverse reactions. Other adverse reactions include transient moderate anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

EpiPen® and EpiPen Jr Auto-Injectors are intended for immediate self-administration as emergency supportive therapy only and are not intended as a substitute for immediate medical or hospital care.

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

NIH-NIAID = National Institutes of Health-National Institute of Allergy and Infectious Diseases.

Some patients who have cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, quinidine, or other anti-arrhythmics. In such patients, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. It should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.

Epinephrine is light sensitive and should be stored in the container tube provided. Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) (See USP Controlled Room Temperature). Do not refrigerate. Before using, check to make sure the solution in the auto-injector is not discolored. Replace the auto-injector if the solution is discolored or contains a precipitate.

Precautions:

(1) General
Epinephrine and EpiPen Jr Auto-Injectors are not intended as a substitute for immediate medical care. In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care. More than two needlesticks of epinephrine may result in anaphylactic or life-threatening or less severe adverse reactions in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylaxis or life-threatening or less severe adverse reactions in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylaxis or life-threatening or less severe adverse reactions in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

Epinephrine should be used with caution in patients who have cardiac arrhythmias, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, quinidine, or other anti-arrhythmics. Epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.

Some patients may be at greater risk of developing adverse reactions after epinephrine administration. These include: hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, pediatric patients under 30 kg (66 lbs.) body weight using EpiPen Jr Auto-Inject, and pediatric patients under 15 kg (33 lbs.) body weight using EpiPen Jr Auto-Inject. Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen Jr or EpiPen Jr Auto-Injector to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

(2) Information for Patients
Complete patient information, including dosage, direction for proper administration and precautions can be found inside each EpiPen Jr/Epipen® Jr Auto-Injector cartridge.

Epinephrine may produce symptoms and signs that include an increase in heart rate, the sensation of a more forceful heartbeat, palpitations, sweating, nausea and vomiting, difficulty breathing, palp, dizziness, weakness or shockiness, headache, apprehension, nervousness, or anxiety. These symptoms and signs usually subside rapidly, especially when the patient is quiet and recumbent. Patients with hypertension or hyperthyroidism may develop more severe or persistent effects, and patients with coronary artery disease could experience angina. Patients with diabetes may develop hyperglycemia following epinephrine administration. Patients with Parkinson’s disease may notice a temporary worsening of symptoms.

Consistency and Mutagenicity, Impairment of Fertility
Epinephrine and other catecholamines have been shown to have mutagenic potential in vitro and to be oxidative mutagen in a BP2 bacterial reverse mutation assay. Epinephrine had a moderate degree of mutagenicity, and was positive in the DNA Repair test with S. subtilis (REC assay), but was not mutagenic in the Salmonella bacterial reverse mutation assay. Studies of epinephrine after repeated exposure in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted. This should not prevent the use of epinephrine under the conditions noted under INDICATIONS AND USAGE.

(5) Usage in Pregnancy
For the rat, there is no study on the acute effect of epinephrine on pregnancy. Epinephrine has been shown to have developmental effects when administered subcutaneously in rats at a dose of 1.2 mg/kg daily for two to three days (approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), in mice at a subcutaneous dose of 1 mg/kg daily for 10 days (approximately 7 times the maximum daily subcutaneous or intramuscular dose on a mg/m^2 basis) and in hamsters at a subcutaneous dose of 0.5 mg/kg daily for 4 days (approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg daily for 10 days (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). Although, there are no adequate and well-controlled studies in pregnant women, epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. Epinephrine should not be used in pregnancy or during labor.

OVERDOSAGE: Epinephrine is rapidly inactivated in the body and treatment following overdose with epinephrine is primarily supportive. If necessary, pressor effects may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking drugs. If prolonged hypertension follows such measures, it may be necessary to administer another pressor drug.

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients.

Overdosage may also result in pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Treatment consists of a rapidly acting alpha-adrenergic blocking drug and/or respiratory support. Epinephrine overdose can also cause transient bradycardia followed by tachycardia and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (preexcitation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasional atrioventricular block. Treatment of arrhythmias consists of administration of a beta-blocking drug such as propranolol.

Overdose sometimes results in extreme pallor and coldness of the skin, metabolic acidosis and kidney failure. Suitable corrective measures must be taken in such situations.

HOW SUPPLIED: EpiPen Jr Auto-Injectors (epinephrine injection, USP, 1:1000, 0.3 mL) are available in individual cartons, NDC 4502 500-00-1, and as EpiPen Jr 2-Pak, NDC 4502 500-00-2, a pack that contains two EpiPen Jr Auto-Injectors; EpiPen Jr Auto-Injector trainer device.

EpiPen Jr Auto-Injectors (epinephrine injection, USP, 1:2000, 0.3 mL) are available in individual cartons, NDC 4502 500-01-0, and as EpiPen Jr 2-Pak, NDC 4502 501-02-1, a pack that contains two EpiPen Jr Auto-Injectors, NDC 1:2000, 0.3 mL and one EpiPen Jr Auto-Injector trainer device.

EpiPen Jr 2-Pak and EpiPen Jr 2-Pak also includes an S-clip to clip two cases together.

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) (See USP Controlled Room Temperature). Contains no latex. Protect from light.

Rx only.

MANUFACTURED FOR Dey, L.P.
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by Mylan Laboratories, Inc.,
A subsidiary of King Pharmaceuticals, Inc.,
Columbia, MD 21044, U.S.A.

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03-500-03 (BRS) March 2009
COVER STORY

The road to monopoly

The proposed PBM merger of Medco and Express Scripts could result in market domination. While retail and specialty pharmacies cry foul, the FTC is taking a long, hard look. PAGE 36

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Opioid pain management

Chronic pain afflicts 35% of Americans, of whom nearly half lack adequate pain relief. Properly managed, opioid drugs can offer the most effective treatment.

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See how many millimeters you can move with EDARBI

EDARBI 80 mg was statistically superior to DIOVAN® 320 mg and BENICAR® 40 mg in reducing 24-hr mean ambulatory and clinic SBP

REDUCTIONS IN 24-HR MEAN AMBULATORY SBP AT WEEK 6

Mean ambulatory baseline:
Study 1 = 144.9 mm Hg

STUDY 1

DIOVAN 320 mg
-10.0 mm Hg

BENICAR 40 mg
-11.7 mm Hg

EDARBI 80 mg
-14.3 mm Hg

P<0.001 vs DIOVAN 320 mg
P=0.009 vs BENICAR 40 mg


- Similar results were observed across two other comparator studies: Study 2 vs BENICAR 40 mg and Study 3 vs DIOVAN 320 mg
- Clinic SBP differences between EDARBI and active comparators were consistent with mean ambulatory results

Study 1 Design: A 6-week, randomized, double-blind, placebo-controlled, forced-titration study in patients (N = 1,291) with clinic SBP ≥ 160 mm Hg and ≥ 180 mm Hg and 24-hr mean SBP ≥ 130 mm Hg and ≥170 mm Hg. The primary endpoint was change in 24-hr mean ambulatory SBP. Placebo lowered 24-hr mean ambulatory SBP by 9.3 mm Hg. Data shown are placebo corrected.

IMPORTANT SAFETY INFORMATION

WARNING: AVOID USE IN PREGNANCY
When pregnancy is detected, discontinue EDARBI as soon as possible. Drugs that act directly on the renin–angiotensin system can cause injury and death to the developing fetus.

- Avoid fetal or neonatal exposure.
- Correct volume or salt depletion prior to administration of EDARBI.
- Monitor for worsening renal function in patients with renal impairment.
- In patients with an activated renin–angiotensin system, as by volume or salt depletion, renin–angiotensin-aldosterone system (RAAS) blockers such as azilsartan medoxomil can cause excessive hypotension. In patients whose renal function may depend on the activity of the renin–angiotensin system, e.g., with renal artery stenosis, treatment with RAAS blockers has been associated with oliguria or progressive azotemia and rarely with acute renal failure and death.
- Monitor renal function periodically in patients receiving EDARBI and NSAIDs who are also elderly, volume-depleted, or who have compromised renal function.
- The most common adverse reaction in adults was diarrhea (2%).

For further information, please see adjacent Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

EDARBI is an angiotensin II receptor blocker indicated for the treatment of hypertension in adults to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. There are no controlled trials demonstrating risk reduction with EDARBI, but at least one pharmacologically similar drug has demonstrated such benefits.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. EDARBI may be used either alone or in combination with other antihypertensive agents.

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Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and maintenance of adequate urine output. Expired oxygenation or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function.

Hypotension in Volume- or Salt-Depleted Patients
In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (eg, those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with Edarbi. Correct volume or salt depletion prior to administration of Edarbi, or start treatment at low doses and increase slowly. Treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has been associated with oliguria or progressive azotemia and rarely with acute renal failure and death. Similar results may be anticipated in patients treated with Edarbi.

Impaired Renal Function
A consequence of inhibiting the renin-angiotensin system, changes in renal function may be anticipated in susceptible individuals treated with Edarbi. In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g., patients with severe congestive heart failure, renal artery stenosis, or volume depletion), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has been associated with oliguria or progressive azotemia and rarely with acute renal failure and death. Similar results may be expected.

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

A total of 4814 patients were evaluated for safety when treated with Edarbi at doses of 20, 40 or 80 mg in clinical trials. This includes 1704 patients treated for at least 6 months; of these, 588 were treated for at least 1 year.

Treatment with Edarbi was well-tolerated with an overall incidence of adverse reactions similar to placebo. The rate of withdrawals due to adverse events in placebo-controlled monotherapy and combination therapy trials was 24% (19/801) for placebo, 22.2% (24/1072) for Edarbi 40 mg, and 27.2% (29/1074) for Edarbi 80 mg. The most common adverse event leading to discontinuation, hypotension/orrheostatic hypotension, was reported by 0.4% (8/2146) patients randomized to Edarbi 40 mg or 80 mg compared to 0% (0/801) patients randomized to placebo. Generally, adverse reactions were mild, not dose related and similar regardless of age, gender and race.

In placebo controlled monotherapy trials, diarrhea was reported up to 2% in patients treated with Edarbi 80 mg daily compared with 0.5% of patients on placebo.

Other adverse reactions with a plausible relationship to treatment that have been reported with an incidence of ≥0.3% and greater than placebo in more than 3300 patients treated with Edarbi in controlled trials are listed below:

Gastrointestinal Disorders: nausea
General Disorders and Administration Site Conditions: asthenia, fatigue
Musculoskeletal and Connective Tissue Disorders: muscle spasm
Nervous System Disorders: dizziness, dizziness postural
Respiratory, Thoracic and Mediastinal Disorders: cough
Clinical Laboratory Findings
In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommon and consistent with administration of Edarbi.

Serum creatinine: Small reversible increases in serum creatinine are seen in patients receiving 80 mg of Edarbi. The increase may be larger when coadministered with chlorothalidone or hydrochlorothiazide.

In addition, patients taking Edarbi who had moderate to severe renal impairment at baseline or who were >75 years of age were more likely to report serum creatinine increases.

Hemoglobin/Hematocrit: Low hemoglobin, hematocrit, and RBC counts were observed in 0.2%, 0.4%, and 0.3% of Edarbi-treated subjects, respectively. None of these abnormalities were reported in the placebo group. Low and high marked abnormal platelet and WBC counts were observed in <0.1% of subjects.

DRUG INTERACTIONS
No clinically significant drug interactions have been observed in studies of azilsartan medoxomil or azilsartan given with amlodipine, antacids, chlorothalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, pioglitazone, and warfarin. Therefore, Edarbi may be used concomitantly with these medications.
Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

in patients who are elderly, volume-depleted (including those on diuretic therapy), or who have compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including azilsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving azilsartan and NSAID therapy.

the antihypertensive effect of angiotensin II receptor antagonists, including azilsartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

USE IN SPECIFIC POPULATIONS

Pregnancy

No dose adjustment with Edarbi is necessary in elderly patients. Of the total patients in clinical studies with Edarbi, 26% were elderly (65 years of age and older). No other differences in safety or effectiveness were observed between elderly patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

Dose adjustment is not required in patients with mild-to-severe renal impairment or end-stage renal disease. Patients with moderate to severe renal impairment are more likely to report abnormally high serum creatinine values.

Hepatic Impairment

No dose adjustment is necessary for subjects with mild or moderate hepatic impairment. Edarbi has not been studied in patients with severe hepatic impairment.

OVERDOSAGE

Limited data are available related to overdose in humans. During controlled clinical trials in healthy subjects, once daily doses up to 320 mg of Edarbi were administered for 7 days and were well tolerated. In the event of an overdose, supportive therapy should be instituted as dictated by the patient’s clinical status. Azilsartan is not dialyzable.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

The effect of demographic and functional factors on the pharmacokinetics of azilsartan was studied in single and multiple dose studies. Pharmacokinetic measures indicating the magnitude of the effect on azilsartan are presented in Figure 1 as change relative to reference (test/reference). Effects are modest and do not call for dosage adjustment.

Figure 1 Impact of intrinsic factors on the pharmacokinetics of azilsartan

<table>
<thead>
<tr>
<th>Population Description</th>
<th>PK</th>
<th>Fold Change and 90% CI</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
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<tr>
<td>&gt;65y/18-45y</td>
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<tr>
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<tr>
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<tr>
<td>Race</td>
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<tr>
<td>White/Black</td>
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</tr>
<tr>
<td>Renal Impairment</td>
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</tr>
<tr>
<td>Mild/Normal</td>
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<td></td>
</tr>
<tr>
<td>Moderate/Normal</td>
<td>Cmax| AUC</td>
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<td></td>
</tr>
<tr>
<td>Severe/Normal</td>
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<td></td>
</tr>
<tr>
<td>ESRD/Normal</td>
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</table>

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Azilsartan medoxomil was not carcinogenic when assessed in 26-week transgenic (Tg.rasH2) mouse and 2-year rat studies. The highest doses tested (450 mg azilsartan medoxomil/kg/day in the mouse and 600 mg azilsartan medoxomil/kg/day in the rat) produced exposures to azilsartan that are 12 (mice) and 27 (rats) times the average exposure to azilsartan in humans given the maximum recommended human dose (MRHD, 80 mg azilsartan medoxomil/day). M-II was not carcinogenic when assessed in 26-week Tg.rasH2 mouse and 2-year rat studies. The highest doses tested (approximately 8000 mg M-II/kg/day (males) and 11,000 mg M-II/kg/day (females) in the mouse and 1000 mg M-II/kg/day (males) and up to 3000 mg M-II/kg/day (females) in the rat) produced exposures that are, on average, about 30 (mice) and 7 (rats) times the average exposure to M-II in humans at the MRHD.

Mutagenesis: Azilsartan medoxomil, azilsartan, and M-II were positive for structural aberrations in the Chinese Hamster Lung Cytogenetic Assay. In this assay, structural chromosomal aberrations were observed with the prodrug, azilsartan medoxomil, without metabolic activation. The active moiety, azilsartan, was also positive in this assay both with and without metabolic activation. The major human metabolite, M-II was also positive in this assay during a 24 hr assay without metabolic activation.

Azilsartan medoxomil, azilsartan, and M-II were devoid of genotoxic potential in the Ames reverse mutation assay with Salmonella typhimurium and Escherichia coli, the in vitro Chinese Hamster Ovary Cell forward mutation assay, the in vitro mouse lymphoma (tk) gene mutation test, the ex vivo unscheduled DNA synthesis test, and the in vivo mouse and/or rat bone marrow micronuclear assay.

Impairment of Fertility: There was no effect of azilsartan medoxomil on the fertility of male or female rats at oral doses of up to 1000 mg azilsartan medoxomil/kg/day (approximately 122 times the MRHD of 80 mg azilsartan medoxomil/kg/day in humans on a mg/m² basis). Fertility of rats also was unaffected at doses of up to 3000 mg M-II/kg/day.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

General Information

Pregnancy: Female patients of childbearing age should be told that use of drugs like Edarbi that act on the renin-angiotensin system during pregnancy can cause serious problems in the fetus and infant including low blood pressure, poor development of skull bones, kidney failure, and death. These consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Discuss other treatment options with female patients planning to become pregnant. Women using Edarbi who become pregnant should notify their physicians as soon as possible.

Distributed by Takeda Pharmaceuticals America, Inc.

For more detailed information, see the full prescribing information for Edarbi at www.edarb.com or contact Takeda Pharmaceuticals America, Inc. at 1-877-825-3327.

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DALIRESP is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

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DALIRESP is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

Warnings and Precautions
- DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Please see additional Important Safety Information, including Warnings and Precautions related to psychiatric events, including suicidality, and weight decrease on the following page.

Please also see Brief Summary of full Prescribing Information that follows, and at www.DALIRESP.com.
Warnings and Precautions (continued)

- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP.

  - Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In controlled clinical trials 5.9% of patients treated with DALIRESP reported psychiatric adverse reactions vs 3.3% treated with placebo. The most common psychiatric adverse reactions were insomnia (2.4% vs 1.0%), anxiety (1.4% vs 0.9%), and depression (1.2% vs 0.9%). Three patients treated with DALIRESP experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) compared to one patient (suicidal ideation) treated with placebo.

- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered.

  - In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP vs 2.1% placebo), weight was prospectively assessed in two 1-year clinical trials. In these studies that compared DALIRESP to placebo, 20% vs 7% experienced moderate weight loss (5-10% of body weight) and 7% vs 2% experienced severe weight loss (>10% body weight). During the follow-up period after discontinuing DALIRESP, the majority of patients regained some of the weight they had lost.

- Use with strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended, as they decrease the exposure and may reduce the therapeutic effectiveness of DALIRESP.

Adverse Reactions

In clinical trials the most common adverse reactions (≥2% and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

Please also see Brief Summary of full Prescribing Information on the following page and full Prescribing Information at www.DALIRESP.com.
The population had a median age of 64 years (range 40-91), 72% were male, 92.9% were Caucasian, and had COPD with a mean prebronchodilator forced expiratory volume in one second (FEV₁) of 8.9 to 81.9% predicted. In these trials, 6.5% of the patients treated with DALIRESP exhibited an adverse reaction compared with 65.5% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9% for placebo. The most common adverse reactions reported by > 2% of patients in the DALIRESP group in 8 controlled clinical trials were:

**Diarrhea**
- **Adverse Reactions**:
  - **Placebo**
    - n (%) = 363 (2.4%)
  - **DALIRESP**
    - n (%) = 299 (1.4%)

**Headache**
- **Adverse Reactions**:
  - **Placebo**
    - n (%) = 194 (1.5%)
  - **DALIRESP**
    - n (%) = 154 (1.0%)

**Nausea**
- **Adverse Reactions**:
  - **Placebo**
    - n (%) = 42 (0.3%)
  - **DALIRESP**
    - n (%) = 38 (0.2%)

**Insomnia**
- **Adverse Reactions**:
  - **Placebo**
    - n (%) = 38 (0.3%)
  - **DALIRESP**
    - n (%) = 23 (0.2%)

**Dizziness**
- **Adverse Reactions**:
  - **Placebo**
    - n (%) = 32 (0.2%)
  - **DALIRESP**
    - n (%) = 29 (0.2%)

**Decreased appetite**
- **Adverse Reactions**:
  - **Placebo**
    - n (%) = 0 (0.0%)
  - **DALIRESP**
    - n (%) = 9 (0.0%)

The table above shows the adverse reactions reported by > 2% of patients treated with DALIRESP 500 mcg daily and Greater Than Placebo during the treatment period.
Knowledge plus application

The Accreditation Council for Pharmacy Education (ACPE) has designated 3 types of continuing education in pharmacy: knowledge-based, application-based, and practice-based.

Pharmacists are very familiar with knowledge-based activities that are designed to enable pharmacists and technicians to acquire factual knowledge. This type of education, while necessary, tends not to affect the practice of pharmacy or the outcomes of patient care.

Application-based learning, on the other hand, requires the pharmacist to apply the information learned in the knowledge-based portion of the activity to typical and problematic case studies, both to increase and to measure pharmacist competency.

With application-based learning, expert faculty uses a mission-critical instructional design process, common in aerospace but rarely used in medicine, to develop a detailed content outline that describes the necessary learning elements, assigns differing levels of criticality to those elements, determines the level of competency expected of the learner for each element, and ultimately constructs the learning activity based on this analysis.

This process gives the learner exactly what is needed to perform the intended task based on criticality and competence. Pharmacists are then able to move on to the second hour, in which they apply the knowledge they have acquired to solving problems posed by the case study scenarios, facilitating both learning and assessment of their application-based competencies.

Evaluation and feedback

Through the online evaluation process, we will be collecting feedback from pharmacists and pharmacy technicians to provide continuous improvement in continuing education that both meets the needs and advances the competencies of pharmacists and pharmacy technicians. As you engage with the materials presented, your comments and suggestions will help us craft ever more effective instructional materials.

A new era

This partnership inaugurates a new era for continuing education programs presented in the pages of Drug Topics. We believe that this new educational approach will enhance your professional development and enable you to offer better care to the patients you serve.

Jill M. Fitzgerald, PharmD, is director of Pharmacy Professional Development and assistant clinical professor at the University of Connecticut School of Pharmacy. For more information about continuing pharmacy education at University of Connecticut, go to www.pharmacyce.uconn.edu.
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Letters

The last thing we need

Re: “Senators call for FDA hearing on drug shortages and gray-market markups” [Hospital Pharmacists’ Report, August 18, 2011]:

This is the most problematic area for pharmacists — mainly for hospital pharmacists but some retail as well. I have been e-mailing FDA for 2 years concerning this issue and have gotten no response. I am certainly glad that it may finally be addressed. I just hope that it is done accurately and investigated properly.

If a price is set, someone must set it, and if the price is inflated 600%, the inflator should be in prison. If the government acts as if it was not aware of this problem, it is not being truthful.

There are many challenges in pharmacy practice. Purchasing medications should not be one of them.

Chuck Chaney, RPh
Enterprise, Ala.

Wolf in sheep’s clothing

Everyone keeps saying that we need fewer pharmacy schools. Then I read that Medco School of Pharmacy is opening in 2012. [Up Front, August 2011]. Medco?? Medco has been the worst PBM to deal with ever. It has been the least transparent PBM, and it is funding this school out of decades of low reimbursements to pharmacists.

A pharmacy school named after a huge mail-order pharmacy represents much of what is wrong with the profession — like less RPh/patient interaction and forced mail-order Rx plans. I find it offensive that a pharmacy school named Medco would have the gall to claim it is going to “educate community pharmacists” when Medco has done its best to destroy community pharmacy.

John Franklin, PharmD
Ogallala, Neb.

Grumpy old pharms

I thought JP took the wrong approach with that customer over the insurance card from Iowa [JP at Large, July 2011]. I personally do not require a technician to remind me to go to the bathroom, wipe the mustard off my face, listen to voice mails, and counsel patients. Good organizational skills go hand-in-hand with being a competent professional. I hope JP will try to show his brother pharmacists a little respect and not stigmatize us as grumpy old dogmatic people who are too good to try and pick up a phone and call a PBM help line to assist a customer.

I felt sorry for that patient, even if he did use some abusive language. But I have had my run-ins with bad patients too, and you can never win. I share JP’s pain.

Marc Braun, MS, RPh
Altadena, Calif.

Kill your cash register

Kudos to Drs. Saliu and Goldman-Levine on their Viewpoint article (“It’s now or never,” July 2011). We are not a profession as long as we allow everyone to treat us as pawns in their “political” system.

One way to appear more professional might be to have prescriptions billed, just as physicians and hospitals bill their services. We can then interact with patients without explaining that the insurance doesn’t cover this, or that the prescription is in the most expensive tier in the plan, or that Congress excluded that one from Medicare Part D.

No money! No cash register! Let the patients deal with their insurance companies or billing organizations. Let’s stop being the bearers of bad news and start looking professional. Give the patients the medications and counseling, and let our employers deal with the billing.

Richard J. Harwood, PhD
Bensalem, Pa.

Corrections: In the August issue, the article on the Walgreens-Johns Hopkins collaboration (page 22) stated that 70% of Walgreens patients have no primary care provider; the correct figure is 40%.

Also in that issue, the anticoagulation column erroneously stated the interaction between clopidogrel and proton pump inhibitors. The interaction is due to inhibition of CYP2C19, which reduces the conversion of clopidogrel to its active metabolite. The potential interaction of aspirin and proton pump inhibitors relates to decreased gastric pH. Drug Topics regrets the errors.

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.
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IN MY VIEW  James Rawlings, RPh

Gunslingers and old dogs

We’ve been hearing a lot about pharmacy robbery lately. It’s not an uncommon event anymore. In Indiana, where I live, we had 45 armed robberies of pharmacies in 2010. California, a state much larger and more populated, had just 61. Several of the pharmacists I know have been robbed, some multiple times. Pharmacists I know have been taken hostage, shot at, pistol-whipped, and threatened in various ways by armed robbers seeking drugs. I hear talk all the time about the “War on Drugs.” This behavior could be called the “War over Drugs.”

The Long Island massacre
Haven Drugs is a pharmacy in Medford, N.Y., on Long Island. On Father’s Day of this year, Haven Drugs was robbed by a gunman and his wife, who was driving the getaway car.

It’s really not accurate to call this a robbery, it was a massacre. The 45-year-old pharmacist on duty, his 17-year-old cashier, and 2 unsuspecting customers were gunned down in cold blood. The suspect didn’t make any demands; he just killed everyone and then got away with a bag full of hydrocodone. When arrested at their home a couple miles from the pharmacy, the 2 were high on stolen pills. Even though police made a positive identification from the store security camera, the couple is pleading not guilty.

I’m sure the public was much more shocked about this than the local pharmacists were. After all, we frequently see bad behavior from drug-seeking individuals. We tend to see bad behavior from just about everyone. I can remember the days when we were treated with respect, but now we’re just whipping boys. It’s not hard for me to imagine someone shooting a pharmacist. It’s just sad it has become so common.

Once was enough
Not everyone is willing to let thugs run rampant. A pharmacist friend named Tom owns a nice little independent pharmacy in central Indiana. It was robbed about 10 years ago, and all the employees were held at gunpoint. When the store reopened, Tom decided to hire a security service and have an armed guard in the store during business hours. From my retail experience, I can tell you that this is not very common. It was also expensive, but Tom thought the peace of mind was worth the cost.

Around the end of May, that investment proved its worth. An armed and masked young man entered the pharmacy and demanded methadone. Don, the security guard, was quick to react. Drawing his gun, he convinced the 23-year-old punk to drop his. As Don said, “He saw my gun was bigger.” Don handcuffed the robber and the police were called. Everything went just the way it was supposed to. The bad guy was arrested and went to jail, and nobody got hurt.

Don was the reluctant hero of this event. To him it was just part of his job, one that he still takes very seriously, even though he’s 78 years old. Yeah, that’s the best part of the story. Don could have retired years ago, but he still enjoys what he does and it looks like he’s still pretty good at it. Don’s a hero to the people he protected that day, although I’m sure that out of respect for him, they don’t make a big deal about it.

Don’t underestimate us old folks, sonny
Older people, like pharmacists, don’t get much respect anymore. Even though I don’t feel old, I know I’m getting older, and I wonder what the younger generation thinks about what I say and do. I’ll bet a lot of people going through that pharmacy over the last 10 years saw Don and wondered how much he would be able to help in a bad situation. I’m sure the perpetrator he apprehended never realized he was there.

The events in Medford, N.Y., and Muncie, Ind., were separated by a few days, but they had very different outcomes. What was the difference? I think it was a different kind of pharmacy owner and an alert, tough, older man who was not quite ready for the rocking chair. In my opinion, both are very special.

Jim “Goose” Rawlings is a senior pharmacist at a hospital in central Indiana. At present he is working on a book about his childhood in central Indiana in the ’60s and ’70s. He can be reached at snoozygoose@comcast.net.
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**References:**
The trick is knowing where to look

There are a lot of things not to like about retail pharmacy, and you don’t need me to tell you what they are. Cranky customers, pointless paperwork, microscopic reimbursements, and creeping depersonalization, just to name a few. You know the drill. All of that pales, however, compared to the feeling I get when a favorite patient dies.

The other day I opened the paper and was greeted with the obituary of a woman who had been coming into the store for a few years now. I would happily have taken yet another cut in third-party dispensing fees not to have seen it. I had always assumed it was something like tardive dyskinesia that had bent her body so cruelly, but I was wrong. According to the day’s paper, it was Lou Gehrig’s disease that took her life, and I felt like a bit of a failure to find that out only by reading it after she was gone.

Day-to-day bravery

I thought a lot about her afterward as I went about the workday routine.

I remembered the way she would call ahead for her prescription total so that she could show up with her check already made out, proving that while her body was under assault, her brain was still sharp enough to find a way to spare her the embarrassment of trying to write out a check or fumble with money at the counter.

I thought about the time I saw her in the makeup aisle, buying mascara, making a stand against the ugliness of the world.

I hadn’t seen her in a few months, and I thought about what those last few months must have been like for her. I don’t have to tell you that Lou Gehrig’s is a horrible way to go.

I liked her, and there was no way I could have changed what happened to her. The fact no one else could have either didn’t make me feel any better.

Courage of another sort

My day continued. I verified another prescription for $1.50, told a man where the potato chips were, and wondered why I got into this profession.

I was snapped out of it when my technician told me there was someone at the counseling window. Another regular customer and another one I kind of liked, despite his habit of asking for Norco refills early each month.

He grabbed my arm and stared straight into my eyes, “Thank you. I mean that.”

Whiplash on a word

To all the other problems of retail pharmacy I could add emotional whiplash. From one extreme to the other in less than 2 minutes. I may end up looking for a chiropractor, but that moment was worth more than all the $1.50 dispensing fees I will ever collect in my lifetime.

“Oh, by the way, you told me once I shouldn’t take that Norco with Tylenol. Is it okay with this?”

I answered this question just as I had all his others and then dove back into the prescription pile. I wondered if that man knew the hard work he was up against to beat a narcotic habit. I know he doesn’t realize how hard I’m rooting for him. Sometimes you just feel like you have to take a stand against the ugliness in the world.

Choose your view

The next lady to come to the counter asked me about shoelaces. The next phone call was someone from corporate, tracking the status of a report and acting as if nothing in this world could be more important.

I didn’t mind.

David Stanley is a practicing community pharmacist in California. He can be reached at drugmonkeyrph@gmail.com.
“She has Medicaid, doesn’t she?”
“Her aunt forgot to apply, and her Medicaid lapsed.”
“I honestly don’t think anything will help her. She’s just another druggie who ended up overdosed in the ER on Friday night. What are we going to do? We can’t save them all. She’ll get pregnant or get AIDS and then we’ll really have to pay.”
“She did it on purpose, Doctor.”
“Did what on purpose?”
“She overdosed on purpose.”
“How do you know?”
“She told me. Her parents were killed in a car crash 2 years ago. Her maternal aunt, a single mother with two teenage girls, took her in. She lives a Cinderella life. Her aunt takes her Social Security checks and banks them. She didn’t overdose because of depression. She did it because of hopelessness.”
“How do you know all that?”
“She told me.”
“Why would she tell you, a pharmacist, and not tell me?”
“Because I asked.”
There was a long pause. He took a deep breath.
“Okay, change it to citalopram. Tell her that I’ll pay it if she can.”
“We’ll split it,” I said.

### Stick, lick, pour, and shut up

This was an older doctor, still living in the 1960s, when doctors were popularly perceived as infallible.

It was so bad back in the day that pharmacists were forbidden to counsel on prescriptions. We were supposed to dispense and mind our own business.

I remember a doctor in Pleasant Hill, Calif., who was in the habit of putting “Take with milk” on his tetracycline prescriptions. I put it on the label, but I made sure that the patients knew it wasn’t right. He called and accused me of interfering with the patient–doctor relationship. I sent him a package insert from Achromycin V in the mail. I highlighted the part about no milk, no antacids. After that, his prescriptions advised: “Do not take with milk.”

### Lives aren’t saved in silos

Modern medical care is not enhanced by a spiky pyramid topped by the doctor as martinet, the authority on everything. Nurses are patient-care specialists. Pharmacists are the last word in drug therapy - martinet, the authority on everything. Pharmacists are the last word in drug therapy - martinet, the authority on everything. Pharmacists are the last word in drug therapy. Doctors diagnose. That’s a tough enough job. Why would they want more?

Doctors depend on tests, but test results can be spurious. Marianne Genetti, executive director of In Need of Diagnosis, has said, “Our system is wonderful at crisis care, but does not have a good record at diagnosis.” According to the Mayo Clinic, autopsies have shown that 20% of patients who died in the intensive care unit had conditions that were either missed or misdiagnosed. According to JAMA, 10% of all hospital deaths involve major diagnostic error.

I am encouraged by the attitude of the young doctors I deal with every work day. They ask questions. They are eager to get all the help they can with drug therapy.

At least, that’s the way it is at the teaching hospital right around the corner.

### Treatment starts in the pharmacy

In the end, pharmacists are still at the bottom of the funnel. Treatment doesn’t start at the doctor’s office. For most patients, a medication is involved; treatment begins with the patient taking the drug, having been advised of the dangers. The pharmacist should never expect the doctor to do the job that is supposed to happen at the pharmacy counseling window.

Most of us work in the pharmacy and don’t even notice the overflowing trash container. We ignore the smell of exhaust fumes flowing into the pharmacy through the drive-through drawer because the patient insists on waiting right there and won’t turn off the engine. We cope with the misplaced new technician who is definitely not committed to working in a pharmacy. And sometimes you have to help doctors who resent their need for help.

There has to be more to it than counting pills, checking the typing, and making sure that the right pills are in the bottle. There has got to be more to it than that. There has to be a chance for us to do something good, instead of just sucking up air. Look around you. The opportunities are endless.

Jim Plagakis is a community pharmacist in Galveston, Texas. You can e-mail him at jplagakis@hotmail.com and cc us at drugtopics@advanstar.com. You can also check out his website at jimplagakis.com.
NCPA's Annual Convention to feature 3 former governors

Former presidential candidate Mike Huckabee, former Vermont Governor Jim Douglas, and former Tennessee Governor Phil Bredesen will headline the Annual Convention and Trade Expo of the National Community Pharmacists Association (NCPA), taking place October 8-12 at the Gaylord Opryland Resort and Convention Center in Nashville, Tenn.

Mike Huckabee, former governor of Arkansas, will be keynote speaker at the opening general session. After being diagnosed with Type 2 diabetes, Huckabee lost more than 100 pounds and began a national campaign for healthy lifestyles.

Douglas and Bredesen will also speak at the convention's general session and will participate in the October 10 Government Affairs Forum. Bredesen, a Democrat, reformed Tennessee’s out-of-control Medicaid program and developed innovative approaches to helping the uninsured. Bredesen is the author of Fresh Medicine: How to Fix, Reform, and Build a Sustainable Health Care System.

States seeking to manage healthcare reform will find the governors' comments helpful, said John Coster, NCPA's vice president of government affairs. "The states are gearing up for Medicaid health benefit exchanges that kick in in 2014. There has been pushback from a lot of states on that," Coster said.

The convention's educational sessions will cover subjects such as PBMs, Medicare Part D, MTM, MAC prices and reimbursement, 340B issues, pharmacy audits, pharmacy staffing, and insulin pumps. "We are really focused on PBMs and developing niche strategies for business. We will have some actual pharmacists and owners who can share their experience on how others can get into this line of business and improve the bottom line," said Douglas Hoey, executive vice president and CEO of NCPA.

— Christine Blank, Contributing Editor

NCPA’s Annual Convention and Trade Expo takes place October 8-12 in Nashville.

IMMUNIZATION

Retail pharmacists well placed to give flu shots to returning schoolchildren

Professional organizations are encouraging retail pharmacists to offer vaccinations as children head back to school this fall.

“As parents are preparing their children for back-to-school, it is important to prepare their kids with the flu vaccine. The flu generally starts in November, and it takes about 2 weeks for immunity to build up,” said Edith Rosato, senior vice president of pharmacy affairs for the National Association of Chain Drug Stores (NACDS).

In addition to marketing vaccines, said Rosato, pharmacies should take advantage of sales of over-the-counter medications to parents and college students. “That would be a fantastic way to expand on the back-to-school season and include vaccines as well,” Rosata said.

Already, many chain and independent pharmacies across the country have active vaccination programs, and more state governments recognize the valuable role that pharmacists play in vaccine administration. “Pharmacy is getting a more recognized role with agencies such as the Centers for Disease Control and Prevention (CDC), which allows us to expand the role of immunizations,” Rosato said.

In fact, CDC recently released a report showing that nearly 20% of Americans received their flu shots from a community pharmacist in a retail setting. “This is a dramatic increase over the past decades and demonstrates pharmacy’s growing role in the healthcare delivery system,” said Stephen Schatz, spokesperson for NACDS.

In addition, a study published January 2008 in Pediatrics found that pharmacies can “effectively augment the vaccination efforts of more traditional settings to deliver vaccines to adolescents… Pharmacies are readily accessible to, and frequently visited by, adolescents. Many of them have extended hours on evenings and weekends, and they are a particularly important source of healthcare in rural communities,” the study’s authors wrote.

In some states, pharmacies can provide vaccinations for such diseases as such as diphtheria and hepatitis, which are required when children go back to school. NACDS is working “diligently” with states that do not allow pharmacists to administer vaccinations beyond the influenza and pneumonia vaccines, encouraging them to change their policies. “For the most part, the states realize that pharmacies are a destination point for healthcare in the community. They do realize that pharmacists are taking a more active role in patient care,” Rosato said.

— Christine Blank, Contributing Editor
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Discount Rx cards a growing trend

Seminole County, Fla., is the latest county government to distribute discount prescription cards to residents. The county recently began offering the Coast to Coast Rx discount prescription cards, which grant chain and independent pharmacy customers an average of 45% savings off the cost of their prescriptions.

The free cards are available to all county residents, regardless of income, age, and other factors. “Obtaining a discount [on prescriptions] is good for customers during these hard economic times, and it doesn’t have a detrimental impact on us,” said Sabrina O’Bryan, legislative and grants program manager for Seminole County.

In fact, offering the card benefits the county, since Coast to Coast’s provider, Financial Marketing Concepts, gives $1.25 per transaction back to Seminole County, which is distributing the card at libraries and government buildings. O’Bryan predicts that the county will earn more than $54,000 annually in royalties from the card. Last year, the county provided a similar prescription discount card from Caremark, which did not make royalty payments to the county, O’Bryan said.

As of May 2011, 35 states had operational PMPs with the capacity to receive and distribute prescription information about controlled substances. Virginia is working toward getting its PMP connected in the near future. And this fall, NABP expects that PMPs in Connecticut, Kansas, North Dakota, South Carolina, and West Virginia will be able to access data across state lines.

NABP has invested “considerable time and resources” to develop PMP InterConnect at the request of member boards of pharmacy and state PMP administrators. PMPs in Ohio and Indiana have already begun deploying PMP InterConnect to select groups of users, who are now able to exchange prescription data between the 2 participating states.

A software system for sharing prescription monitoring programs (PMPs) between states became fully operational in August. The National Association of Boards of Pharmacy (NABP) has been working for the past 8 months to develop PMP InterConnect, which is expected to reduce prescription drug abuse and “doctor shopping.” With the new software, practitioners and law enforcement officials can query multi-state PMPs through a central hub.

“Without the NABP InterConnect, a pharmacist or physician would have to identify every state in which a patient had seen another physician or used another pharmacy and make separate queries to each of those states. Such a system is cumbersome and ineffective,” said Carmen Catizone, executive director of NABP.

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Virginia is working toward getting its PMP connected in the near future. And this fall, NABP expects that PMPs in Connecticut, Kansas, North Dakota, South Carolina, and West Virginia will be able to access data across state lines. NABP estimates that in 2012, approximately 30 states will be participating in InterConnect.

As of May 2011, 35 states had operational PMPs with the capacity to receive and distribute prescription information about controlled substances to authorized users, according to the Drug Enforcement Administration. Thirteen states (Alaska, Arkansas, Delaware, Florida, Georgia, Maryland, Montana, Nebraska, New Jersey, Oregon, South Dakota, Washington, and Wisconsin), 1 U.S. territory (Guam), and the District of Columbia have enacted legislation to establish PMPs, but the programs are not fully operational.

PMP InterConnect is funded by NABP and is underwritten by NABP through an unrestricted grant from Purdue Pharma. For information on the new InterConnect, visit www.nabp.net.

— Christine Blank, Contributing Editor

Carmen Catizone

Drug Topics, September 2011
At Teva, our goal is to make every link the strongest.

When you supply one out of every six prescriptions written in the United States, you never forget that millions of people are relying on the integrity of your supply chain. If a breakdown occurs, it’s vital to spot the problem as soon as possible and solve it rapidly, efficiently—and for good.

That’s why at Teva, we focus on strengthening every link. Starting with a zero defect mindset, we’re building our most robust quality control organization ever, with dedicated scientists, proprietary technology, and a company-wide culture of continuous improvement. If this makes us sound obsessive about ensuring the quality of our products and services, well, it’s because we are.
Software app offers patients medication instructions in 12 languages

Pharmacies can create easy-to-understand medication handouts in any of 12 languages for patients and/or caregivers using the new Meducation SMART application from Polyglot Systems Inc. in Morrisville, N.C.

Meducation SMART can generate medication instructions in English, Spanish, simplified Mandarin Chinese, traditional Mandarin Chinese, Cantonese Chinese, Korean, Haitian Creole, Italian, French, Arabic, Russian, and Bengali, with Polish to follow soon.

The application is a new version of Meducation, a web-based tool that produces patient medication instructions, said Sims Preston, CEO of Polyglot.

The company recently won the $5,000 prize from Children’s Hospital Boston and Harvard Medical School in the SMART Platform Apps Challenge for its new application. The challenge was created to spur innovation in making web applications that can interface with electronic medical records or personally controlled health records.

Along with Polyglot’s win with the Meducation SMART software, 6 other companies won honorable mention awards.

What it does
The application uses the SMART (Substitutable Medical Applications, Reusable Technologies) programming interface to obtain the medication list and then generate medication instructions for patients that are easy to read by both patients and caregivers.

“It is a simple insight that if you can improve communications between healthcare providers and patients, good things happen,” Preston said. The current version of the application can be used by pharmacies, healthcare facilities, physician’s offices, “or anyone who plays a role in communicating with the patient,” he said.

“Communicating more effectively improves health outcomes and reduces costs,” Preston said, pointing out that with clearer instructions, patients and caregivers make fewer mistakes with medications. “It is going to make care more efficient and help save money.”

Words, pictures, videos
The patient information handouts created with the current Meducation application are written to be understood at a fifth- to sixth-grade reading level and are formatted to improve comprehension as much as possible, Preston said. Each instruction on the sheet is 1-line long, and all instructions are spaced out on the page to improve clarity.

Each information sheet is built up from single sentences and phrases, Preston said. “We use outside medical translation firms. We take all the content we want translated and send it to 2 companies,” he said. The 2 translations have to agree before they can be used.

Charts are used to show how often to take the medicine and how much to take, and drug information is updated continuously, he added. “We incorporate pictures instead of words where we can and increase the amount of white space. These are all design features to increase comprehension,” Preston said. “It is not just a matter of language or reading comprehension.”

Extra copies of the medication instructions can be created for caregivers in whichever language they prefer, Preston said. It is also easy to enlarge the font size of the instructions for people with vision problems.

In addition, patients can go online and use a code printed on their instructions to see their medication information or to view a growing library of instructional videos, Preston said. The online videos provide more information about certain drugs or demonstrate the use of devices such as inhalers, glucose meters, and peak flow meters. These videos can also be used to educate patients in healthcare facilities.

Application users
Meducation is licensed to Costco for use in its pharmacies in New York and North Carolina, and to Community Care of North Carolina, a network of primary-care clinics. CarePoint Inc. has recently integrated Meducation into its GuardianRx Total Pharmacy and Patient Management System.

An independent pharmacy can go online and use Meducation for $90 a month, Preston said. There are different fee structures for hospitals and physicians’ offices, he added.

In addition to the SMART Challenge award, Polyglot has received a grant from the National Institutes of Health to create multilingual informed consent forms and hospital discharge information, Preston said.

Valerie DeBenedette is a medical news writer in Putnam County, N.Y.
FACT: 90% of consumers now expect their pharmacist to tell them when an Authorized Generic version of a generic prescription drug is available.* And given the choice, patients express a clear preference for the identical experience an Authorized Generic offers.


*Refer National Poll
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Ongoing concerns about the estimated 200 million pounds of unused dispensed prescription and over-the-counter drugs improperly disposed of annually outside the healthcare setting have led to the creation of major regulatory initiatives during the past year, and spurred wider adoption of highly cost-effective programs for safe drug disposal.

Pharmacy professionals and retailers alike are increasingly affected by worries that unused medications are entering drinking water by being flushed through sewer systems that cannot, with current technology, remove them. Proactive awareness of the latest regulatory actions and remedial alternatives is thus essential.

State and federal take-backs
At least 20 states now have take-back collection programs for unused medications. Also, government agencies such as the Veterans Administration (the nation’s largest medication subscriber) and states such as Iowa and North Dakota are making this solution available to veterans and other patients through grants for community pharmacies.

The federal government is slowly entering the regulatory mix as well. The Secure and Responsible Drug Disposal Act of 2010, although focusing on disposal of controlled substance medications, more generally encourages public and private entities to develop new ways to collect and dispose of certain other pharmaceuticals in a secure, convenient, and responsible manner to prevent their introduction into the environment.

Retail initiatives
In the search for safe drug-disposal alternatives, some of the largest retail dispensers of prescription drugs in the country, along with such organizations as the National Community Pharmacists Association, are presenting individual consumers with alternatives for disposal of unused medications.

These include postage-paid envelopes or in-store take-back programs whereby unused pharmaceuticals are returned to the pharmacy location by the consumer and placed by the pharmacist in specialty boxes for storage, transportation, and ultimate treatment.

![Image](www.sharpsinc.com)

The most widely used processes offer numerous advantages, including ease of use, online tracking that confirms receipt of shipments, and assurance of destruction that will be witnessed by licensed law-enforcement professionals.

By either means, unused medications are safely sent to a fully permitted treatment facility for proper treatment. This solution is a secure, convenient, turnkey alternative for proper disposal of unused patient-dispensed medications, whether prescription or over-the-counter drugs, with the exception of controlled prescriptions.

Advantages for pharmacies
The most widely used processes offer numerous advantages, including ease of use for pharmacies of all sizes, online tracking that confirms receipt of shipments, and assurance of destruction that will be witnessed by licensed law-enforcement representatives.

The market for this solution to the problem of how to dispose of unused patient medications is estimated at more than $1 billion per year. For pharmacists, it is an efficient and cost-effective way to take a leading role in raising awareness of the dangers and the problems connected with the need to dispose of unused pharmaceuticals, as well as the most efficient and convenient solutions.

Unused medications disposed in this manner are kept not only from water systems, but also from landfills, if consumers previously discarded them in household trash. At the same time, the offer of this option helps introduce new, environmentally conscious customers to their local community pharmacy.

Enhanced pharmacy profile
Solutions are still emerging for proper disposal of unused medications.

State and federal regulation may well continue to expand, but many such proposals are likely to incorporate disposal initiatives led by the private sector.

The greater use of disposal by mail or through in-pharmacy take-back programs creates a further opportunity for patient counseling by pharmacists. The pharmacy becomes synonymous with safety and sustainability — and thus is part of the solution and not part of the problem.

David P. Tusa is chief executive officer and president of Sharps Compliance Corp., a provider of management solutions for medical waste and unused dispensed medications generated outside the healthcare facility setting (www.sharpsinc.com).
Pharmacists are frontline guardians of drug quality

One of a pharmacist’s professional responsibilities is to employ strategic problem-solving approaches to identify, report, and communicate drug-quality problems. Those problems are addressed through follow-up and evaluation by regulatory agencies.

Such a process ensures availability to the public of safe and effective drugs, as well as reduction of potential health risks associated with the quality, safety, and effectiveness of marketed drug products.

Once a drug receives approval from FDA, pharmaceutical manufacturers are required to ensure that their products meet standards of quality, sterility, purity, identity, and strength.1 Drug-quality standards set by FDA encompass the product’s manufacturing, labeling, and packaging processes.

Despite those standards of quality, anything affecting the drug or processes involving the drug may be called into question once the product reaches the general public.

Importance of reporting
Drug-quality reporting relies on pharmacists and other healthcare professionals who interact with patients to identify and report potential problems. A report should be submitted for any problem involving packaging, labeling, contamination, lack of effect, deterioration, physical change, tampering, or adverse drug reactions.2

Defects in the quality of drug products are sources of preventable adverse events. Drug quality should be of critical concern to all healthcare professionals and consumers because substandard medications can lead to treatment failure, adverse drug events, prolonged illness, development of


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drug resistance, distrust of the healthcare system, waste of limited financial resources, and death.1

Review of the reporting system
Since the 1970s, FDA has operated the Drug Quality Reporting System (DQRS). The program encourages healthcare providers to voluntarily report observed or suspected product defects and problems associated with drug-product quality.

Reports submitted to FDA through the DQRS are generated by FDA’s centralized MedWatch reporting system. FDA evaluates drug-quality reports received through MedWatch and can use the information to issue drug recalls, drug safety alerts, product label changes, seizure of products, and packaging and reformulation of products.

Today, pharmacists are integrated into every aspect of the healthcare system, enabling them to advocate for drug-quality reporting.

Reports received by DQRS are classified into 1 of 3 levels of action based on severity: Priority 1 indicates imminent or serious health hazard, Priority 2 indicates potentially significant manufacturing problems, and Priority 3 requires routine follow-up by FDA.

Priority 1 and 2 reports are directed to FDA for immediate action. FDA shares the information with the U.S. Pharmacopeia (USP) to enhance compendial standards for drug products.2 The DQRS provides pharmacists a means to efficiently act on information related to defective drug products and drug-product quality.3

USP standards
Drug products are required to comply with USP standards for identity, strength, purity, packaging, and/or labeling.1 Drug quality is stratified using a classification system. A substandard classification denotes that a manufactured drug product has been improperly produced, handled, or stored. A product is classified as counterfeit when the identity, strength, or source has been deliberately mislabeled.1

USP sets the compendial standard according to which drugs are manufactured. It establishes criteria for identity, uniformity, potency, sterility, and strength for all medications.

Incidents of poor drug quality have been numerous over the years. A notable example was the worldwide contamination of heparin as a result of oversulfated chondroitin sulfate (OSCS) in 2008. The contaminated heparin led to symptoms of hypotension, facial swelling, tachycardia, urticaria, and nausea, and in some cases also resulted in death.4

A more recent example of poor drug quality occurred with the anticoagulant dabigatran etexilate (Pradaxa, Boehringer Ingelheim). The medication has potential for breakdown when exposed to moisture, with resultant loss of potency. In response to that finding, FDA issued a recommendation that dabigatran be dispensed only in the original bottle or blister packet.5

Another instance of poor drug quality occurred with a branded generic of warfarin sodium (Jantoven, Upsher-Smith Laboratories). It was reported to have drug-quality problems when a 10-mg container was mislabeled as a 3-mg container. In that case, a patient could receive 3 times the intended dose, with the possibility of excessive anticoagulation and a risk of life-threatening hemorrhage.1

Pharmacists and reporting
Pharmacists are among the most accessible of healthcare providers when it comes to addressing issues of drug quality and the reporting of adverse events.

In 1993, when MedWatch was launched, pharmacists outnumbered physicians 55% to 16%, respectively, in adverse-event reporting, and it is likely that this ratio has remained the same in recent years.5

Today, pharmacists are integrated into every aspect of the healthcare system. This enables pharmacists to be advocates for drug-quality reporting and to play a significant role in increasing awareness of drug-product quality in the marketplace. In addition, pharmacists can provide active post-market surveillance through reporting of drug-quality defects. This will have a positive impact on drug quality, which will result in a reduction of preventable adverse drug events.

The critical role that pharmacists play in the monitoring of drug-quality identification and reporting represents 1 more vital contribution that adds value to the profession and supports protection of public health.

FDA’s MedWatch Form 3500, used for voluntary reporting, is posted at http://www.fda.gov/medwatch/getforms.htm.

References

Cassandra Esperant and Elina Varghese are PharmD candidates on rotation in Pharmacy Benefits Management Services, Department of Veterans Affairs, Washington, D.C., where Vaiyapuri Subramaniam is Associate Chief Consultant. The views and opinions expressed in this article do not necessarily reflect the views of the Department of Veterans Affairs.
Mari Edlin

Community pitches in to help rebuild tornado-ravaged pharmacy

Some would call it a miracle — a community pharmacy flattened by a tornado 1 mile wide and 6 miles long on Sunday, May 22, was back up and running the following Saturday. That’s what happened when friends, neighbors, and business associates came together for Sheree and David Starrett, pharmacists and owners of a Medicine Shoppe franchise in Joplin, Mo., for the past 27 years.

The Starretts had no idea that their return home from a brief vacation would be precipitated by a text sent by a pharmacy technician that simply said, “Store gone.” Thus began the longest week of the couple’s lives, a week that also overflowed with demonstrations of goodwill and community spirit.

By Monday morning, Starrett was sitting in the living room of his Joplin home, which was untouched by the tornado but lacking electrical power. Sitting with him were David Burnett, a pharmacy business consultant from Cardinal Health, which acquired Medicine Shoppe in 1995, and Bob Kloeppel, franchise business consultant for Medicine Shoppe.

“We asked ourselves the pros and cons of rebuilding, whether David could even get back on his feet,” Burnett said. It didn’t take long for the group to come to a decision. After that, everything fell into place.

Lucky finds and a new location
The first order of business was to cancel a large order heading for the store; a Cardinal Health sales manager took care of that. Then the Starretts salvaged everything they could from the rubble, which to their surprise included the undamaged server containing the store’s patient data and a safe full of controlled substances.

By Monday night, the Starretts had a lead on a new location; unfortunately, the space was not suitable for a pharmacy. As luck would have it, the ideal building stood across the street, only 12 blocks from the original shop. Now the group just needed to locate the landlord.

Wasting no time, a friend made the introduction on Tuesday and the landlord and the Starretts shook hands to close the deal, with formal papers to follow.

Two hours later, the new store was equipped with new locks on its doors, and Starrett had the keys in his pocket. By afternoon, he had arranged for phone and cable lines and a security system.

Relocating their store also meant paperwork for the Starretts, who had to reapply for a state pharmacy license and open an account number for the new address, so that the Medicine Shoppe could rebuild its inventory. Thanks to Missouri pharmacy regulations created to cover “disasters” and some intervention by Cardinal Health, the Starretts were able to get the ball rolling right away.

“Our primary goal was minimizing the inconvenience to our customers as much as possible,” Starrett says. “The tornado left so many people hanging.”

Burnett and Starrett quickly contacted a nearby independent pharmacy and prepared the owner for a bevvy of displaced customers. Starrett shared patient prescriptions so there would be little gap in coverage.

Back in business
There was plenty of behind-the-scenes action involved in getting the pharmacy back up and running; a point-of-sale computerized system had to be set up, advertising created, settlement made with insurance claims adjustors, and the store’s first order — 1,153 lines of product totaling $153,000 — placed.

“The whole episode seems like it happened 6 months ago, and it’s only been 6 or 7 weeks,” Starrett said. “Help from Cardinal Health, the Medicine Shoppe, the community, and even as far away as Mexico, Mo., was indispensable. Even [consultant Burnett’s] fraternity brothers turned out to stock new inventory.”

Counting his blessings, Starrett said, “We certainly are lucky to be alive.” As he well knows, not everyone in the community was so fortunate.

MARI EDLIN is a healthcare writer in Mill Valley, Calif.
Medication adherence depends on the drug and the patient

Before the 1980s, patient medication adherence was studied from the prescriber’s point of view. Recent qualitative research explores the patient’s perspective and cites the futility of labeling patients as noncompliant. In fact, patients perform their own cost-benefit analyses and may or may not choose to take drugs as prescribed, making separate decisions about each drug, according to Colleen A. McHorney, PhD.

McHorney, a U.S. outcomes researcher for Merck, presented her research on medication adherence at the PQA/URAC Medication Adherence Summit held earlier this year in Washington, D.C. The conference provided stakeholders with tools to improve the quality of medication use across health-care settings.

One drug at a time
Patients make different decisions about adherence for each medication, McHorney said. Her research is based on the Harris Interactive Chronic Illness Panel, which recruited adults with asthma, hypertension, diabetes, hyperlipidemia, osteoporosis, or other cardiovascular disease. The Harris Poll is a for-profit market research organization that recruits respondents, samples opinions, and may provide incentives for participation.

Study respondents were required to be persistent (compliant) with a medication for 1 disease and nonpersistent or nonfulfilling (meaning they stopped use or did not start) with a medication for a second, different disease. Survey ques-

Affordable Health Care Through

Making medicines more accessible is important to us. Innovation in research, processes, and technologies is key to ensuring that quality, lower-cost alternatives reach people who need them, including generic products, biosimilars, and OTCs.
tions included 5 scales, including perceived need for medication, side-effect concerns, medication-safety concerns, perceived disease severity, and knowledge about the prescribed medication. The 32-item survey was completed by each respondent once for the persistent medication and again for the nonpersistent/nonfilled medication. Results indicate that noncompliance may be driven by patients’ perceptions of their need for a drug and of its side effects.

**Subject to change**

McHorney presented other adherence research. Patient adherence patterns may be gray rather than black and white, and patients may renegotiate their adherence as their reasons or prescribed medications change over time. Side effects from a new drug may represent a potential “loss” to the patient and may outweigh the patient’s understanding of the future, long-term benefits of the new medication.

While patients also seldom tell prescribers that they do not want a medication or do not intend to take it, most physicians believe that most of their patients are compliant with prescribed medications, survey research revealed. One study demonstrated that even newly discharged myocardial infarction patients may adhere to prescribed medication inconsistently.

Other studies cited show that less than one-third of the time do physicians communicate to their patients the risks of medications and the duration of therapy needed, while believing that they did so nearly half the time. One researcher found that physicians averaged just 49 seconds explaining a new drug to the patient.

This research did not study pharmacists’ interactions with patients, McHorney said.

**Future of research**

McHorney said that future research could include examination of how medication beliefs are formed and how and why they change; determination of how healthcare systems can better meet patient’s needs for information about their diseases and treatment; provision of incentives to prescribers to perform patient-centered prescribing; and investigation of the role of social networks in medication adherence.

Detailed patient demographic information was not presented, and the study is based on self-reported information from individuals by means of the internet. Despite these limitations, this research demonstrates measurable differences in behaviors presented by an individual patient and offers clues as to the cause of nonadherence.

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**Susan J. Bliss** practices pharmacy in Oregon and writes articles for pharmacists.
Could this merger put your business at risk?

Fred Gebhart, Contributing Editor

The proposed acquisition of Medco Health Solutions by Express Scripts Inc. (ESI) has generated more headlines than agreement. Medco and ESI love the deal. Retail pharmacy wants to scuttle it.

Interested outsiders aren’t finding much common ground, either. Pharmacy benefit consulting and auditing firm The Burchfield Group gave the proposed merger a 90% chance of success. Morningstar stock analyst Matthew Coffina gave the proposed merger a 60% chance of failure. ESI’s hometown newspaper, the St. Louis Post-Dispatch, said in an editorial that the merger should be viewed skeptically.

“We’re talking about the big 3 PBMs that dominate the industry, taking 2 of them and making them into 1,” said Russell Gay, executive director of the Independent Specialty Pharmacy Coalition (ISPC). ISPC has called on the Federal Trade Commission (FTC) to block the merger.

“It would tilt the balance so far that nobody could compete against it, not even Caremark,” Gay said. “We would be talking about consolidation moving into an effective monopoly of the PBM business.”

Or maybe not. Burchfield President and CEO Brian Bullock, RPh, MBA, told Drug Topics that while the merger would create a behemoth, smaller PBMs would keep competition lively.

“There are a number of middle-tier players who have shown themselves to be quite nimble,” Bullock said. “I would name MedImpact, Catalyst Rx, and others. You shouldn’t discount OptumRx, which is going to become a pretty substantial player pretty quick with UnitedHealth Group. The market has viable options.”

Winners and losers

Some of the potential winners and losers are obvious. The merger would be a great deal for Medco shareholders, who

The merger by the numbers

- **The parties:** Express Scripts, Inc. and Medco Health Systems
- **The value:** $29.1 billion
- **The revenue:** Express Scripts $44.9 billion, Medco $66 billion (2010)
- **The employees:** Express Scripts 13,170, Medco 24,625
- **The savings:** $1 billion when fully integrated
- **The approvals:** Federal Trade Commission, Department of Justice, state attorneys general, shareholders of both companies

Source: Express Scripts
stand to receive $71.36—a combined value of cash and stock in the new company—for each share of Medco stock. That’s a 28% premium on the closing price of $55.78 on July 20, the day before the announcement.

ESI is another big winner. The company dominates the PBM world, with 90 million covered lives and 13.5% of the market as of the third quarter 2010, according to the Pharmacy Benefit Management Institute (PBMI). CVS/Caremark is No. 2, with 85.1 million lives and 12.7%. Medco is No. 3, with 65 million lives and 9.7%. The combined company, still called Express Scripts, would cover 155 million lives, about 23% of the market. That translates into control of 35% of total U.S. pharmaceutical spending, according to Morningstar’s Coffina.

The National Community Pharmacists Association (NCPA) said the ESI-Medco combination would control about 25% of Medicare Part D scripts, 52% of the specialty pharmaceutical market, and 60% of the mail order market. The National Association of Chain Drug Stores (NACDS) said the combination would own 80% of the market for large employer plans.

“It will be very difficult for anyone to compete,” said Don Bell, senior vice president and general counsel of NACDS. “When a company has that much market power, it will harm both consumers and employers. Retail pharmacy is stuck in the middle. This combined company would be able to force consumers to use mail order, its own mail order. It would have greater power to exclude pharmacies from its networks.”

Bullock agreed that the retail channel has the most to lose.

“The PBM market, spearheaded by the Big Two, Express Scripts and Caremark, will drive a more aggressive deal in the retail channel,” he predicted.

The NACDS board of directors voted to oppose the merger, but individual chains are keeping mum. When asked about reports that CVS Caremark President and CEO Larry Merlo recused himself from the decision to oppose the merger, Bell declined to discuss the board action.

CVS spokesman Michael DeAngelis also declined to confirm or deny reports that the chain did not take part in the vote. During a quarterly earnings call in early August, Merlo put questions about the proposed merger off limits.

“But, assuming the proposed transaction is completed, I’m more confident than ever that CVS Caremark can effectively compete in this vibrant industry,” he told analysts. “The success we’re having in both the 2011 and 2012 selling seasons clearly demonstrates that our model is resonating with payers.”

Walgreens also talked around the merger.

“It does not change our current position with Express Scripts,” Walgreens’ spokesman Michael Polzin said. “We expect the proposed deal will need to go through a thorough process to get FTC approval.”

Plan sponsors and payors could find themselves winners in the short term. ESI is projecting $1 billion in synergies from the merger. PBMI Executive Director Brenda Motheral, MBA, PhD, predicted that ESI clients will expect to share the savings. Expected savings could allow other PBMs to grow.

“Bringing together 2 very big companies is not without operational pain,” Bullock noted. “It’s a market-share grab opportunity. There will be an impact on price this fall or early next year before this merger even clears. Plan sponsors could end up with better arrangements. When CVS and Caremark merged, competitors scrambled to offer a lower price point to secure new business. We will see the same phenomenon.”

The regulatory wild card

ESI and Medco want to complete the merger during the first half of 2012. The FTC, the Department of Justice (DOJ), and state attorneys general could challenge the deal in court if they have antitrust concerns.

“The FTC is going to put a lot of energy and effort around the question of long-term impacts and whether the market can remain competitive with a merger of this size,” Motheral said. “Even if this merger doesn’t happen, other mergers and acquisitions are going to happen. Scale counts for a lot in this marketplace.”

FTC and DOJ assess the potential impact on competition. Bell noted that most states have similar laws designed to promote competition. It is not unusual for states such as New York, Pennsylvania, and California to launch their own antitrust investigations.

If regulators step in, it wouldn’t be the first time. In 1998, FTC blocked proposed mergers between wholesalers McKes-
“This is a highly problematic merger. When a merger reduces the number of effective competitors from 3 to 2, it raises very significant competitive concerns.”

– David Balto, ISPC general counsel

son-AmeriSource and Cardinal Health-Bergen Brunswig. The commission won an injunction in federal court because the 2 merged companies would have controlled over 80% of the prescription drug wholesale market. McKesson and Cardinal Health remained independent and AmeriSource merged with Bergen Brunswig to form the current 3 market leaders.

This is a highly problematic merger,” said David Balto, former policy director for the FTC’s Bureau of Competition and now ISPC general counsel.

“When a merger reduces the number of effective competitors from 3 to 2, it raises very significant competitive concerns. The FTC has been pretty aggressive in the past in blocking mergers that reduced the number of competitors from 3 to 2.

“In this case, it may be even more problematic than just going from 3 competitors to 2. Some plans may not be comfortable with the CVS Caremark model. For those plans, this is a merger to monopoly.”

Cutting a deal

ESI and Medco were clearly aware of potential antitrust concerns. In the merger terms filed with the Securities and Exchange Commission, the companies offered to divest 1 or more mail-order facilities (except the ESI facility in St. Louis), up to $30 million worth of specialty pharmacy or infusion services (except the ESI facility in Indianapolis), and up to $115 million worth of contracts. The companies also agreed that they would not divest more than 35 million adjusted drug claims, a combination of retail Rx and mail-order claims.

Retail pharmacy wants more. ISPC, NACDS, and NCPA have asked FTC to block the proposed merger. All 3 have descended on FTC staff and commissioners to argue their case. It’s a good bet that ESI and Medco are arguing their own case.

“We started having meetings with individual commissioners the first week following the announcement,” Gay said. “We have a relationship built on their investigation of Caremark. FTC spent a lot of time with us trying to understand concerns not only of community pharmacies, but how it affects patients and health plans.”

NACDS and NCIPA are compiling economic analyses to bolster their opposition. NCIPA is orchestrating e-mails, phone calls, faxes, and letters from community pharmacists to members of Congress and state legislators. John Coster, PhD, RPh, NCIPA senior vice president for government affairs, said that members copied the association on more than 4,000 e-mails sent to members of Congress in 1 week.

“That’s just e-mail contacts that we know about,” Coster said. “We have no way to track calls and letters. How members make that contact doesn’t matter, as long as they get something to their member so that Congress realizes this is a matter of concern.”

At least 1 representative, John Conyers (D-MI), has asked the House Judiciary Committee to look into the planned merger.

FTC’s “second request”

On Friday, September 2, FTC issued a “second request,” for additional information for a comprehensive review of the proposed merger of ESI and Medco, said Balto.

“The commissioners appear to see their past lax PBM policy (which led to no second request for CVS Caremark) as a mistake. They don’t want to make the same mistake twice,” he said.

NACDS and NCIPA issued a joint statement, applauding the FTC’s further investigation. “This is an important step in the careful consideration of a proposed merger that would have anticompetitive effects on patients, consumers, the market and the entire healthcare delivery system,” the statement said.

The ISPC also issued a statement commending the FTC’s decision to issue a second request of the merger.

“We are glad to see the FTC will be taking a detailed look at how further consolidation of the PBM and specialty markets may negate efforts to contain healthcare costs,” said Gay. “This merger would have a significant and harmful impact in the critical specialty market. Specialty drugs are the most expensive drugs and serve the most vulnerable patients. The FTC will need to focus ... on the specialty market to truly understand the far-reaching implications of this deal.”

Contributing Editor Fred Gebhart works all over the world as a freelance writer and editor, but his home base is in San Francisco.
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Please read adjacent Brief Summary of full Prescribing Information, including Boxed Warnings.
WARNING: BLEEDING RISK
- BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).
- Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).
- Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).
- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).

WARNING: ASPRIN DOSE AND BRILINTA EFFECTIVENESS
- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).

BRIEF SUMMARY of PRESCRIBING INFORMATION:
For full Prescribing Information, see package insert.

INDICATIONS AND USAGE
Acute Coronary Syndromes
BRILINTA is a P2Y12 platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis (see Clinical Studies (14) in full Prescribing Information). BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily (see Warnings and Precautions (5.2) and Clinical Studies (14) in full Prescribing Information).

DOSEAGE AND ADMINISTRATION
Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA. BRILINTA can be administered with or without food. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

CONTRAINDICATIONS
History of Intracranial Hemorrhage: BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population (see Clinical Studies (14) in full Prescribing Information).

Active Bleeding: BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage (see Warnings and Precautions (5.1) and Adverse Reactions (6.1) in full Prescribing Information).

Severe Hepatic Impairment: BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins (see Clinical Pharmacology (12.3) in full Prescribing Information).

WARNINGS AND PRECAUTIONS
General Risk of Bleeding
Drug-induced platelet dysfunction including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased (see Adverse Reactions (6.1) in full Prescribing Information). In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]). When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding. If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (see Warnings and Precautions (5.5) and Adverse Reactions (6.1) in full Prescribing Information).

Concomitant Aspirin Maintenance Dose: In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg daily (see Dosage and Administration (2) and Clinical Studies (14) in full Prescribing Information).

Moderate Hepatic Impairment: BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Dyspnea: Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption. In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

Discontinuation of BRILINTA: Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

Strong Inhibitors of Cytochrome CYP3A Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nefluramine, ritonavir, saquinavir, teplitremycin and voriconazole (see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in full Prescribing Information).

Cytochrome CYP3A Potent Inducers Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbazapine, and phenobarbital (see Drug Interactions (7.2) and Clinical Pharmacology (12.3) in full Prescribing Information).

ADVERSE REACTIONS
Clinical Trials Experience
The following adverse reactions are also discussed elsewhere in the labeling:
- Dyspnea (see Warnings and Precautions (5.4) in full Prescribing Information).

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. BRILINTA has been evaluated for safety in more than 10,000 patients, including more than 3,000 patients treated for more than 1 year.

Bleeding: PLATO used the following bleeding severity categorization:
- Major bleed – fatal/life-threatening. Any one of the following: fatal, intracranial; intrapercardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL, transfusion of 4 or more units (whole blood or packed red blood cells [PRBCs]) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intracranial with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL, transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

<table>
<thead>
<tr>
<th>Condition</th>
<th>N=9186</th>
<th>N=814</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Major + Minor</td>
<td>8.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Major</td>
<td>4.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Fatal/Life-threatening</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Intracranial/Fatal/Life-threatening</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel. In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 CABC bleeds (KMP)

<table>
<thead>
<tr>
<th></th>
<th>BRILINTA</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Major</td>
<td>85.8</td>
<td>86.9</td>
</tr>
<tr>
<td>Fatal/Life-threatening</td>
<td>48.1</td>
<td>47.9</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.9</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in in vitro tests and BRILINTA is a reversibly binding P2Y12 inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel. No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused prominent discontinuation of study drug in 2.3% of BRILINTA patients and 1.9% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these drug-related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

<table>
<thead>
<tr>
<th>Table 3 Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRILINTA (%)</strong></td>
</tr>
<tr>
<td>N=9235</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
</tbody>
</table>

*Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal dyspnea.*

Bradycardia In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythms (including ventricular pauses). PLATO excluded patients at increased risk of bradyarrhythms (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardia-related syncpe and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively. In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel. Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities Serum Uric Acid. Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group). Serum Creatinine: In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

DRUG INTERACTIONS Effects of other drugs. Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP2C19.

CYP3A inhibitors [see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3) in full Prescribing Information].

CYP3A inducers [see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3) in full Prescribing Information].

Aspirin Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA [see Warnings and Precautions (5.2) and Clinical Studies (14) in full Prescribing Information].

Effect of BRILINTA on other drugs Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

Simvastatin, lovastatin BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg [see Clinical Pharmacology (12.3) in full Prescribing Information].
The model

The medication management system investigated in the prospective cohort study had 2 components.

Prescription medications for 1 group of patients were dispensed through their local pharmacy using a calendar card system (Medicine-On-Time, Hunt Valley, Md.). As medication management issues arose, the other group of patients received assistance from a health educator. Study participants were clients in a state Medicaid home- and community-based waiver program who chose to receive services in the community despite their eligibility for nursing-home care.

The outcome of nursing-home admissions was compared in an intervention group that included 273 clients who received the medication management service and a standard-care control group of 800 persons matched by age, race, sex, and start date in the Medicaid waiver program; the second group received medications in traditional prescription vials without the services of a medication coordinator.

Mean duration of participation in the study was about 9 months for the intervention group and 8 months for the controls. During that time, there were 6 (2.2%) nursing-home admissions among the participants receiving medication management services and 40 (5.0%) in the control group. Results of a logistic regression analysis adjusting for numerous variables that could affect nursing-home admission showed the intervention independently predicted nursing-home admission, with the intervention group being 66% less likely than the controls to be admitted to a nursing home. During the 120 days after discontinuation of the medication management system, the nursing-home admission rate was 5.9% in both groups, providing further evidence that the intervention was effective.

Positive outcomes

Schulz, a professor at South Carolina College of Pharmacy, Columbia, told Drug Topics, “Medication management in this study involved the calendar card system as well as the service coordinator. In addition to the pharmacist, other active participants were the physicians, patients, caregivers, and case managers. These various people constituted the patients’ provider and support network for medication management.”

The study’s message for pharmacists, said Schulz, is that “using a calendar card and coordinating medication management in a way that engaged the patients’ support network yielded positive outcomes. In this study, the benefit was avoiding nursing home admission and allowing the frail elderly to remain in their community.”

Pharmacists’ role

The study results have implications for pharmacists faced with a need to establish their worth beyond dispensing. Schulz said, “There is an important and growing societal need for medical therapy management, and while this function was fulfilled by a masters-trained health educator in our study, it is a legitimate role for pharmacists. This opportunity may be overlooked by pharmacists working in a busy pharmacy, but it deserves attention as the profession looks to its future.”

Tools and benefits

The medication calendar cards used in the study feature 30 easy-to-open blister packs, each holding all medications (up to 6) that are to be taken at a specific time of day. As a pharmacy-directed method of medication sorting, the cards provide a safety advantage. The Medicine-on-Time program also incorporates software that essentially establishes the pharmacist as a drug-therapy case manager, said Ian Salditch, CEO, Medicine-on-Time.

“Medicine-on-Time is designed to create a closed loop that keeps the pharmacy dispensing the medication, and the patient and the prescribing physicians on the same page about medication orders, to avoid problems relating to refills or failure to capture new prescriptions or discontinuation orders,” he said, adding, “This research documents a tangible benefit from helping the elderly to manage their medications. Offering this type of service is a way that pharmacists can prove their worth in the healthcare arena and justify higher fees for their services.”

Cheryl K. Guttman has worked as a hospital pharmacist and is now a freelance medical writer in Deerfield, Ill.
**NEW DRUG REVIEW** Craig I. Coleman, PharmD

**New therapies approved for chronic hepatitis C infection, type 2 diabetes**

**Boceprevir** *(Victrelis; Schering, a subsidiary of Merck)*

Boceprevir was granted FDA marketing approval for the treatment of adult patients with chronic hepatitis C genotype 1 infection, with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy. Boceprevir is a hepatitis C virus (HCV) non-structural protein 3 (NS3)/4A serine protease inhibitor that must be administered with peginterferon alfa and ribavirin.

**Efficacy.** The efficacy of boceprevir was evaluated in two phase 3 clinical trials, SPRINT-2 and RESPOND-2. In both trials, about two-thirds of patients receiving boceprevir in combination with pegylated interferon and ribavirin experienced a significantly increased sustained virologic response (HCV no longer detectable in the blood at 24 weeks after stopping treatment) compared to pegylated interferon and ribavirin alone.

**Safety.** The most commonly reported adverse reactions in subjects receiving the combination of boceprevir with pegylated interferon and ribavirin were fatigue, anemia, nausea, headache, and dysgeusia. The addition of boceprevir to peginterferon alfa and ribavirin is associated with greater decreases in hemoglobin concentrations and more neutropenia compared with peginterferon alfa and ribavirin alone. Consequently, complete blood counts must be obtained in patients prior to initiating boceprevir and at weeks 4, 8, and 12, and should be monitored closely at other time points.

**Dosing.** Boceprevir capsules are administered at a dose of 800 mg orally 3 times daily (every 7 to 9 hours) with food. In patients without cirrhosis, boceprevir should be initiated after 4 weeks of peginterferon alfa and ribavirin therapy. Following initiation, response-guided therapy (duration of therapy dictated by viral response) is recommended for most individuals. However, in some targeted subgroups (e.g., patients with cirrhosis or null responders to previous peginterferon alfa and ribavirin therapy), a longer duration of therapy (44 weeks of boceprevir) is recommended. Discontinuation of boceprevir is recommended in patients who do not achieve HCV-RNA levels <100 IU/mL at week 12 or detectable HCV-RNA levels at week 24. Boceprevir is a strong inhibitor of CYP3A4/5, so co-administration with drugs that are highly dependent on CYP3A4/5 for clearance and for which elevated blood concentrations are associated with serious events is contraindicated. Since boceprevir is partly metabolized by CYP3A4/5, potent inducers of these enzymes may reduce boceprevir’s efficacy and should not be co-administered.

**Linagliptin tablets** *(Tradjenta, Boehringer Ingelheim)*

FDA granted marketing approval for a new dipeptidyl peptidase-4 (DPP-4) inhibitor, linagliptin. Linagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

**Efficacy.** Linagliptin’s efficacy was established in 8 randomized, double-blind, placebo-controlled trials involving approximately 3,800 patients with type 2 diabetes. Clinical trials evaluated linagliptin as monotherapy, and when administered in combination with metformin, a sulfonylurea, metformin plus a sulfonylurea, and pioglitazone. Overall, linagliptin 5 mg taken once daily provided statistically significant reductions in hemoglobin A₁c, fasting plasma glucose, and 2-hour postprandial glucose, when compared to metformin, a sulfonylurea, metformin plus a sulfonylurea, or pioglitazone alone. Linagliptin has not been studied in combination with insulin.

**Safety.** The safety of linagliptin has been evaluated in more than 4,000 patients with type 2 diabetes during clinical trials. Adverse reactions in short-term (<24 weeks) trials included nasopharyngitis, hyperlipidemia, hypertriglyceridemia, cough, and weight increase. After 52 weeks’ treatment with linagliptin, adverse reactions included arthralgia (5.7%), back pain (6.4%), and headache (5.7%). The incidence of hypoglycemia was similar to placebo when linagliptin was administered as monotherapy or in combination with metformin, or with pioglitazone. When linagliptin was administered in combination with metformin and a sulfonylurea, 22.9% of patients reported hypoglycemia compared to only 14.8% of patients administered placebo in combination with metformin and a sulfonylurea.

**Dosing.** The recommended daily dose for linagliptin is 5 mg taken once daily with or without food. When linagliptin is co-administered with a sulfonylurea, the sulfonylurea dose may need to be decreased to attenuate the risk of hypoglycemia. No dose adjustment is recommended in kidney or liver dysfunction. Linagliptin’s efficacy may be reduced when administered concomitantly with a P-glycoprotein/CYP 3A4 inducer. In these cases, alternative treatment strategies are recommended.

Craig I. Coleman is associate professor of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, Conn., and director of the Pharmacoeconomics and Outcomes Studies Group, Hartford Hospital.
Outpatient treatment of pulmonary embolism safe for low-risk patients

Despite practice guidelines recommending outpatient care for hemodynamically stable patients with pulmonary embolism (PE), most PE patients still receive hospital-based treatment. A recent international study suggests that outpatient care is a safe, effective alternative for select low-risk patients.

The study was conducted at 19 emergency departments in 4 countries. Investigators randomly assigned 344 patients with acute, symptomatic PE and a low risk of death to initial outpatient or inpatient treatment with subcutaneous enoxaparin (>5 days) followed by oral anticoagulation (>90 days).

In the primary analysis, 1 outpatient (0.6%) developed recurrent venous thromboembolism within 90 days; in the inpatient group, none did. One patient (0.6%) from each treatment group died within 90 days. Two outpatients (1.2%) and no inpatients experienced major bleeding within 14 days. Three outpatients (1.8%) and no inpatients developed major bleeding by 90 days. Outpatients had a mean length of stay of 0.5 days; for inpatients it was 3.9 days. The investigators concluded that for appropriate patients, outpatient treatment of PE can be a safe and cost-effective replacement for inpatient care.


Cost-effectiveness of stroke prevention in AF varies by stroke risk and INR control

Stroke can be a devastating outcome for atrial fibrillation (AF) patients. Several medications have shown clinical benefit for stroke prevention in AF, but little cost-effectiveness information on these therapies exists. U.S. researchers recently compiled data from various trials to create a decision-analysis model comparing the cost-effectiveness of various antithrombotic agents.

The researchers found that for a patient with an average risk of major hemorrhage (~3%/yr), the most cost-effective therapy depended solely on stroke risk. To determine stroke rate they used a CHADS2 score, including risk factors for congestive heart failure, hypertension, age >75 years, diabetes mellitus, and history of stroke or transient ischemic attack. Only aspirin was cost-effective unless benefit outweighs risk.

New factor Xa inhibitor approved by FDA

FDA recently approved rivaroxaban (Xarelto), an oral, once-daily factor Xa inhibitor, for prevention of deep vein thrombosis (DVT) in patients undergoing knee- or hip-replacement surgery. The drug is approved for use at a dose of 10 mg once daily for 35 days following hip replacement and for 12 days following knee replacement.

The FDA approval for rivaroxaban was based largely on data from the EINSTEIN DVT trial. This study included 3,449 patients with acute DVT. The rivaroxaban group had a recurrence rate of 2.1% versus 3.0% for the enoxaparin/vitamin K antagonist (warfarin or acenocoumarol) group. Rates of bleeding were the same, at 8.1% in each group.

The manufacturer recommends avoiding use of rivaroxaban in patients with severe renal failure (creatinine clearance <30 mL/min) and caution in patients with hepatic failure. Also to be avoided is concomitant administration with combined P-glycoprotein and strong CYP3A4 inhibitors, which cause significant increases in rivaroxaban exposure. Avoid use with other anticoagulants or platelet aggregation inhibitors unless benefit outweighs risk.


Anna D. Garrett is manager, Outpatient Clinical Pharmacy Programs, Mission Hospital, Asheville, N.C., and president and founder of the National Association of Women in Health Care (www.nawhc.com). She also is a Drug Topics board member. She can be reached at anna.garrett@msj.org.
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Depression treatment update

Despite the number of available and effective antidepressants, patients with major depressive disorder (MDD) often experience recurrent episodes. Remission is the aim of treatment; however, whether that can be better achieved with monotherapy or the use of combination drugs has prompted much debate. Findings of the CO-MED study, published in The American Journal of Psychiatry (May online issue), may help guide clinicians in the treatment of chronic and/or recurrent major depression of a nonpsychotic nature.

Three regimens investigated
As described in the article by Madhu A. Trivedi, MD, of the University of Texas Southwestern Medical Center in Dallas, a lead study investigator, 3 regimens used as first-step treatment were examined.

Patients received escitalopram (Lexapro) plus placebo, bupropion (Wellbutrin) plus escitalopram, or venlafaxine (Effexor) plus mirtazapine (Remeron). “Broad inclusion and minimal exclusion criteria ensured a reasonably representative participant group,” said Dr. Trivedi.

A 12-week study period was chosen for the primary analysis to provide for sufficient time for maximal dosing, if needed, and to allow most cases of depression that could remit to do so.

Monotherapy holds its own
The authors concluded that the remission and response rates at 12 and 28 weeks were not different among the treatment groups, and found no clinical advantage over escitalopram-placebo from either combination of antidepressants.

The only difference seen was the increased side-effect burden among patients taking venlafaxine plus mirtazapine. Ear aches, blurred vision, and irritability were the most commonly reported side effects of the combination regimen, which has been dubbed “California Rocket Fuel” by psychiatrist Stephen M. Stahl, MD.

Megan Maroney, PharmD, clinical assistant professor at Ernest Mario College of Pharmacy and clinical pharmacy specialist in Psychiatry at Monmouth Medical Center in Long Branch, NJ, finds the study results encouraging: they appear to provide a basis for use of monotherapy before use of dual antidepressants. “The advantages of monotherapy would include decreased side effects and cost, and greater compliance to therapy, whereas combination treatment may increase adverse events and cost without additional benefits for most patients, and may make compliance more difficult,” she said.

Study limitations
“It is important to keep in mind that the study does have some limitations,” Maroney said. “The first limitation of the trial is its single-blind design, meaning that clinicians were not blind to treatment. Additionally, previously published data indicate better efficacy with combination drugs in patients who have melancholic features. Only 20% of participants in this study had melancholic features,” she said.

The study authors acknowledge that the medication doses used in the CO-MED study may have been insufficient in a large enough proportion of patients to preclude the benefits otherwise available from combination therapy.

Benefits of combination therapy
“The benefits of combination therapy have been evident in other studies when higher drug doses were used (i.e., 225 mg/day of venlafaxine and 30 mg/day of mirtazapine),” said Maroney.

The rationale for a higher venlafaxine dose, she said, stems from the fact that effects on the norepinephrine system are apparent only at doses of at least 225 mg/day. In addition, the favorable effects of mirtazapine are more evident at doses of 30 mg/day and higher, and it is possible that sedative side effects may be diminished as well.

The use of mirtazapine plus a selective serotonin reuptake inhibitor (SSRI), such as paroxetine or fluoxetine, has also resulted in significantly greater remission rates than monotherapy in previous trials, said Maroney. “It would have been interesting to see the use and outcome of this combination therapy in CO-MED.”

Weighing the pros and cons
Maroney supports the use of combination treatment, especially mirtazapine plus SSRI, if the first treatment has been of sufficient dose and duration but not of adequate therapeutic benefit. She acknowledges that the decision to use combination antidepressants must be weighed against anticipated side effects, such as weight gain and sedation. She encourages pharmacists to counsel patients on the potential benefits and side effects of antidepressant agents, and to emphasize the importance of adherence to medication.

Monica Shah is a hospital pharmacist and healthcare journalist based in Bellm, N.J.
Colcrys® (colchicine, USP) tablets are indicated for prophylaxis and the treatment of gout flares.

Colcrys is contraindicated in patients with renal or hepatic impairment who are concurrently prescribed P-gp inhibitors or strong inhibitors of CYP3A4 as life-threatening or fatal toxicity has been reported. Dose adjustments of Colcrys may be required when co-administered with P-gp or CYP3A4 inhibitors. The most common adverse events in clinical trials for the prophylaxis and treatment of gout were diarrhea and pharyngolaryngeal pain. Rarely, myelosuppression, thrombocytopenia, and leukopenia have been reported in patients taking colchicine. Rhabdomyolysis has been occasionally observed, especially when colchicine is prescribed in combination with other drugs known to cause this effect. Monitoring is recommended for patients with a history of blood dyscrasias or rhabdomyolysis.

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**INDICATIONS AND USAGE**

**COLCRYS® (colchicine, USP) tablets** are indicated for prophylaxis and the treatment of gout flares.

- **Prophylaxis of Gout Flares**: COLCRYS is indicated for prophylaxis of gout flares.
- **Treatment of Gout Flares**: COLCRYS is indicated for treatment of acute gout flares when taken at the first sign of a flare.
- **Familial Mediterranean fever (FMF)**: COLCRYS is indicated in adults and children 4 years or older for treatment of familial Mediterranean fever (FMF).

**CONTRAINDICATIONS**

- Patients with renal or hepatic impairment should not be given COLCRYS in conjunction with P-gp or strong CYP3A4 inhibitors (this includes all protease inhibitors, except Fosamprenavir). In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses.

**WARNINGS AND PRECAUTIONS**

- **Familial Mediterranean fever (FMF)**: COLCRYS is indicated in adults and children 4 years or older for treatment of familial Mediterranean fever (FMF).

**Drug Interactions**

Colchicine is a P-gp and CYP3A4 substrate. Life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses.

**Neuromuscular Toxicity**: Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic use in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, or benzbafibrate (themselves associated with myotoxicity) or cyclosporine with COLCRYS may potentiate the development of myopathy. Monitor for toxicity and if present consider temporary interruption or discontinuation of COLCRYS.

**Adverse Reactions**

**Prophylaxis of Gout Flares**: The most commonly reported adverse reaction in clinical trials of colchicine for the prophylaxis of gout was diarrhea.

**Treatment of Gout Flares**: The most common adverse reactions reported in the clinical trial with COLCRYS for treatment of gout flares were diarrhea (23%) and pharyngolaryngeal pain (3%).

**FMF**: Gastrointestinal tract adverse effects are the most frequent side effects in patients initiating COLCRYS, usually presenting within 24 hours, and occurring in up to 20% of patients given therapeutic doses. Typical symptoms include cramping, nausea, diarrhea, abdominal pain, and vomiting. These events should be viewed as dose-limiting if severe as they can herald the onset of more significant toxicity.

**Drug Interactions**

COLCRYS is a substrate of the efflux transporter P-glycoprotein (P-gp). Of the cytochrome P450 enzymes tested, CYP3A4 was mainly involved in the metabolism of colchicine. If COLCRYS is administered with drugs that inhibit P-gp, most of which also inhibit CYP3A4, increased concentrations of colchicine are likely. Fatal drug interactions have been reported. Physicians should ensure that patients are suitable candidates for treatment with COLCRYS and remain alert for signs and symptoms of toxicities related to increased colchicine exposure as a result of a drug interaction. Signs and symptoms of COLCRYS toxicity should be evaluated promptly and, if toxicity is suspected, COLCRYS should be discontinued immediately. See full Prescribing Information for a complete list of reported potential interactions.

**Use in Specific Populations**

- In the presence of mild to moderate renal or hepatic impairment, adjustment of dosing is not required for treatment of gout flare, prophylaxis of gout flare, and FMF but patients should be monitored closely.
- In patients with severe renal impairment for prophylaxis of gout flares the starting dose should be 0.3 mg/day, for gout flares no dose adjustment is required but a treatment course should be repeated no more than once every 2 weeks. In FMF patients, start with 0.3 mg/day and any increase in dose should be done with close monitoring.
- In patients with severe hepatic impairment, a dose reduction may be needed in prophylaxis of gout flares and FMF patients; while a dose reduction may not be needed in gout flares, a treatment course should be repeated no more than once every 2 weeks.
- For patients undergoing dialysis, the total recommended dose for prophylaxis of gout flares should be 0.3 mg given twice a week with close monitoring. For treatment of gout flares, the total recommended dose should be reduced to 0.6 mg (1 tablet) x 1 dose and the treatment course should not be repeated more than once every two weeks. For FMF patients the starting dose should be 0.3 mg per day and dosing can be increased with close monitoring.
- Pregnancy: Use only if the potential benefit justifies the potential risk to the fetus.
- Nursing Mothers: Caution should be exercised when administered to a nursing woman.
- Geriatric Use: The recommended dose of colchicine should be based on renal function.

**References**

LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

The immunizing pharmacist
A natural progression from drug dispensing to vaccine administration

Pharmacists have, by now, overcome most legal obstacles to the right to immunize patients and have overwhelmingly demonstrated their value by increasing patient immunization rates. As the most accessible healthcare professionals, pharmacists are poised to provide immunizations to millions of people who visit pharmacies each week. Pharmacists also have the requisite knowledge of medications to ensure the proper and safe storage of vaccines.

A new role

Thanks in large part to successful education of state legislatures by national and state pharmacy associations, pharmacists now have yet another role in helping patients that goes beyond the traditional dispensing of drugs.

In addition to helping persuade state legislatures to implement laws allowing for pharmacist immunizing practices, many state pharmacy associations have helped large numbers of pharmacists obtain training to administer immunizations, and these services are providing patients with much-needed access.

Currently all 50 states, the District of Columbia, and Puerto Rico allow pharmacists to immunize patients. In this setting, pharmacists may now undergo training in vaccine administration and are able to expand their pharmacy practice.

Laws and regulations

Many state pharmacy practice acts, regulations, or guidelines describe how a pharmacist may gain qualifications to immunize patients and what restrictions exist when engaging in patient immunizations.

Laws and regulations governing pharmacist immunization rights vary from state to state, so pharmacists must understand what is and is not locally permitted. For example:

- Some states might require a patient to present a new prescription, while others allow a pharmacist to perform the immunization pursuant to a standing protocol.
- Some very progressive states, such as Idaho, recently passed legislation allowing pharmacists to prescribe agents for active immunization for patients 12 years of age or older.

Some very progressive states, such as Idaho, recently passed legislation allowing pharmacists to prescribe agents for active immunization for patients 12 years of age or older.

- Some states provide that a pharmacist may immunize only adults, while other states specify the ages of children who may be immunized by a pharmacist.
- Not all states allow pharmacists to administer the same types of vaccines. Depending on the state, there may be limits on the types of vaccines that a pharmacist may administer to patients.
- Finally, pharmacists must be sure to comply with the laws governing training and accreditation standards in their states in order to be eligible to immunize patients.

A good match

There are several ways pharmacists can get involved with immunization services:

- Pharmacists are natural advocates for patients and have many opportunities to discuss the importance of immunizations with them.
- Pharmacists are uniquely positioned to identify patients who are at risk for vaccine-preventable diseases on the basis of their medication profiles. Pharmacists can verify patient profiles and disease histories, and assess patients’ immunization status.

Other options

Pharmacists who administer immunizations can have the most direct impact on patient care. Pharmacists who do not wish to give immunizations can offer value to patients and enhance their own visibility by partnering with nurses or physician assistants and offering more convenient times and locations for such immunizations.

At present, pharmacists can administer vaccines to patients in accord with state laws and regulations. As the profession evolves its service offerings and new specialty drugs requiring administration by a healthcare professional enter the marketplace, it will be all the more necessary for pharmacists to seek legal and regulatory authorization to engage in this mode of drug administration and patient care.

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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Opioid pain management: Balancing risks and benefits

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In the United States today, pain is the single most common reason for seeking medical care. An estimated 9% of American adults report moderate to severe noncancer pain — the focus of this article — and many of these patients report suboptimal pain management.1 Thirty-five percent of Americans suffer from chronic pain and more than 50 million Americans are partly or totally disabled by chronic pain. In addition, 50 million workdays are lost per year, and the estimated annual cost in lost productivity, medical costs, and lost income is $560 billion to $635 billion.2,3 Yet 40% to 50% of patients in routine practice settings fail to achieve adequate pain relief.1 This establishes that much more needs to be done to educate healthcare professionals in the safe and proper use of the most effective class of pain medications, the opioids. It is hoped that this educational activity will contribute to the achievement of that goal.

Barriers to the use of opioid therapies

Although opioids provide effective pain relief, there are several potential barriers to their use. These include poor communication between healthcare provider and patient, fear of disciplinary action or prosecution on the part of the provider, concern for potential abuse, inadequate training, patient factors (including fear of addiction and side effects), socioeconomic and psychological factors associated with taking opioids on a chronic basis, lack of knowledge on the part of the patient, and possibly reimbursement issues, depending on the situation.

At the same time, there are clear data to show that patients are undertreated for pain.4,5 Prescribers are often unwilling to treat pain sufficiently or aggressively, and in some cases they fail to take it seriously or they place it low on their list of priorities. One of the major patient factors is fear of addiction.4 However, the fear of addiction is often greater than the incidence of misuse and abuse.4

Abstract

Pain has a high prevalence in medical practice, yet nearly half of all patients do not receive adequate treatment for pain. Although a wide variety of opioids provide effective pain relief, barriers to their use often result in undertreatment, especially for chronic pain. Extended-release products are most useful in treating chronic pain, while rapid-release products are most useful in controlling acute and breakthrough pain. Opioids work as agonists and/or antagonists at endogenous delta, kappa, and mu opioid receptors and mostly belong to one of four chemical categories: phenanthrenes, benzomorphans, phenylpiperidines, or diphenylheptanes. Patients’ adverse reactions to the members of one class are often a predictor of how they will react to other members of that class. Opioids such as methadone that block NMDA receptors may be particularly effective in treating neuropathic pain, but the long half-life and polymorphic differences associated with methadone require careful dosing strategies as well as a specific method for calculating dosing equivalencies when patients transition to methadone from other opioids. Bone pain, connective tissue pain, and neuropathic pain usually require adjuvant therapies with NSAIDs, anti-inflammatories, or anticonvulsants, although these medications may increase the risk of undesirable side effects, especially in elderly patients. Risks of opioid therapy include gastrointestinal disorders, hyperalgesia, and addiction/abuse. New “abuse-deterrent” formulations have become available, and FDA’s new Risk Evaluation and Mitigation Strategy (REMS) program is currently focused on educating healthcare providers about the risks and appropriate use of extended-release and rapid-onset opioids.
EDUCATIONAL OBJECTIVES

**Goal:** To assist pharmacists and pharmacy technicians with pain management issues related to risks and benefits of opioid use in their practice settings.

After participating in this activity, pharmacists should be able to:
- Describe the risks and benefits of opioid and nonopioid agents available for pain relief.
- Describe the techniques for minimizing multiple dosing and overdosing, and calculate opioid equivalencies.
- Respond appropriately to patients’ allergic reactions to opioids.
- Select the optimal opioid agent(s) for treatment of patients with specific comorbidities.

After participating in this activity, pharmacy technicians should be able to:
- Describe the risks and benefits of opioid and nonopioid agents available for pain relief.
- Identify the techniques for minimizing multiple dosing and overdosing.
- Recognize appropriate responses to patients’ allergic reactions to opioids.

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 both the knowledge-based and application-based activities, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity/activities, passing the quiz/quizzes with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the online system. Pharmacy technicians are eligible to participate in the knowledge-based activity and will receive 0.1 CEU (1 contact hour) for completing the activity, passing the quiz with a grade of 70% or better, and completing the online evaluation. Statements of credit are available via the online system.

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priority list of medical problems to address. Among prescribers there is lack of knowledge about pain, fear of tolerance and addiction to opioids, and fear of regulatory agencies.

Regulatory issues vary by state. Most states have “prescription monitoring programs” that track controlled substance prescriptions, while others, unfortunately, do not. But that is now changing. Figure 1 is a schematic of various states and their position with regard to prescription monitoring.

**Acute vs. chronic pain**

Acute pain typically has a clearly identifiable cause. We know what the issues are; most acute pain is readily treatable; and the pain will subside within an expected period of time. Chronic pain, on the other hand, is defined as pain that has been present for 3 months or longer, and it does not necessarily have an identifiable pathology. It often involves sleep deprivation as well as a host of other behavioral health issues, such as anxiety and depression. Often, chronic pain cannot be measured as readily as acute pain.

Sedation for acute pain may be desirable in situations where the patient is anxious about the pain; for example, when someone has an acute debilitating injury requiring surgery, sedation may be appropriate. Sedation is generally not desirable in the treatment of chronic pain. There may be some end-of-life situations, however, in which the patient may be so distressed that sedation would be an appropriate palliation.

As with any chronic disorder, patients with chronic pain need to be on a regular dosing schedule, and PRN should be used only for breakthrough pain. If a patient is receiving a PRN prescription every 30 days, the pharmacist should contact the prescriber and suggest that the patient be switched to an extended-release product, because it is no longer a PRN situation. Meanwhile, the patient is being exposed to peaks and troughs, which could adversely affect both mood and toxicity.

The **Clinical Treatment Guidelines** from the American Pain Society (APS) and the American Academy of Pain
Management (AAPM) for noncancer pain include definitions of “monitoring use” and “therapeutic goals.”

**How opioids work**

Agonists are those medications that have a binding affinity to the opiate receptors. Agonists cause analgesic activity and respiratory depression, decrease gastrointestinal (GI) activity, and have a number of other effects, depending on their association with receptor type(s) and the binding affinities. Opioids work as agonists, antagonists, or mixed agonist/antagonists at various endogenous opioid receptors. The various opioid receptors include delta, kappa, and mu. Mu-1 plays the largest role in analgesia.

The antagonists have a higher affinity for those same opiate receptors, but they do not have analgesic activity. Using the metaphor of the lock and key, the opiate represents the key, the receptor represents the corresponding key hole, and they are both magnetized. In this case, the antagonist key may be a stronger magnet, but it cannot turn the lock.

Mu and kappa opioid receptors cause analgesia. Mu-1 receptor agonists that have some degree of kappa activity are the most useful for analgesia. Mu-1 receptor subtypes have been isolated, indicating that genetic polymorphism is an important consideration in therapeutic response. Mu-2 receptors, on the other hand, are most often associated with bothersome opioid side effects rather than analgesia. Delta receptors have been studied, but thus far none has been approved for human use.

**Choosing a specific opioid**

As shown in Figure 2 (page 50), there are four categories of opioids, plus a fifth category of “hybrids.” It is important to remember that if a patient cannot tolerate one member of a certain class, that patient is less likely to tolerate another medication from that category.

It is important to know, as Figure 2 makes clear, that certain medications in the phenanthrene class are missing a hydroxyl group, while others are not. The ones lacking the 6-hydroxyl group are marked with an asterisk (Figure 2). In the author’s experience, these medications tend to be better tolerated than the phenanthrenes with that hydroxyl group.

For example, if a patient can tolerate hydrocodone but needs an extended-release product, then the patient will tolerate oxymorphone or oxycodone, because those two medications lack the 6-hydroxyl group just as does hydrocodone. The patient who cannot tolerate codeine is very unlikely to tolerate morphine, because codeine is metabolized to morphine, and they are both hydroxylated.

If a patient is able to tolerate meperidine, then that patient also will be likely to tolerate fentanyl, because fentanyl and meperidine are in the same chemical class. Figure 2 is organized so that the risk of cross-allergenicity decreases as one moves from left to right on the chart. Although true allergic reactions to opioids are relatively rare, a patient with a true allergy to oxycodone also will be allergic to all the other medications in that class. As will be discussed later, morphine is not a good medication to use in a patient with compromised renal function. For patients who are not tolerant of the drowsiness associated with opioids, oxycodone might be a useful option, because it often causes wakefulness, agitation, and insomnia. The benzomorphanes are generally not used for pain management, but they are used to decrease motility for patients with diarrhea.

The next group of medications is the phenylpiperidines, which includes the fentanyl family as well as meperidine. Fentanyl and its chemical relatives (alfentanil, sufentanil, and remifentanil) have the least histamine reactivity compared to all other opioids, and therefore are among the most well tolerated.

If transdermal fentanyl is most desirable and a patient regularly experiences breakthrough pain prior to the scheduled 72-hour-interval change, the manufacturer recommends either reducing the dosing interval to 48 hours or increasing the dosage while keeping the interval constant. The author recommends reducing the dosing interval as the preferred strategy, since a higher-dose patch will deliver more medication than the patient actually requires. If a rash develops beneath the patch, consideration could be given to using triamcinolone in the form of aerosol spray on the area just before placement. Providers occasionally prescribe oral inhaled steroids, otherwise intended for administration with handheld devices, to prevent skin irritation, but this has not been studied and is not FDA approved for this purpose. Also, it is far more expensive and certain inhalers have built-in spacers that would preclude external application applicability. Topical creams, ointments, or gels are not options because they would compromise patch adhesion. Finally, if patch adherence is a problem, an occlusive dressing may be placed over the fentanyl patch.

Meperidine is one of the most toxic opioids, and it has a very high incidence of neurotoxicity (including escalated seizure risk) due to its desmethyl-meperidine (also known as nor-meperidine) metabolite. Caution should be exercised if meperidine is dispensed with other medications that reduce seizure threshold, such as theophylline, phenothiazines, SSRIs, and SNRIs. Both fentanyl and hydromorphone offer viable alternatives for parenterally administered patient-controlled analgesia (PCA) in patients who are unable to tolerate morphine.

Most opioids may be used in the presence of hepatic dysfunction if use is started at low doses and carefully escalated, as...
Continuing Education

OPIOID PAIN MANAGEMENT

Figure 2. Classes of opioids

**PHENANTHRENES**

MORPHINE

Rx EXAMPLES: morphine, codeine, hydrocodone*, hydromorphone*, levorphanol*, oxycodone*, oxymorphone*, buprenorphine, butorphanol*, naloxone*, heroin (diacetyl-morphine)

CROSS-SENSITIVITY RISK:

PROBABLE

POSSIBLE

LOW RISK

**BENZOMORPHANS**

PENTAZOCINE

pentazocine, diphenoxylate, loperamide

**PHENYLPIPERIDINES**

MEPERIDINE

meperidine, fentanyl, sufentanil, alfentanil, remifentanil

**DIPHENYLHEPTANES**

METHADONE

methadone, propoxyphene

* These agents lack the 6-OH group of morphine, possibly decreasing cross-sensitivity within the phenanthrene group.

Source: Ref 18

physical tolerance will develop commensurate with accumulated doses. Compared to other opioids, methadone and levorphanol must be even more carefully titrated in circumstances of hepatic dysfunction because their metabolism is more complex and they both have a high volume of distribution. While transdermal administration is generally a good alternative in the presence of hepatic dysfunction, the author advises against use in a jaundiced patient, as elevations in bilirubin may have a significant impact on fentanyl transdermal absorption.

The diphenylheptanes are represented by propoxyphene and methadone. Although propoxyphene is no longer commercially available in the United States, previous use is a good predictor of whether a patient will tolerate methadone.

All the opioids — with the exception of levorphanol and methadone — have very similar pharmacokinetics in terms of time to peak and half-life, and their effects usually last from 3 to 6 hours. But we have to delineate those opioids that are substrates for 3A4 and 2D6. These include fentanyl, tramadol, oxycodone (to a more limited extent), and to a greater extent, methadone. And because of that, these medications have a higher risk of medication interactions due to the cytochrome P450 system.

Angioedema and difficulty breathing are the specific hallmarks of dangerous medication allergies, but these are rarely seen with opioids. Opioids may, however, cause significant pruritus and GI upset often mislabeled as allergy. Pruritus, which is not a true allergy, is most often the result of a histamine reaction. Fentanyl, sufentanil, and remifentanil are the least likely to cause pruritus because they have the least histamine reactivity.

**Opioids with unique mechanisms**

Some opioids have unique mechanisms that may increase effectiveness in treating certain pain types.

An understanding of the role of norepinephrine in treating pain reveals that certain opioids may be more useful than other opioids for treating neuropathic pain symptoms. Mitchell Max showed that desipramine and amitriptyline were equally useful for diabetic neuropathy. Amitriptyline blocks reuptake of norepinephrine and serotonin, and desipramine blocks reuptake of norepinephrine alone. Fluoxetine blocks only reuptake of serotonin, and fluoxetine and placebo respond equally poorly.
With regard to antidepressant pharmacology, blocking reuptake of 
norepinephrine is the most important element for efficacy in 
treating neuropathic pain.\textsuperscript{16}

Some opioids, including tapentadol and tramadol, have a 
mechanism of action that makes them useful in treating 
neuropathic pain. While tapentadol blocks reuptake of 
norepinephrine most significantly, tramadol also blocks reuptake of 
both norepinephrine and serotonin, with increased risk of 
serotonin syndrome and seizure. Tramadol’s affinity to mu-1 
receptors is 6,000 times less binding than that of morphine, 
while that of tapentadol is just 19 times less binding than 
that of morphine. The benefit of tramadol in treating neu-
ropathic pain therefore does not derive from its opioid- or 
serotonin-reuptake-blocking activity, but most likely from its 
norepinephrine-reuptake-blocking activity alone. Another 
discernible difference between tramadol and tapentadol is 
that tramadol is a pro-drug requiring hepatic metabolism to 
its active form. This is not the case with tapentadol.\textsuperscript{24}

\textbf{Methadone}

Methadone not only blocks reuptake of epinephrine; in addition 
to its opioid activity, it also blocks NMDA (N-methyl-D-
aspartase) receptors, which are found at the ends of certain 
nerve fibers, and, when stimulated, cause pain. Blocking the 
NMDA receptors will diminish pain.\textsuperscript{24}

There are several ways one can block neuropathic pain: by 
surgically severing the nerve, by injecting lidocaine into the 
nerve, or by blocking it at the terminal end of the nerve, at 
the actual receptor. The same patient may tolerate oxycodone 
but not respond to it and may respond well to methadone 
but not tolerate it. One way to ascertain whether the NMDA 
blockade was the key to success for the patient is to try an 
opioid that blocks NMDA but is chemically similar to oxy-
codone, in this case, levorphanol. Levorphanol also has an 
effect on kappa receptors, and pharmacists should recognize 
that the chemical enantiomer of levorphanol is, in fact, dex-
tromethorphan (DM). DM retains the antitussive properties 
but lacks significant analgesic activity at commercially avail-
able doses.\textsuperscript{27}

\textbf{Dosing strategies}

There are numerous dosing charts available that provide ways 
of equating one opioid to another. The problem with many of 
these charts, however, is that they fail to base their calculations 
on chronic dosing. Rather, they base it on acute dosing of an 
opiate-naïve patient. For example, in the case of a patient who 
is not at steady state, 60 mg of oral morphine is equivalent to 
10 mg of injectable morphine. But when a patient is on chronic 
opioid therapy and is at a steady state, the equivalency requires 
only 30 mg of oral morphine — a 3:1 ratio, as opposed to the 
6:1 ratio required for an episode of acute pain.\textsuperscript{12}

Methadone dosing calculations present a far greater chal-
lenge because of methadone’s very long half-life, high volume 
of distribution, and polymorphic differences among patient 
groups. As the dose of morphine (or morphine equivalent) 
increases, the amount of methadone needed to replace it 
decreases. This is important, because if a patient is on a very 
high dose of morphine, and the calculation of the methadone 
equivalent is based on the lower dose of morphine, the patient 
can overdose.

Moreover, methadone conversions do not work the same 
way in both directions. Thus, if a person is converting from 
methadone to morphine, simply interrupting the adminis-
tration of methadone will not cause it to disappear from the 
body immediately, because of the pharmacokinetic param-
eters explained earlier. Therefore, if methadone administra-
tion is terminated and the patient is immediately put on an 
equivalent dose of morphine, there will be two doses of differ-
ent opioids in the patient’s body at the same time for several 
days. This is plainly dangerous.

The problem is reversed, however, if methadone is in-
troduced when the patient has been on another opioid, be-
cause several days will pass before the methadone reaches 
steady state. In this case, it is necessary to gradually increase 
the methadone while slowly decreasing the dosage of the other 
opioid.

Since there is enormous variability among opioids with re-
gard to pharmacokinetics, therapeutics, and pharmacodynam-
ics, no one conversion applies to every patient. It should also 
be noted that because of incomplete cross-tolerance among 
opioids, it is recommended that pharmacists reduce the calcu-
lated equianalgiesic conversion starting dose by 20% to 25%.\textsuperscript{12}
This will reduce the risk of a dosage overestimate and the risk 
of a fatal outcome.

Genetic polymorphism plays a very large role in the titra-
tion of methadone from one patient to the next. Ripamonti’s 
conversion is just one approach (Figure 3).\textsuperscript{28}

There is no limit to how high an opioid dose can be es-
calated, as long as it is a pure opioid and can be tolerated 
without dose-limiting side effects. The only exceptions are the 
opioids meperidine and pentazocine. Meperidine produces 
a toxic metabolite called “nor-meperidine,” also known as 
desmethyl-meperidine, and pentazocine carries a risk of dys-
phoria at regular doses and neurotoxicity at higher doses. 
Dosage limits do, however, apply to medications in which 
opioids are combined with other products, such as acetamino-
phen, ibuprofen, or atropine alkaloids, all of which have 
clear dosage limitations. That said, there are dosage limitations 
with all opioid medications, owing to their side effects and the 
possibility that the patient may develop hyperalgesia, which 
means that the opioid is actually causing pain. In a patient

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
Morphine dosage & Morphine-to-methadone ratio \\
\hline
30-90 mg/day & 3.70 to 1 \\
91-300 mg/day & 7.75 to 1 \\
>300 mg/day & 12.25 to 1 \\
\hline
\end{tabular}
\caption{Dose ranges: Morphine to methadone}
\end{table}
who has been taking opioids for a long time and who still has pain, it is important to make that connection and consider hyperalgesia as a cause.29

**Therapeutics: Administration and drug interactions**

Numerous methods of administration are available with opioids, including sublingual, oral, buccal (effervescent and passive), rectal, intravenous, intramuscular, subcutaneous, intra-nasal, topical, intra-sinal (epidural and intrathecal), and transdermal.

Certain drug interactions should be noted. Codeine requires conversion to morphine by 2D6 isoenzymes upon first pass through the liver.30 But a number of selective serotonin reuptake inhibitors (SSRIs) (excluding fluvoxamine) inhibit 2D6 isoenzymes, which would inhibit the metabolism of codeine into morphine. This, of course, would render the codeine completely useless in terms of its analgesic effect.30 Another complication arises from the fact that approximately 9% of Caucasians are poor metabolizers of 2D6 isoenzymes, while Asians and African-Americans generally metabolize 2D6 medications efficiently.31,32 For this reason, it is necessary to use caution when dispensing codeine to people on SSRIs. In this case, fluvoxamine would be the SSRI antidepressant treatment of choice, since it inhibits 1A2 rather than 2D6.33,34

The interaction of methadone with inducers and inhibitors of CYP450 3A4 isoenzymes is an extremely important issue, because there is a high risk of dangerous interactions between these two medications.35 Potent 3A4 inducers could lower serum methadone by 40%, and the opposite is true for enzyme inhibitors such as erythromycin, which can increase serum methadone by 40%. Two of the most commonly prescribed potent 3A4 inducers are phenytoin and carbamazepine, which could lower serum methadone concentrations.

**Adjuvant therapies**

In general, opioids are the treatment of choice for cancer pain. But in the specific case of bone or nerve involvement, adjunctive medication therapy is often required.

Certain types of pain do not respond well to opioids as a single pharmacological approach. These include bone pain, connective tissue pain, and neuropathic pain. For these types of pain, there are pharmacologic alternatives that more precisely address the pathology. Nevertheless, opioids are relatively safe if prescribed in the proper dose, and there are relatively few cases of overdose when treating chronic pain.12

Nonsteroidal anti-inflammatory drugs (NSAIDs) are useful as adjuvant therapies because they are very effective in treating inflammatory pain. Other types of medications that are useful in treating neuropathic pain may vary in effectiveness. It may also be useful to employ rational polypharmacy by selecting medications with various mechanisms of action, administered at low doses, so that efficacy can be increased with a lower side-effect profile.37

Anti-inflammatory agents may be more effective than opioids against bone or connective tissue pain because they specifically prevent inflammation by blocking prostaglandins.38 However, when NSAIDs are used as adjuvant therapy with opioids, pain can be more effectively managed than when either medication is used alone.39 When antidepressants are being considered as an adjuvant to opioid therapy, it is important that the medications selected block the reuptake of norepinephrine, as opposed to those that block the reuptake of serotonin and/or dopamine alone.26

Norepinephrine specifically affects pain in the descending pathway from the central nervous system, whereas opioids affect pain in the ascending pathway.39 Thus, blocking the uptake of norepinephrine enhances opioid activity at the spinal level, at the CNS level, and also at the peripheral level, because it stimulates inhibitory nerves. Serotonin-norepinephrine reuptake inhibitors (SNRIs) plus secondary and tertiary tricyclics all affect norepinephrine, which is key here.25 In addition to its opioid activity, tapentadol does, in fact, block the reuptake of norepinephrine. The same is true of methadone; however, tapentadol and methadone are very different in chemistry, pharmacology, and pharmacokinetics.

In general, the anticonvulsants are useful in treating neuropathic pain, because to various degrees they affect ion influx into the neurons themselves. Other contemporary anticonvulsants, such as gabapentin and pregabalin, block voltage-gated calcium channels within the synaptic cleft. These medications combine with the alpha-2-delta subunit on the calcium channels, the net effect of which is to narrow the channel so that less calcium can flow into the cleft. Less calcium influx decreases the stimulation of glutamate, which, in turn, diminishes the eventual outflux of neuroamines (i.e., norepinephrine, serotonin, and dopamine).

Adjuvant medications — such as NSAIDs, SNRIs, and anticonvulsants — used to treat chronic pain may present a greater risk of side effects than opioids. Gabapentin has a significant risk for GI discomfort as well as risk for falls or gait issues.40 SNRIs can increase blood pressure and may increase bleeding risk.41,42 Tricyclic antidepressants, all of which have significant anticholinergic activity, can cause lethargy, arrhythmias, urinary retention, and constipation.43

Chronic use of NSAIDs increases the risk of kidney dysfunction, especially in diabetics who already are at risk. Virtually all diabetic patients should be taking angiotensin-converting enzyme (ACE) inhibitors to protect against diabetic nephropathy, and ACE inhibitors increase the renal toxicity of NSAIDs.43 If diabetic patients are not on ACE inhibitors, they should be — and that’s a “double whammy.”42 And since NSAIDs increase fluid retention, they inherently have an effect on the fluid dynamics and elevation of blood pressure. Thus, hypertension is also a potential issue with NSAID therapy.43

Finally, all NSAIDs have the potential for increasing risk of GI mucosal perforation. The traditional non-COX (cyclo-oxygenase) selective NSAIDs carry greater risk because of their prominent effect on COX-1 enzyme inhibition, which ultimately results in diminished thromboxane A2, platelet dysfunction, and reduced GI protective prostaglandins. Their COX-2 inhibiting activity is more specific and primarily involved with reducing pain, inflammation, and fever. It is for this reason that COX-2
specific inhibitors have a lesser risk of perforation, ulcer, and bleed compared to the traditional NSAIDs. However, through a negative feedback within the arachidonic acid cascade, decreased prostacyclin (PGI-2) may increase risk of clotting or formation of a thromboembolism with the COX-2 selective agents. Therefore the more selective agents carry particularly greater risk for the patient with coronary artery disease.52

Polypharmacy in the elderly
Elderly populations have increased need for pain medication even as they are less tolerant of medication side effects. In the elderly patient, side effects can be minimized and efficacy maximized by treating the patient with minimal doses of multiple medications.

Opioids may be the best choice for elderly patients, because they often have compromised renal function, achlorhydria, and greater susceptibility to GI bleeding, as well as multiple co-morbid conditions such as hypertension and coronary artery disease, all of which increase risk with NSAID use. A reasonable strategy for pain management in the elderly may be use of opioids and occasional small PRN doses of NSAIDs or COX-2 inhibitors.

In general, morphine should be avoided in elderly patients or in any patient with compromised kidney function, because morphine is metabolized into a 6-glucuronide (M6G or morphine 6-glucuronide) metabolite, lending to significant risk for neurotoxicity.20 Oxycodone and most other dehydroxylated phenanthrenes have only the M3G or at least lack the M6G component.20 The M6G metabolite is an active analgesic, but it accumulates over time, whereas the M3G metabolite is inactive and does not cause neurotoxicity.20

Antiepileptic medications such as carbamazepine and gabapentin are risky for several reasons. Carbamazepine may be risky for the patient on multiple medications, as it is a potent 3A4 enzyme inducer and thus carries a very high risk of drug interactions. Carbamazepine also has anticholinergic activity, lending to sedation, urinary retention and/or constipation, all of which are undesirable in elderly patients. Gabapentin is risky in the elderly population because it is associated with a very high risk of falls. Anticholinergics, including carbamazepine and the tricyclic antidepressants, are listed in the Beer’s criteria, a compilation of medications to be avoided in the elderly.50

Risks of opioids
The concept of risk stratification with regard to aberrant behavior was formulated by Gourlay, who advocates evaluating patients with “universal precautions,” in which patients are designated as low risk, moderate risk, and high risk in several distinct risk areas.51 For example, a patient who never had substance abuse would be considered low risk, a patient with a past history of substance abuse would be considered moderate risk, and the patient with a current history of substance abuse would be considered high risk.

Smoking, because of the addictive nature of nicotine, is similarly divided into low, moderate, and high risk. Psychological factors also have a bearing on risk, including behavioral issues such as psychosis, post-traumatic stress disorder, or schizophrenia. In addition, younger patients are at higher risk than older patients, and patients who have been the victims of sexual abuse have a very high risk of addiction.52

Elderly patients who require chronic opioid therapy should be prescribed around-the-clock extended-release opioid products, as these will remain effective through the night. While extended-release products have not been shown to be any more or less efficacious when compared to their immediate-release counterparts, they have been shown to be superior in terms of compliance, tolerability, more consistent pain control, and improved sleep.53

GI side effects of opioids include nausea, vomiting, urinary retention, and constipation; unlike sedation, constipation does not improve with continual opioid use.20

Pharmacists should be aware of the potential outcome of the hypoadrenal axis, whereby estrogen levels in women and testosterone levels in men can diminish. Pharmacists have a unique opportunity to counsel the elderly patient about the fact that chronic opioid use may lower hormone levels sufficiently to cause lethargy and depression.

Such patients also may be at risk of osteoporosis if this is not taken into consideration and monitored appropriately. Consider the example of an elderly patient with a chronic low-back disorder resulting from significant osteoarthrosis of the spine. The patient has been treated for many years with opioids and subsequently develops osteoporosis, which is not diagnosed. The patient subsequently fractures a vertebrae in the lower back and experiences even more pain than was originally caused by the osteoarthrosis.

A significant risk of unsatisfactory treatment of acute pain is the development of a chronic pain syndrome, which can occur even after abatement of the original pathology. The cause of this is nerve remodeling, known as “neuroplasticity.”54 If pain is not treated for weeks at a time after certain surgical procedures, chronic pain can persist even after the surgical wounds have healed. The surgeries most commonly associated with this type of neuroplasticity are wedge resection of the lung, breast augmentation, inguinal hernia, Cesarean section, and removal of a limb or digit.55

The pharmacist’s role in neuroplasticity, particularly in the community setting, is to educate patients about the importance of taking their medications, even if the medications are opioids. Many patients are afraid of taking opioids because they know these drugs are “narcotics” and they are afraid of becoming addicted. Pharmacists have a unique opportunity to educate patients about the differences between addiction, tolerance, and dependence, and to explain the importance of treating acute pain on an ongoing basis in order to avoid the risk of chronic pain syndrome.

If for any reason the patient cannot tolerate the medication, the pharmacist should intervene. If the problem is constipation, the pharmacist can suggest prophylactic laxatives. If the problem involves a previous history of nausea or vomiting, the
pharmacist can speak to the provider about prescribing a more appropriate opioid, based on the chemistry.66

In such cases, patients should be prescribed immediate-release medications and the dosage should be escalated slowly over a period of days to weeks. Once the dose is adequately titrated, the patient can be placed on an extended-release product and can use the immediate-release product for breakthrough pain. This applies to most opioids, which have a short half-life, but it excludes methadone and levorphanol, which have much longer half-lives. In the case of methadone or levorphanol, the titration process is slower and dosage adjustments are generally made weekly rather than 2 to 3 days apart.

Respiratory depression is extremely rare in patients receiving chronic opioid therapy, unless they intentionally or unintentionally overdose. But respiratory depression can occur in cases where a patient is prescribed both benzodiazepines and opioids. Benzodiazepines are not respiratory depressants, but they do decrease respiratory drive, the result of which is diminished respiration. Barbiturates, on the other hand, are in fact respiratory depressants, so patients taking barbiturates such as phenobarbital, butalbital (most often in the form of Fioricet), are at risk for respiratory depression.20

Dose escalation of opioids needs to be made slowly, particularly with methadone and levorphanol.12 A high-dose opioid therapy is defined in the opioid guidelines as a morphine dose equivalent of 200 mg/day or greater.12

**New medications to mitigate risk**

“Abuse-deterrent” formulations do not have an official FDA designation as such, but FDA is encouraging drug manufacturers to develop formulations that are “abuse-deterrent.”67 However, reimbursement from managed care for such products is likely to lag behind.58

Some abuse-deterrent medications are delivered in formulations that are resistant to crushing and will turn into a “pancake” instead of breaking up into a powdery substance that could be abused by snorting (inhaling). In other cases, crushing causes the tablets to break up into large, sharp-edged pieces that would be extremely difficult, uncomfortable, or impossible to snort.

While the street desirability of abuse-deterrent products seems to be reduced, the problem remains, in that abusers of medication have simply moved on to other formulations. Abusers are beginning to use immediate-release products to accomplish the same goals. Fortunately, the substance-abuse community is often one step ahead of industry and government efforts to mitigate risk.

**Risk management and REMS**

Opioid risk tools are available from many sources. See S. Passik and COT Guidelines by APS/AAPM for validated tools, as well as the “Clinical guidelines for the use of chronic opioid therapy.”121 Informed consent and opioid management plans are available online at http://www.paincareproviders.com/FORMS/Contract.pdf.

FDA initiated the REMS program in part because of the misuse of opioids. The mission of the program is to ensure that providers are properly educated about the risks and appropriate uses of these medications, and the pharmaceutical companies are tasked with the responsibility of providing that education. The REMS program, which is the focus of the next monthly activity in this series, is currently targeting long-acting or extended-release dosage forms and rapid-onset opioids.

**Conclusion**

Opioids are among the most effective medications available for the control of most types of pain, but lack of knowledge about their properties, risks, and proper use has hindered their appropriate usefulness. As a result, significant numbers of patients continue to receive inadequate pain management.

As healthcare providers understand more about the risks and the benefits of opioid pain therapy as an important part of the analgesic armamentarium, they will be able to manage their patients’ pain ever more effectively, to the benefit of all.

**References**


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48. Aneja A, Farkouh ME. Adverse cardiovascular effects of...
OPIOID PAIN MANAGEMENT

56. Fudin J, Levasseur DJ, Passik SD, Kirsh KL, Coleman J. Chronic pain is defined as pain that has been present for _______ or longer and may not have an identifiable pathology:
   a. 10 days
   b. 30 days
   c. Three months
   d. Six months

2011 CEU credit request

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The case-study activity that follows the test questions is available for pharmacists only. Upon successful completion of the quiz with a grade of 70% or better and upon completing the online course evaluation, the learner will receive 0.1 CEU (1 contact hour) of credit.

For questions concerning the online CPE activities, e-mail cpehelp@advanstar.com.

1. Chronic pain is defined as pain that has been present for _______ or longer and may not have an identifiable pathology:
   a. 10 days
   b. 30 days
   c. Three months
   d. Six months

2. Of the various opioid receptors, the _____ receptor plays the largest role in analgesia:
   a. Delta
   b. Kappa
   c. Mu-1
   d. Mu-2
   e. Beta

3. Opioids may have the following activity on various opioid receptors:
   a. Agonist
   b. Antagonist
   c. Mixed agonist/antagonist
   d. None of the above
   e. All of the above

4. Certain medications in the phenanthrene class are missing the 6-hydroxyl group. These medications tend to be _______ than phenanthrenes that include the 6-hydroxyl group.
   a. Tolerated better
   b. Tolerated less well
   c. More effective
   d. Less effective
   e. None of the above

5. Which of the following have a high volume of distribution and long half-life?
   a. Methadone and propoxyphene
   b. Levoxynol and methadone
   c. Fentanyl and methadone
   d. Morphine and hydromorphone
   e. Morphine and hydrocodone
   f. None of the above

6. A problem with many dosing equivalency charts is that they base their calculations on:
   a. Acute dosing of an opiate-tolerant patient
   b. Chronic dosing of an opiate-tolerant patient
   c. Acute dosing of an opiate-naïve patient
   d. Chronic dosing of an opiate-naïve patient
   e. None of the above

7. Differences in dosing requirements for methadone from one patient to the next may significantly vary because of:
   a. Degree of tolerance
   b. History of drug abuse
   c. Genetic polymorphism
   d. Pharmacokinetics
   e. Incomplete cross-tolerance

8. If a patient has been taking large doses of opioids for a long time and still has pain, it is important to consider the possibility of:
   a. NSAID overdose
   b. Norepinephrine reuptake
   c. Hyperalgesia
   d. Toxic metabolites
   e. Inhibition of 2D6 isozymes

9. Dangerous interactions are most likely to occur between methadone and:
   a. Fentanyl 2-isoenzymes
   b. 2D6 isozymes
   c. 1A2 isozymes
   d. CYP340 3A4 isozymes
   e. None of the above

10. Elderly patients, or any patient with compromised kidney function, should avoid _______ because it is metabolized into a 6-glucuronide metabolite and thus carries a significant risk of neurotoxicity.
    a. Methadone
    b. Oxycodeone
    c. Dehydroxylated phenanthrenes
    d. Fentanyl
    e. Morphine
A. Patient needs methadone conversion
A 57-year-old woman with chronic pain resulting from postherpetic neuralgia has been taking extended-release morphine 30 mg PO Q8H for the past 20 months. She is using a 5% lidocaine patch daily and is taking pregabalin 100 mg PO three times daily. She is also taking oxycodone/acetaminophen 5/325 PO Q4H PRN, and her total daily average dose of oxycodone is 4 tablets per day. The physician attempts a trial with methadone because of its NMDA properties, but is unsure about an appropriate dosing schedule.

1. As a pharmacist, your first step is to calculate a methadone dose as published by Ripamonti suggesting which of the following:
   a. Dosage calculations have a linear conversion depending on current morphine dose.
   b. Methadone should be reserved for patients requiring heroin maintenance only.
   c. Polymorphic differences among patients receiving methadone are unimportant.
   d. Dosage calculations have a triphasic conversion depending on current morphine dose.

2. You advise the physician first to convert the existing dosage to its morphine equivalent; second, to convert the calculated morphine dosage to the equivalent methadone dosage; and third, to consider the variable pharmacokinetics of methadone versus most other opioids.

Using the charts below, you find that the daily morphine equivalent dosage would be:

### Dose ranges: Morphine to methadone

<table>
<thead>
<tr>
<th>Morphine dosage</th>
<th>Morphine-to-methadone ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-90 mg/day</td>
<td>3.70 to 1</td>
</tr>
<tr>
<td>91-300 mg/day</td>
<td>7.75 to 1</td>
</tr>
<tr>
<td>&gt;300 mg/day</td>
<td>12.25 to 1</td>
</tr>
</tbody>
</table>

Source: Ref 28

### Oral opioid analgesic equivalency table

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Equianalgesic dose - oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>130-200 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>See * below</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>4 mg</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20 mg</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10 mg</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

*Transdermal 25 µg/h = 45 mg of oral sustained release morphine

Source: Ref 18

3. Now convert the daily morphine dosage to its daily methadone equivalent, which in this case would be:
   a. 120 mg
   b. 240 mg
   c. 300 mg
   d. 320 mg

4. Finally, it will be necessary to factor in the difference in the pharmacokinetics between methadone and the morphine and oxycodone the patient has been taking. The appropriate dosing schedule for this patient would therefore be:
   a. Stop the morphine and oxycodone and immediately start the full methadone regimen.
   b. Stop the morphine and oxycodone and gradually raise the methadone dose over a period of several days.
   c. Gradually taper off the current cumulative opioids (using oxycodone or morphine IR alone) while gradually raising the methadone dose over a period of several days.
   d. Immediately start the full methadone regimen while gradually tapering off the morphine and oxycodone over a period of several days.

5. In the event that this patient has a neuropathic pain syndrome, it might be useful to prescribe tapentadol, because it has reuptake blockade properties for:
   a. Serotonin receptors
   b. Dopamine receptors
   c. Norepinephrine receptors
   d. NMDA receptors

B. Patient needs adjuvant medications
An 82-year-old man with hormone-refractory prostate cancer has been suffering with metastatic bone pain in the pelvic region for the past 15 months. He is currently taking extended-release morphine at 100 mg/day (50 mg PO Q12H), but the pain is still severe, and he wants the physician to increase the morphine dosage.

1. The physician is reluctant to increase the morphine dosage, because:
   a. The patient may become addicted.
   b. Morphine metabolizes into a 6-glucuronide, which carries a significant risk of neurotoxicity.
   c. At this dosage the morphine is likely to be causing increased pain due to remodeling.
   d. Morphine metabolizes into a 3-glucuronide, which can impair kidney function in the elderly.

2. As the pharmacist, you recommend that the physician prescribe an adjuvant medication consisting of:
   a. Antidepressants
   b. Anticonvulsants
   c. NSAIDs
   d. Short-acting opioids

3. The patient does so well on NSAID therapy that the physician decides to taper off the morphine. The optimal dosing regimen for this patient would be:
   a. Discontinue morphine immediately, because to taper at this dose is not necessary.
   b. Morphine sulfate immediate release 15 mg PO Q4H, taper by 1 tablet every 2-3 days.
   c. Convert to extended-release morphine 30 mg PO Q8H and decrease by 30 mg each day for 3 consecutive days.
   d. Convert to hydromorphone 16 mg PO Q4H and decrease by 2 mg every other week.
4. The optimal route of administration for this therapy would be:
   a. Oral
c   b. Transdermal
d. Intramuscular

C. Patient taking extended-release oxycodone with previous history of substance abuse
A 37-year-old woman with a history of substance abuse, sharing, and selling her prescriptions presents to her primary care doctor. She does have findings on physical assessment that are consistent with her reported symptoms of severe back pain subsequent to an auto accident 6 months earlier. She has no prescriptions for opioids at this time and denies using any such medications for more than 2 years, aside from a 1-week supply of acetaminophen and hydrocodone issued in the ER immediately following the accident.

The patient has been examined by an orthopedic surgeon, who found no evidence of any condition for which surgical intervention was indicated. An anesthesiologist recommended medication treatment, as the patient had a recent deep vein thrombosis that presumably was due to her birth control medication; for this she is receiving warfarin prophylactically.

The patient is receiving lisinopril 40 mg PO QAM for the treatment of hypertension, levothyroxine 0.1 mg PO QAM, and simvastatin 40 mg PO QAM. She has no history of heart failure, coronary artery disease, or diabetes, all of which could be specific indications for an ACE inhibitor. The patient was given a prescription for hydroxymorphine 2 mg PO Q4H PRN to use daily for pain. The doctor has good reason to suspect that the patient may be drug-seeking.

1. The prescriber requests your assistance in selecting an opioid to mitigate risk and asks what products may have a lesser street value and/or abuse potential. Select the best response:
   a. Extended-release morphine
   b. Replacement of hydroxymorphone IR with a fentanyl patch (presentation of used patches required for renewal)
   c. A and B
d. None of the above

2. If the patient was not receiving warfarin, which of the above medications could be replaced with any number of alternatives so that NSAIDs were a safer option?
   a. Lisinopril
   b. Levothyroxine
c. Simvastatin
d. All of the above
e. None of the above

3. Which of the following are significant risks for issuing an NSAID to this patient?
   a. Concomitant use of lisinopril, because of higher potential for kidney dysfunction
   b. Concomitant use of warfarin, because of higher bleeding risk
c. There is no risk of kidney dysfunction or bleeding if a COX-2 specific NSAID is used.
d. A and B
e. None of the above

4. The patient is ultimately placed on generic extended-release morphine 30 mg PO Q12H, because her insurance co-pays were too high. The doctor reluctantly agreed to this Rx but would give only a 1-week supply. At today’s office visit, the patient complains of severe pruritus and describes it as “bugs crawling under my skin.” She denies shortness of breath, swollen tongue/lips, or a rash. This reaction to morphine is:
   a. A classic allergy to morphine
   b. A result of the 6-beta-hydromorphine metabolite
c. An indicator that all opioids will present the same risk of pruritus
d. A histamine reaction, but not a true allergy
e. None of the above

5. Since this patient had a reaction to morphine, a hydroxylated phenanthrene, which of the following would be reasonable alternative(s) based on their chemistry, irrespective of cost, co-pay, or insurance issues?
   a. Transdermal fentanyl
   b. Codeine
c. All of the above
d. None of the above

D. Patient with nausea, on opiates
A 40-year-old woman has undergone significant breast reduction due to cervical pain that presumably was aggravated by the weight of her breasts. She suffered significant breast pain postoperatively and refused opioids except for unbearable pain, in large part because previous experience with several different opioids for her neck caused significant constipation and severe gastrointestinal upset. For the most part, she endured several weeks of pain.

Now she is taking hydrocodone 10 mg/APAP 500 mg at a dosage of 2 tablets PO Q4H regularly to control pain and has been experiencing increasing bouts of nausea with occasional vomiting and constipation. Although the surgical wound is healing normally, the pain does not seem to be abating; in fact, the breast pain is now described as “shooting and burning” from the incision site and in surrounding areas.

1. The appearance of chronic pain following untreated surgical pain of the breast could be described by:
   a. Respiratory depression
c. Hypo-adrenal syndrome
   b. Neuroplasticity
d. Addiction

2. The pharmacist consults with the prescribing physician and recommends an alternative opioid. He recommends tapentadol, because:
   a. It has less incidence of gastrointestinal upset and constipation.
b. It is the most cost-effective therapy.
c. It has significant dopamine activity lending to its antidepressant properties.
d. It is an effective opioid that is not a controlled substance.

3. Assuming that this patient was using all of the hydrocodone/APAP, what would be your concern as a pharmacist?
   a. That she is addicted
   b. That the acetaminophen dose is too high
c. That the hydrocodone dose is too high
d. All of the above
e. None of the above

4. Which of the following statements is true?
   a. Hydrocodone and fentanyl have a similar chemical structure and are both dehydroxylated.
b. Hydrocodone and methadone have a similar chemical structure and only one is dehydroxylated.
c. Hydrocodone, oxycodone, hydromorphone, and oxymorphone have similar chemical structures.
d. All of the above
Millions suffer from acute or chronic pain every year. According to the American Academy of Pain Medicine (AAPM), reduced productivity caused by pain costs employers somewhere between $60 billion and $100 billion annually. AAPM adds that chronic pain affects 116 million Americans, more than the number of patients affected by diabetes, heart disease, and cancer combined.

Small wonder that the Consumer Healthcare Products Association (CHPA) lists analgesics as the second-highest OTC sales category for 2010 (after cough/cold-related items). And manufacturers have been hard at work adding new products. Aspirin/acetaminophen ... body wraps ... cold packs ... They might be called the ABC’s of new OTC treatments for aches, pains, and bruises.

Aspirin
Bayer HealthCare’s Consumer Care division has introduced Bayer Advanced Aspirin, clinically proven to relieve tough pain twice as fast as previous Bayer Aspirin tablets did. Two dental-pain efficacy studies evaluated Bayer Advanced Aspirin Extra Strength 500-mg and Regular 325-mg tablets and found that both dosages demonstrated meaningful faster pain relief. Bayer Advanced Aspirin dissolves 6 times more quickly, enters the bloodstream 4 times as fast, and provides pain relief twice as fast as before.

Acetaminophen
Adults are not the only ones dealing regularly with pain. Infants, toddlers, and children endure their share of pain caused by issues ranging from teething to falls to chronic ailments. For babies and children, acetaminophen is among the most commonly used agents of pain and fever relief. FDA has noted that it is generally safe and effective “if you follow the directions on the package.”

An FDA Advisory Panel met this past May to discuss how to minimize medication errors and make children’s OTC medications that contain acetaminophen safer to use. Among its recommendations was limitation of children’s acetaminophen products to a single strength instead of the more confusing 7 strengths available in liquid, chewable, and tablet forms. The panel also suggested that standards for dosing devices be established, as some companies are using milliliters while others use cubic centimeters or teaspoons.

Also in May, CHPA announced plans to convert liquid acetaminophen products for children under 12 years of age to just 1 strength (160 mg/5 mL). In addition, the industry is voluntarily standardizing the unit of measurement “mL” on dosing devices for these products.

In July, Prestige Brands Inc.’s new Pedia Care and Little Remedies single-concentration acetaminophen products began reaching store shelves. Both products will offer additional product enhancements, including age-appropriate dosing devices:
- Infant products will now contain a special dosing syringe and flow restrictors on the bottles.
- Children’s products, for ages 2 to 11 years, will feature bottles with flow restrictors and will continue to include dosing cups.
- Both infant and children’s formula...
CHPA noted that during the transition, “there will be a period when both concentrations of infants’ acetaminophen liquid products (the concentrated drops and the new 160 mg/5 mL concentration) will be available in stores and in medicine cabinets.”

Consumers may need extra help reading and comparing product labels. Albert Hwang, vice president, OTC products for Prestige Brands, stated in the company’s product announcement, “The new infant formula is less concentrated and the dose is therefore more than in the older infant formulation. And while reading and following package directions is always recommended to obtain accurate dosing instructions, it will be even more important while the 2 concentrations are available.”

Homeopathic
For those looking for homeopathic pain relief, Boiron is introducing Arnicare Tablets, containing the single active ingredient Arnica montana, a popular botanical in use throughout the world since the 1500s.

The quick-dissolving tablets help relieve muscle aches and pain from minor injuries, overexertion, and falls; they also help reduce pain, swelling, and discoloration from bruises. Arnicare Tablets do not cause drowsiness. They work naturally without side effects or drug interactions and may be safely used in conjunction with Arnicare topicals, which are available in gel, cream, or ointment formulas. Product should reach store shelves in early fall.

Hot/cold products
Health Enterprises has added 3 new hot/cold items to its pain-relief category.

The 9”x24” Back & Body Wrap can be used on large areas of the body to relieve pain and reduce swelling. It can be placed in the freezer for cool therapy or warmed in the microwave for heat therapy. The wrap will not leak if overheated and remains flexible when frozen.

The Instant Cold & Reusable Hot/Cold Pack can be reused either hot or cold and contains no ammonium nitrate. Unlike other instant cold packs that are disposed of after 20 minutes of use, the Instant Cold & Reusable Hot/Cold Pack can be reused either hot or cold. The consumer squeezes the product to activate it. After it returns to room temperature, it can be placed in the freezer for cold therapy or in the microwave for heat therapy and reused.

Dana K. Cassell, a frequent contributor to Drug Topics, lives in North Stratford, N.H.
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When President Obama was facing challenges in negotiations over raising the debt ceiling, he spoke to the nation, urging the American people to make their voices heard and contact their members of Congress to pressure them to come to what he called a balanced solution.

The next day, many Americans heeded this call to action; it was reported that website traffic had crashed several members’ websites and that the capitol switchboard was handling more than 35,000 calls per hour, almost double the average rate.

After a compromise was reached, the President thanked Americans, saying that it was their phone calls and e-mails that made such a deal possible.

When people express their opinions and hold their elected officials accountable, we see the essence of democracy.

Making our voices heard
As independent community pharmacists, we are both healthcare providers and small-business owners, and we face several challenges that impact both these important roles. In order to effect positive solutions to these challenges, we too must make our voices heard.

As small-business owners, we are squeezed by the pharmacy benefit managers (PBMs), who reimburse us at rates that are often lower than our acquisition costs. They also seek to further swell their coffers through burdensome audits that often penalize us for minor bookkeeping errors, when to search for intentional fraudulent practices would be more to the point.

This squeeze may be further exacerbated by the recently proposed merger of PBM giants Express Scripts and Medco, which would create a behemoth in the PBM industry, to the detriment of patients and pharmacists.

In our role as healthcare providers, we spend many hours preventing errors and serving the patients who rely on our counsel and expertise. They depend on us to help them use their medications correctly and adhere to their prescription regimens properly. Many of us have heard from patients who received the wrong prescription by mail order or did not receive their mail-order medications on time, and who called upon us because we were the only healthcare professional they could turn to for assistance.

Some independent pharmacists have simply accepted these PBM-generated challenges as a fact of doing business, one that is often derided as also commoditizing the profession of pharmacy. Others have been forced to close their stores because they could not withstand these PBM practices.

This problem can be remedied if enough of us take the action necessary to bring about change. We need to make our voices heard, and we need to support legislation that has been introduced in Congress that helps to level the playing field.

The Pharmacy Competition and Consumer Choice Act, H.R. 1971/S. 1058, addresses many PBM abuses. It prohibits practices such as extrapolation and it forces PBMs to focus audits on identifying acts of intentional fraud, which is where they should be focused, rather than on penalizing pharmacies for typographical or bookkeeping errors.

In addition, H.R. 1946, the “Preserving Our Hometown Independent Pharmacies Act,” would allow independent pharmacies to join together to negotiate contracts with PBMs in the way retail chains negotiate now. To be sure, the PBMs would still have the upper hand, but at least independent pharmacies would have a stronger voice during negotiations.

We all need to contact our members of Congress and urge them to support this legislation.

We also need to express our opposition to further concentration among PBMs by demanding that our members of Congress urge the FTC to block the ESI-Medco merger.

While these legislative solutions may not address all our challenges, they are important steps forward. As pharmacists, we must take it upon ourselves to educate health-plan sponsors and our elected officials about our unique role in healthcare. And we must impress upon them the necessity of their support for solutions to the challenges facing our industry. One way for you to do this is to visit www.ncpa-actioncenter.com and send an e-mail to your members of Congress.

After all, if we do not tell our story, who will?

Bob Greenwood, RPh

Bob Greenwood is president of the National Community Pharmacists Association (http://www.ncpanet.org/).
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