Counterfeit drug war continues 21 | When does compounding become manufacturing? 42 | Study: Post-MI beta blocker doses are too low 29

DrugTopics.com

Drug Topics

VOL. 154 NO. 12

Voice of the Pharmacist

December 2010

2011 Business Outlook Survey

Community and hospital pharmacists prepare to steer their course PAGE 22

CE CREDIT: 2.0 ACPE

An update on *Clostridium difficile* infection PAGE 30

Earn CE credit for this activity at DrugTopics.com

AN ADVANSTAR PUBLICATION

Visit us at ASHP Booth 677

What's most important in outpatient pharmacies?

Keeping patients safe.

The challenges and demands of an outpatient pharmacy can take away from patient care. QS/1®'s NRx® supports outpatient pharmacies with easy-to-use processing and multiple inventory management, including 340B. Our end-to-end pharmacy system and services work together so you can work with safety and confidence. To provide great service. To improve lives. **Every day.**

QS/1®

1.800.231.7776
www.qs1.com

With your support, Amneal has become the fastest growing generic manufacturer in the U.S.*

- Superior quality products all made in the USA
- Fully FDA cGMP-compliant manufacturing facilities
- Widely recognized Customer Response team
- Market-competitive pricing

amneal®
PHARMACEUTICALS

*IMS Health, National Prescription Audit, June 2010 - Prescriptions of unbranded generics

Drug Topics®

Editorial Mission: *Drug Topics*, a monthly news magazine guided by an editorial advisory board of pharmacy experts, reports on all phases of community, retail, and health-system issues and trends. We offer a forum for the bench pharmacist to share practical ideas for better pharmacy management and patient care.

EDITORIAL

DIRECTOR OF EDITORIAL Dan Schwartz

EDITOR-IN-CHIEF Julia Talsma
(440) 891-2792 jtalsma@advanstar.com

MANAGING EDITOR Julianne Stein
(440) 826-2834 jstein@advanstar.com

ASSOCIATE EDITOR Christina Phillis
(440) 891-2766 cphillis@advanstar.com

EDITORIAL ASSOCIATE Alicia Hoisington

CONTRIBUTING EDITORS Christine Blank, Fred Gebhart, Jim Plagakis, RPh, Gretchen L. Schwenker, PhD

SALES AND MARKETING

PUBLISHER James Granato
(732) 346-3071 jgranato@advanstar.com

ACCOUNT MANAGER Lisa Noble
(732) 346-3060 lnoble@advanstar.com

SALES SUPPORT ADMINISTRATOR Samyu Ganesh
(732) 346-3077 sganesh@advanstar.com

LIST MANAGER Tamara Phillips
(440) 891-2773 / tphillips@advanstar.com

PERMISSIONS AND LICENSING Maureen Cannon
(440) 891-2742 or (800) 225-4569 ext. 2742
Fax: (440) 891-2650 / mcannon@advanstar.com

DISPLAY AND CLASSIFIED ADS Heather Schlosser
(440) 891-2779 hschlosser@advanstar.com

CLASSIFIED RECRUITMENT Joanna Shippoli
800-225-4569 x 2615 jshippoli@advanstar.com

REPRINT SERVICES
(800) 290-5460, ext. 100 / AdvanstarReprints@theYGSgroup.com
(717) 505-9701, ext. 100 (international inquiries)

PRODUCTION

SENIOR PRODUCTION MANAGER Terri Johnstone
(218) 740-6310

CIRCULATION

SUBSCRIPTION CUSTOMER SERVICE/ADDRESS CHANGES
(877) 922-2022 / magazines@superfill.com
PO Box 6079, Duluth, MN 55806-6079, USA

CONTACT US

24950 COUNTRY CLUB BLVD., SUITE 200
NORTH OLMSTED, OHIO 44070
MAIN NUMBER: (440) 243-8100
MAIN FAX NUMBER: (440) 891-2735
CUSTOMER SERVICE: (877) 922-2022
CLASSIFIED AND RECRUITMENT SALES: (800) 225-4569
E-MAIL ADDRESS: DRUGTOPICS@ADVANSTAR.COM
WEBSITE: HTTP://WWW.DRUGTOPICS.COM

ADVANSTAR COMMUNICATIONS

Joseph Loggia
CHIEF EXECUTIVE OFFICER

Tom Ehardt
EXECUTIVE VICE PRESIDENT, CHIEF ADMINISTRATIVE OFFICER

Steve Sturm
EXECUTIVE VICE PRESIDENT, CHIEF MARKETING OFFICER

Ted Alpert
EXECUTIVE VICE PRESIDENT, FINANCE, CFO

Georgiann DeCenzo
EXECUTIVE VICE PRESIDENT

Eric Lisman
EXECUTIVE VICE PRESIDENT

J. Vaughn
VICE PRESIDENT, INFORMATION TECHNOLOGY

Francis Heid
VICE PRESIDENT, MEDIA OPERATIONS

Nancy Nugent
VICE PRESIDENT, HUMAN RESOURCES

Ward D. Hewins
VICE PRESIDENT, GENERAL COUNSEL

Danny Phillips
EXECUTIVE VICE PRESIDENT

Chris DeMoulin
EXECUTIVE VICE PRESIDENT

℞ only

Indication: Metformin hydrochloride tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes mellitus.

Adverse reactions: The most common adverse reactions, reported in > 5% of metformin-treated patients, are: diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

Contraindications and precautions:
Metformin hydrochloride tablets are contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
2. Known hypersensitivity to metformin hydrochloride.
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

Before initiation of metformin therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and metformin discontinued if evidence of renal impairment is present.

WARNINGS: LACTIC ACIDOSIS

Lactic acidosis is a rare but serious, metabolic complication that can occur because of metformin accumulation. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function and by use of the minimum effective dose. Other conditions that increase the risk of lactic acidosis include: sepsis, dehydration, excess alcohol intake, hepatic insufficiency and acute congestive heart failure.

When lactic acidosis occurs, it is fatal in approximately 50% of cases. The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years).

The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, metformin should be discontinued and the patient hospitalized immediately.

Metformin treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis.

Please see adjacent Brief Summary of Prescribing Information, including BOXED WARNING with complete details about lactic acidosis.

Mylan Metformin is Berry Nice.

Introducing

Blackberry-scented

***Mylan* Metformin Hydrochloride™**

Tablets, USP

A metformin tablet that doesn't smell like fish.

- A *blackberry-scented* formulation designed to mask the "fishy smell" associated with some metformin tablets[1]
- Therapeutically equivalent to Glucophage®*
- Available in 500 mg, 850 mg and 1000 mg tablets

*Registered trademark of Bristol-Myers Squibb.

Reference: 1. Pelletier AL, Butler AM, Gillies RA, et al. Metformin Stinks, Literally. *Ann Intern Med*. 2010;152:267-268.

METFORMIN HYDROCHLORIDE TABLETS, USP
500 mg, 850 mg and 1000 mg

Rx Only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE: Metformin hydrochloride tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes mellitus.

CONTRAINDICATIONS: Metformin hydrochloride tablets are contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS).
2. Known hypersensitivity to metformin hydrochloride.
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also PRECAUTIONS.)

WARNINGS:

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 mcg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug-related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS.)

PRECAUTIONS: General: ***Macrovascular Outcomes:*** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin hydrochloride tablets or any other anti-diabetic drug.

Monitoring of Renal Function: Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive metformin. In patients with advanced age, metformin should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥ 80 years of age, renal function should be monitored regularly and, generally, metformin should not be titrated to the maximum dose (see WARNINGS and DOSAGE AND ADMINISTRATION in full prescribing information).

Before initiation of metformin therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and metformin discontinued if evidence of renal impairment is present.

Use of Concomitant Medications That May Affect Renal Function or Metformin Disposition: Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see PRECAUTIONS: Drug Interactions), should be used with caution.

Radiologic Studies Involving the Use of Intravascular Iodinated Contrast Materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, metformin should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be normal.

Hypoxic States: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on metformin therapy, the drug should be promptly discontinued.

Surgical Procedures: Metformin therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving metformin.

Impaired Hepatic Function: Since impaired hepatic function has been associated with some cases of lactic acidosis, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} Levels: In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin and any apparent abnormalities should be appropriately investigated and managed (see PRECAUTIONS: Laboratory Tests).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes: A patient with type 2 diabetes previously well controlled on metformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, metformin must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS).

Hypoglycemia: Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold metformin and temporarily administer insulin. Metformin may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with either metformin or sulfonylurea monotherapy, combined therapy with metformin and sulfonylurea may result in a response. Should secondary failure occur with combined metformin/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

Information for Patients: Patients should be informed of the potential risks and benefits of metformin and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections, should be explained to patients. Patients should be advised to discontinue metformin immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving metformin.

Metformin hydrochloride tablets alone do not usually cause hypoglycemia, although it may occur when metformin is used in conjunction with oral sulfonylureas and insulin. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. (See Patient Information in full prescribing information.)

Laboratory Tests: Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also DOSAGE AND ADMINISTRATION in full prescribing information).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

Drug Interactions (Clinical Evaluation of Drug Interactions Conducted with Metformin):
Glyburide: In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see DOSAGE AND ADMINISTRATION: Concomitant Metformin Hydrochloride Tablet and Oral Sulfonylurea Therapy in Adult Patients in full prescribing information).

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Pregnancy: ***Teratogenic Effects. Pregnancy Category B:*** Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, metformin should not be used during pregnancy unless clearly needed.

There are no adequate and well controlled studies in pregnant women with metformin. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers: Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If metformin is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: The safety and effectiveness of metformin for the treatment of type 2 diabetes have been established in pediatric patients ages 10 to 16 years (studies have not been conducted in pediatric patients below the age of 10 years). Use of metformin in this age group is supported by evidence from adequate and well controlled studies of metformin in adults with additional data from a controlled clinical study in pediatric patients ages 10 to 16 years with type 2 diabetes, which demonstrated a similar response in glycemic control to that seen in adults. (See CLINICAL PHARMACOLOGY: Pediatric Clinical Studies in full prescribing information.) In this study, adverse effects were similar to those described in adults. (See ADVERSE REACTIONS: Pediatric Patients.) A maximum daily dose of 2000 mg is recommended. (See DOSAGE AND ADMINISTRATION: Recommended Dosing Schedule: Pediatrics in full prescribing information.)

Geriatric Use: Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, metformin should only be used in patients with normal renal function (see CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY: Pharmacokinetics in full prescribing information). Because aging is associated with reduced renal function, metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of metformin (see also WARNINGS and DOSAGE AND ADMINISTRATION in full prescribing information).

ADVERSE REACTIONS: In a U.S. double-blind clinical study of metformin in patients with type 2 diabetes, a total of 141 patients received metformin therapy (up to 2550 mg per day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the metformin patients, and that were more common in metformin- than placebo-treated patients, are listed in Table 1.

Table 1. Most Common Adverse Reactions (> 5%) in a Placebo-Controlled Clinical Study of Metformin Monotherapy*

Adverse Reaction	Metformin Monotherapy (n = 141)	Placebo (n = 145)
	% of Patients	
Diarrhea	53.2	11.7
Nausea/Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal Discomfort	6.4	4.8
Headache	5.7	4.8

* Reactions that were more common in metformin- than placebo-treated patients.

Diarrhea led to discontinuation of study medication in 6% of patients treated with metformin. Additionally, the following adverse reactions were reported in ≥ 1 to $\leq 5\%$ of metformin patients and were more commonly reported with metformin than placebo: abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

Pediatric Patients: In clinical trials with metformin in pediatric patients with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

OVERDOSAGE: Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see WARNINGS). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Manufactured in India by:
Matrix Laboratories Limited
Secunderabad — 500 003, India
Code No.: MH/DRUGS/25/NKD/89
Manufactured for:

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

REVISED JANUARY 2010
BS:MX:METB:R1ppt

Vol. 154 No. 12
December 2010

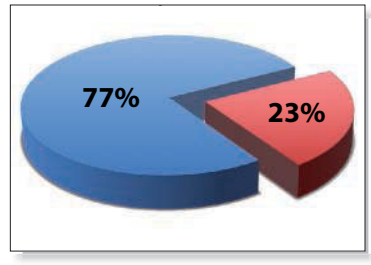
Drug Topics®

GETTY IMAGES/COMSTOCK IMAGES

DIGITAL EDITION

Subscribe to the monthly digital edition of *Drug Topics* and receive the journal electronically with live links. Go to http://drugtopics.com/digital.

Drug Topics (ISSN# 0012-6616) is published monthly and Drug Topics Digital Edition (ISSN# 1937-8157) is issued every week by Advanstar Communications, Inc., 131 West First St., Duluth, MN 55806-2065. One-year subscription rates: $61 in the United States & Possessions; $109 in Canada and Mexico; all other countries, $109. Single copies (prepaid only) $10 in the United States; $10 in Canada and Mexico; all other countries, $15. Include $6 per copy for U.S. postage and handling. Periodicals postage paid at Duluth, MN 55806 and additional mailing offices. POSTMASTER: Please send address changes to Drug Topics, P.O. Box 6079, Duluth, MN 55806-6079. Canadian G.S.T. number: R-124213133RT001. Publications Mail Agreement Number 40017597. Printed in the U.S.A. Subscription inquiries/address changes: toll-free (888) 527-7008, or dial direct (218) 723-9477.



COVER STORY

COUNTER POINTS

ISSUES & TRENDS

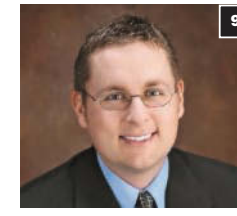
CHAINS & BUSINESS

CLINICAL

REGULATORY & LEGAL

PRODUCT UPDATES

CONTINUING EDUCATION



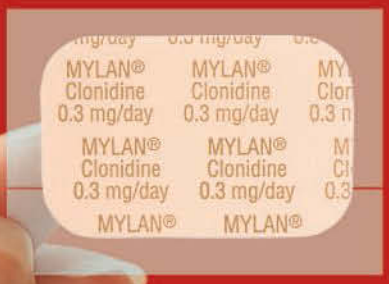
CE

WWW.DRUGTOPICS.COM

- Visit the *Drug Topics* blog: A new forum for pharmacist voices (http://drugtopics.com/blog)
- FDA hears testimony on approval pathway for biosimilars (http://drugtopics.com/biosimilars)
- The future of genetics and genomics (http://drugtopics.com/genomics)
- Ohio becomes a hub for prescription monitoring (http://drugtopics.com/hub)

Patch Appeal

Actual Size



Actual Size

Small size. No metal. Easy-open packaging.

The *Mylan* CLONIDINE TRANSDERMAL SYSTEM is much smaller than the Par Generic Clonidine patch—closer in size to the brand.[1,2] It contains no metal so it doesn't need to be removed during an MRI to avoid potential skin burns;[1,2] and it has an easy-open tab so there's no need to cut the pouch open with scissors like the Par patch.[1]

The *Mylan* CLONIDINE TRANSDERMAL SYSTEM is designed with patients in mind.

Mylan Clonidine Transdermal System, USP™

INDICATION: Clonidine Transdermal System is indicated in the treatment of hypertension. It may be employed alone or concomitantly with other antihypertensive agents.

IMPORTANT SAFETY INFORMATION: Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in symptoms such as nervousness, agitation, headache, and confusion accompanied or followed by a rapid rise in blood pressure and elevated catecholamine plasma concentrations. Such reactions appear to be associated with higher doses or continuation of concomitant beta-blocker treatment and special caution is therefore advised in these situations.

Rare instances of hypertensive encephalopathy, cerebrovascular accidents and death have been reported after clonidine withdrawal. When discontinuing therapy with Clonidine, the physician should reduce the dose gradually over 2 to 4 days to avoid withdrawal symptomatology.

The most frequent adverse reactions to Clonidine are dermatological, including erythema and/or pruritus. Systemic adverse reactions with transdermal clonidine were mild and included dry mouth, drowsiness, fatigue, headache, and lethargy and sedation.

Please see adjacent Brief Summary of Prescribing Information.

References: **1.** Par Clonidine Transdermal System Prescribing Information. **2.** Catapres-TTS Prescribing Information.

Mylan® Pharmaceuticals

Proven Medicine. Just More Affordable.™

800.RX.MYLAN • www.mylanpharms.com

CLONIDINE TRANSDERMAL SYSTEM, USP

℞ only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE: CLONIDINE TRANSDERMAL SYSTEM, USP is indicated in the treatment of hypertension. It may be employed alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS: CLONIDINE TRANSDERMAL SYSTEM should not be used in patients with known hypersensitivity to clonidine or to any other component of the therapeutic system.

WARNINGS: Withdrawal: Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and confusion accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. The likelihood of such reactions to discontinuation of clonidine therapy appears to be greater after administration of higher doses or continuation of concomitant beta-blocker treatment and special caution is therefore advised in these situations. Rare instances of hypertensive encephalopathy, cerebrovascular accidents and death have been reported after clonidine withdrawal. When discontinuing therapy with CLONIDINE TRANSDERMAL SYSTEM, the physician should reduce the dose gradually over 2 to 4 days to avoid withdrawal symptomatology.

An excessive rise in blood pressure following discontinuation of CLONIDINE TRANSDERMAL SYSTEM therapy can be reversed by administration of oral clonidine hydrochloride or by intravenous phentolamine. If therapy is to be discontinued in patients receiving a beta-blocker and clonidine concurrently, the beta-blocker should be withdrawn several days before the gradual discontinuation of CLONIDINE TRANSDERMAL SYSTEM.

ADVERSE REACTIONS: Clinical trial experience with CLONIDINE TRANSDERMAL SYSTEM: Most systemic adverse effects during CLONIDINE TRANSDERMAL SYSTEM therapy have been mild and have tended to diminish with continued therapy. In a 3-month multiclinic trial of CLONIDINE TRANSDERMAL SYSTEM in 101 hypertensive patients, the systemic adverse reactions were, dry mouth (25 patients) and drowsiness (12), fatigue (6), headache (5), lethargy and sedation (3 each), insomnia, dizziness, impotence/sexual dysfunction, dry throat (2 each) and constipation, nausea, change in taste and nervousness (1 each).

In the above mentioned 3-month controlled clinical trial, as well as other uncontrolled clinical trials, the most frequent adverse reactions were dermatological and are described below.

In the 3-month trial, 51 of the 101 patients had localized skin reactions such as erythema (26 patients) and/or pruritus, particularly after using an adhesive cover throughout the 7-day dosage interval. Allergic contact sensitization to CLONIDINE TRANSDERMAL SYSTEM was observed in 5 patients. Other skin reactions were localized vesiculation (7 patients), hyperpigmentation (5), edema (3), excoriation (3), burning (3), papules (1), throbbing (1), blanching (1), and a generalized macular rash (1).

In additional clinical experience, contact dermatitis resulting in treatment discontinuation was observed in 128 of 673 patients (about 19 in 100) after a mean duration of treatment of 37 weeks. The incidence of contact dermatitis was about 34 in 100 among white women, about 18 in 100 in white men, about 14 in 100 in black women, and approximately 8 in 100 in black men. Analysis of skin reaction data showed that the risk of having to discontinue CLONIDINE TRANSDERMAL SYSTEM treatment because of contact dermatitis was greatest between treatment weeks 6 and 26, although sensitivity may develop either earlier or later in treatment.

In a large-scale clinical acceptability and safety study by 451 physicians in a total of 3,539 patients, other allergic reactions were recorded for which a causal relationship to CLONIDINE TRANSDERMAL SYSTEM was not established: maculopapular rash (10 cases); urticaria (2 cases); and angioedema of the face (2 cases), which also affected the tongue in one of the patients.

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

Body as a Whole: Fever; malaise; weakness; pallor; and withdrawal syndrome.

Cardiovascular: Congestive heart failure; cerebrovascular accident; electrocardiographic abnormalities (i.e., bradycardia, sick sinus syndrome disturbances and arrhythmias); chest pain; orthostatic symptoms; syncope; increases in blood pressure; sinus bradycardia and atrioventricular (AV) block with and without the use of concomitant digitalis; Raynaud's phenomenon; tachycardia; bradycardia; and palpitations.

Central and Peripheral Nervous System/Psychiatric: Delirium; mental depression; hallucinations (including visual and auditory); localized numbness; vivid dreams or nightmares; restlessness; anxiety; agitation; irritability; other behavioral changes; and drowsiness.

Dermatological: Angioneurotic edema; localized or generalized rash; hives; urticaria; contact dermatitis; pruritus; alopecia; and localized hypo or hyper pigmentation.

Gastrointestinal: Anorexia and vomiting.

Genitourinary: Difficult micturition; loss of libido; and decreased sexual activity.

Metabolic: Gynecomastia or breast enlargement and weight gain.

Musculoskeletal: Muscle or joint pain; and leg cramps.

Ophthalmological: Blurred vision; burning of the eyes and dryness of the eyes.

Adverse Events Associated with Oral Clonidine Therapy: Most adverse effects are mild and tend to diminish with continued therapy. The most frequent (which appear to be dose-related) are dry mouth, occurring in about 40 of 100 patients; drowsiness, about 33 in 100; dizziness, about 16 in 100; constipation and sedation, each about 10 in 100. The following less frequent adverse experiences have also been reported in patients receiving clonidine hydrochloride, USP tablets, but in many cases patients were receiving concomitant medication and a causal relationship has not been established.

Body as a Whole: Fatigue, fever, headache, pallor, weakness, and withdrawal syndrome. Also reported were a weakly positive Coombs' test and increased sensitivity to alcohol.

Cardiovascular: Bradycardia, congestive heart failure, electrocardiographic abnormalities (i.e., sinus node arrest, junctional bradycardia, high degree AV block and arrhythmias), orthostatic symptoms, palpitations, Raynaud's phenomenon, syncope, and tachycardia. Cases of sinus bradycardia and AV block have been reported, both with and without the use of concomitant digitalis.

Central Nervous System: Agitation, anxiety, delirium, delusional perception, hallucinations (including visual and auditory), insomnia, mental depression, nervousness, other behavioral changes, paresthesia, restlessness, sleep disorder, and vivid dreams or nightmares.

Dermatological: Alopecia, angioneurotic edema, hives, pruritus, rash, and urticaria.

Gastrointestinal: Abdominal pain, anorexia, constipation, hepatitis, malaise, mild transient abnormalities in liver function tests, nausea, parotitis, pseudo-obstruction (including colonic pseudo-obstruction), salivary gland pain, and vomiting.

Genitourinary: Decreased sexual activity, difficulty in micturition, erectile dysfunction, loss of libido, nocturia, and urinary retention.

Hematologic: Thrombocytopenia.

Metabolic: Gynecomastia, transient elevation of blood glucose or serum creatine phosphokinase, and weight gain.

Musculoskeletal: Leg cramps and muscle or joint pain.

Oro-otolaryngeal: Dryness of the nasal mucosa.

Ophthalmological: Accommodation disorder, blurred vision, burning of the eyes, decreased lacrimation, and dryness of the eyes.

OVERDOSAGE: Hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis. The frequency of CNS depression may be higher in children than adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma and seizures. Signs and symptoms of overdose generally occur within 30 minutes to 2 hours after exposure. As little as 0.1 mg of clonidine has produced signs of toxicity in children.

If symptoms of poisoning occur following dermal exposure, remove all CLONIDINE TRANSDERMAL SYSTEMS. After their removal, the plasma clonidine levels will persist for about 8 hours, then decline slowly over a period of several days. Rare cases of CLONIDINE TRANSDERMAL SYSTEM poisoning due to accidental or deliberate mouthing or ingestion of the patch have been reported, many of them involving children.

There is no specific antidote for clonidine overdosage. Ipecac syrup-induced vomiting and gastric lavage would not be expected to remove significant amounts of clonidine following dermal exposure. If the patch is ingested, whole bowel irrigation may be considered and the administration of activated charcoal and/or cathartic may be beneficial. Supportive care may include atropine sulfate for bradycardia, intravenous fluids and/or vasopressor agents for hypotension and vasodilators for hypertension. Naloxone may be a useful adjunct for the management of clonidine-induced respiratory depression, hypotension and/or coma; blood pressure should be monitored since the administration of naloxone has occasionally resulted in paradoxical hypertension. Tolazoline administration has yielded inconsistent results and is not recommended as first-line therapy. Dialysis is not likely to significantly enhance the elimination of clonidine.

The largest overdose reported to date, involved a 28-year old male who ingested 100 mg of clonidine hydrochloride powder. This patient developed hypertension followed by hypotension, bradycardia, apnea, hallucinations, semicoma, and premature ventricular contractions. The patient fully recovered after intensive treatment. Plasma clonidine levels were 60 ng/mL after 1 hour, 190 ng/mL after 1.5 hours, 370 ng/mL after 2 hours, and 120 ng/mL after 5.5 and 6.5 hours. In mice and rats, the oral LD_{50} of clonidine is 206 and 465 mg/kg, respectively.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED NOVEMBER 2009
BS:CTS:R9

As part of our ongoing initiative to encourage dialogue between pharmacists working in different environments, each month Drug Topics *presents an editorial by a guest columnist writing on a subject of his or her choice. Send us your feedback; we look forward to sharing it in an upcoming issue.*

Guest editorial

Marvin Moore, PharmD

Time to get out the big fat crayon

I continually receive surveys from pharmacy organizations, pharmacy practice residents, university faculty, and others, asking for my opinion on medication therapy management (MTM). The frustrating thing is that these surveys focus mainly on barriers.

There is usually a section instructing me to checkmark all the barriers to providing MTM that I perceive. Then the survey asks me to rank the barriers according to some order of magnitude. Next I'm asked how I feel about certain barriers (e.g., "On a scale of 1 to 10, how does the lack of patient awareness affect the number of MTM services you provide?"). By the time I get to the last section (which, by the way, is a blank box asking me to list any other barriers that I may know of, so that they can undoubtedly add more items to their previous sections), I just want to shout, "ENOUGH, ALREADY!"

Yes, barriers to providing MTM do exist for pharmacists. I'm not about to say that providing MTM is as easy (or as comfortable) as verifying prescriptions, counseling a patient, or scribbling down a refill authorization. But we all have to figure out a way to do it — we should feel an obligation to do it.

Many community pharmacists are providing MTM in one form or another, although not enough. The literature is full of examples of pharmacists successfully implementing MTM and providing high-level patient care in Asheville Project-type programs.

- The Pharmacy Society of Wisconsin created an MTM program that reimburses pharmacists in the state for both acute interventions and more comprehensive care.
- The federal government recognized the importance of MTM when it created Medicare Part D.
- Even the medical profession is claiming that pharmacists are underutilized and need to be part of the team.

Yet it seems to me as if provision of MTM by pharmacists is more of a niche than the norm right now. This has to change.

If you are a pharmacist in an independent community pharmacy that is not currently providing MTM, start! If you don't know how, pick up the phone and call one of the thousands who have figured it out.

If you are in an upper-level management position in a chain pharmacy organization that is not allowing pharmacists time to provide MTM, figure out a way! Make it a priority. The pharmacists working under you need your support. Start with paying them to be out of the workflow 1 hour a week. Offer them an incentive to provide MTM, and hold them accountable. Create new ways to make use of technicians. Think of it as an investment in the future … an advancement of the profession.

Let's stop focusing on barriers and listing reasons why we cannot provide MTM. Years ago (when what is now referred to as MTM was called pharmaceutical care) a pharmacy professor for whom I have a great deal of respect would from time to time be confronted by a pharmacist or student who was skeptical about providing high-level patient care. When said skeptic would rattle off the typical laundry list of issues (lack of time, lack of tools, lack of space, etc.) that stood in the way, the professor's response was "You can provide pharmaceutical care with a blank sheet of paper and a big fat crayon. Just do it."

I think it's time for all of us to start coloring.

Marvin Moore, PharmD, *is a community pharmacist in Two Rivers, Wis., and a* Drug Topics *board member. He can be reached at marvmoore4@hotmail.com.*

Letters

Placebos and healing

"Re: "When to Lie?" [Regulatory & Legal, November 2010]: ...Daniel Moerman, a medical anthropologist and author of dozens of peer-reviewed articles on the placebo effect, warns that to withhold the prescription of placebos could be considered unethical in one sense, as they can be powerfully therapeutic. He particularly warns against prohibiting the use of placebos in clinical trials, in which researchers face the same ethical dilemma as every doctor and pharmacist."

Regulatory & Legal ETHICAL PRACTICE

A question of ethics: When to lie?

Kenneth R. Baker, BS Pharm, JD

I teach a course in ethics at Midwestern University College of Pharmacy in Glendale, Ariz. Recently I presented my students with an ethical problem, asking them to decide on a correct course of action. Their answers surprised me so much that I presented the same problem to some practicing pharmacists over the next week. In every case, the answers given by the students were different from the responses of the practicing pharmacists.

The problem I set was this. The student, now a graduate pharmacist, is directed by the boss, the pharmacist-in-charge (PIC), to fill a prescription by emptying the contents of a C III sedative capsule and replacing them with lactose. The PIC explains that the doctor is prescribing a placebo and that over the past few months the pharmacist and physician have been slowly replacing active ingredient with inactive ingredient, until now the capsules contain only lactose. The new capsules are working as well as the regular medication worked, and the patient reports that she is sleeping well throughout the night.

The PIC then tells the student/pharmacist to label the prescription with the name of the regular C III sedative and to store, in counseling the patient, the strength of the drug and the importance of avoiding an overdose. In other words, the student is told to lie to the patient. Then the PIC departs; he will not return until his regular shift the following day.

The class assignment was to work through a decision-tree algorithm leading to the ultimate decision: What would the student/pharmacist do when the patient arrives?

Not one of the students was willing to fill the prescription or counsel the patient if it meant lying. They came to this conclusion in spite of the fact that they had been assigned to watch 2 videos extolling the necessity and use of placebos. Intellectually, the students understood the value of the placebo effect, but somehow the situation was different when it became a question of what the students were willing to do to make the patient believe in the placebo.

If a pharmacist believes that he or she cannot participate in a deception, what are the alternatives?

In this instance, the student/pharmacist could tell the patient that she will have to wait to pick up her prescription until the PIC is on duty.

The practicing pharmacists saw no ethical problem in the concept that sometimes it is okay to lie, that issues are not always black and white, but can be gray ...

Would the answer ever be to tell the patient the truth? In that case, the patient would learn that her doctor and her regular pharmacist had been lying to her.

When the same question was presented to 6 pharmacists who had been practicing for several years, they gave the opposite answer. Every one of them would fill the prescription by replacing the active ingredients with an inert substance. In addition, all of them would counsel the patient as if she were receiving the drug named on the label.

They all understood that the label was technically wrong and that there was a risk that the patient would someday discover the deception. However, all were strongly motivated to provide the patient with the full effect of the prescribed medication, even though it was the placebo effect that had actually been prescribed.

The practicing pharmacists saw no ethical problem in the concept that sometimes it is okay to lie, that issues are not always black and white, but can be gray, and that choices may depend on the consequences of the act.

Who is right? Perhaps it is heartening to find that at some early stage in our careers, our ethical values are absolute: It is never okay to lie to a patient. To students, virtues are pure and ethics are black and white, with little contrast.

Perhaps it is also good to find that as we move through life the choices become more difficult, as we discover when we deal with real patients and find that the consequences of our actions can have a real effect. The 6 older, practicing pharmacists have all had to make tough choices; some have actually participated in placebo treatment.

It would be interesting to ask today's students the same question in 20 years.

How would you answer?

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

KEN BAKER *consults in the areas of pharmacy error reduction, communication, and risk management. He is a pharmacist and an attorney of counsel with the Arizona law firm Renaud Cook Drury Mesaros, PA. Contact him at kenb@renaudcookdrury.com.*

58 DRUG TOPICS November 2010 WWW.DRUGTOPICS.COM

For more from Robert Speers, including details of a groundbreaking study mixing placebo prescriptions with prescriptions for specific therapeutic agents, go to the new DT Blog at www.drugtopics.com.

Robert Speers, MA
BOULDER, COLO.

Context is everything

During my 31 years of pharmacy practice, I have been asked to fill capsules for the placebo effect. Each time, I did fill the prescription with the placebo, after I evaluated the patient's usage and abuse to determine that the physician's choice for placebo was the correct therapy and in the best interests of the patient. Most of these patients were abusing their prescription drugs. It worked every time, and I never had a problem with patient or family.

As a Christian pharmacist, I do not think that deception or a lie is OK unless it is in the best interests of patient care. I did not lie to the patients when counseling, as most of these prescriptions were for refills.

Students have not seen this type of patient in a practical setting and lack the first-hand knowledge to make this call. Believe me, when they see the patients who need this therapy, they will quickly change their minds.

Mark Barclay, RPh
VENICE, FLA.

Score 1 for placebo ... make that 2

In 1957, I was a brand-new pharmacist in a New York hospital. An elderly female patient of the arthritis clinic adjacent to my pharmacy had no clinical disease in reality but constantly sought treatment. The rheumatologist, the director, and I conferred and decided to give her a 2-month supply of saccharin tablets with ad lib refills to be taken 1 tid.

This went well for several months, with the patient reporting good results, until she came to my window one day, shouting, and accused us of giving her substandard medication. The previous night she had tried to commit suicide by taking the entire supply — "And look at me: I'm standing right here in front of you, and I'm alive!"

We sent her for a psych consult. I didn't know whether to laugh or to cry.

Irving Gerber, RPh
FAIR LAWN, N.J.

Correction: *The Web Exclusive article "Propofol shortage leads to allergy warnings about European product" noted in the Table of Contents of the November 2010 issue stated that Fresenius Propoven (propofol) 1% contained peanut oil. It does not. The statement was taken from an inaccurate press release. The label of the European product contains the following statement: "...the product contains soybean oil and there are reports of cross allergies between soybean and peanut oil."* Drug Topics *regrets the error.*

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.

Convenient 2-Pak contains
2 Auto-Injectors and a trainer.

#1 PRESCRIBED AUTO-INJECTOR
MORE THAN 25 YEARS
FOR ANAPHYLAXIS*

Help at-risk patients prepare for a life-threatening anaphylactic emergency…

EpiPen and EpiPen Jr Auto-Injectors

There is no AB-rated substitute

- The FDA has not determined a therapeutic equivalent to BX-rated EpiPen Auto-Injector
- No absolute contraindications to use in life-threatening situations
- EpiPen Auto-Injector delivers epinephrine with speed and simplicity
- Only EpiPen Auto-Injector has a unique, user-friendly design with the added safety of automatic needle protection before and after use

EpiPen carton	NDC 49502-500-01
EpiPen 2-Pak	NDC 49502-500-02
EpiPen Jr carton	NDC 49502-501-01
EpiPen Jr 2-Pak	NDC 49502-501-02

Indications

EpiPen and EpiPen Jr Auto-Injectors (0.3 and 0.15 mg epinephrine) 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. 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.

*Data on file. SDI Health, Physician Disease & Diagnosis Audit, Drug Uses for Dx Code 9950-Anaphylactic Shock, 1990-2009.

www.EpiPen.com

EpiPen 2-Pak® EpiPen Jr 2-Pak®
(Epinephrine) Auto-Injectors 0.3/0.15 mg

DEY® A Mylan Company

EpiPen 2-Pak® EpiPen Jr 2-Pak®

(Epinephrine) Auto-Injectors 0.3/0.15mg

EpiPen® 0.3 mg EPINEPHRINE AUTO-INJECTOR
EpiPen® Jr 0.15 mg EPINEPHRINE AUTO-INJECTOR

BRIEF SUMMARY. See package insert for full Prescribing Information.

DO NOT REMOVE ACTIVATION CAP UNTIL READY FOR USE.
THIS UNIT CONTAINS NO LATEX.

INDICATIONS AND USAGE: EpiPen® and EpiPen® Jr Auto-Injectors are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitos), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. EpiPen® and EpiPen® Jr Auto-Injectors are intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Selection of the appropriate dosage strength is determined according to patient body weight (See DOSAGE AND ADMINISTRATION section of the full Prescribing Information).

Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

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

CONTRAINDICATIONS: There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS: EpiPen® and EpiPen® Jr Auto-Injectors should **only** be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK. Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis.

Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Treatment should be directed at vasodilation in addition to further treatment of anaphylaxis. **(see ADVERSE REACTIONS)**. Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection.

DO NOT INJECT INTRAVENOUSLY. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes 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 if the patient is sulfite-sensitive.

Epinephrine should be administered with caution in patients who have heart disease, 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, or anti-arrhythmics, 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 carrier 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

EpiPen® 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 sequential doses of epinephrine should only be administered under direct medical supervision.

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which epinephrine should be used. It must be clearly determined that the patient is at risk of future anaphylaxis, since the following risks may be associated with epinephrine administration **(see DOSAGE and ADMINISTRATION section of the full Prescribing Information)**.

Epinephrine should be used with caution in patients who have cardiac arrhythmias, coronary artery or organic heart disease, hypertension, 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. 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® Auto-Injector, and pediatric patients under 15 kg (33 lbs.) body weight using EpiPen® Jr Auto-Injector.

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® 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®/EpiPen® Jr Auto-Injector carton.

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, pallor, dizziness, weakness or shakiness, headache, apprehension, nervousness, or anxiety. These symptoms and signs usually subside rapidly, especially with rest, quiet and recumbency. 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 increased blood glucose levels following epinephrine administration. Patients with Parkinson's disease may notice a temporary worsening of symptoms.

In case of accidental injection, the patient should be advised to immediately go to the emergency room for treatment. Since the epinephrine in the EpiPen® Auto-Injector is a strong vasoconstrictor when injected into the digits, hands or feet, treatment should be directed at vasodilation if there is such an inadvertent administration to these areas. **(see ADVERSE REACTIONS)**.

(3) Drug Interactions

Patients who receive epinephrine while concomitantly taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripelennamine and diphenhydramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol. The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs, such as phentoloamine. Ergot alkaloids may also reverse the pressor effects of epinephrine.

(4) Carcinogenesis, Mutagenesis, Impairment of Fertility

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro* and to be an oxidative mutagen in a *WP2* bacterial reverse mutation assay. Epinephrine had a moderate degree of mutagenicity, and was positive in the DNA Repair test with *B. 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

Pregnancy Category C: There is no study on the acute effect of epinephrine on pregnancy. Epinephrine has been shown to have developmental effects when administered subcutaneously in rabbits 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.

ADVERSE REACTIONS: Adverse reactions to epinephrine include transient, moderate anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or certain drugs **[see PRECAUTIONS, Drug Interactions]**. Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. The potential for epinephrine to produce these types of adverse reactions does not contraindicate its use in an acute life-threatening allergic reaction.

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area **(see WARNINGS)**. Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoaesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

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 hypotension follows such measure, 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 overdosage 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 (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-blocking drug such as propranolol.

Overdosage 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® Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) are available in individual cartons, NDC 49502-500-01, and as EpiPen 2-Pak®, NDC 49502-500-02, a pack that contains two EpiPen® Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) and one EpiPen® Auto-Injector trainer device.

EpiPen® Jr Auto-Injectors (epinephrine injection, USP, 1:2000, 0.3 mL) are available in individual cartons, NDC 49502-501-01, and as EpiPen Jr 2-Pak®, NDC 49502-501-02, a pack that contains two EpiPen® Jr Auto-Injectors (epinephrine injections, USP, 1:2000, 0.3 mL) and one EpiPen® Auto-Injector trainer device.

EpiPen 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.,
NAPA, CALIFORNIA, 94558, U.S.A.
by Meridian Medical Technologies, Inc.,
a subsidiary of King Pharmaceuticals®, Inc.,
Columbia, MD 21046, U.S.A.

03-500-03 (BRS) **March 2009**

DEY®

JP AT LARGE Jim Plagakis, RPh

Pharmacy then and now

In 1989, an RPh complained that she was expected to work off the clock after her shift had ended. I told her that she should not put up with it. I told her that she was a pharmacist, not a high school dropout stocking shelves. The day I work off the clock will be the day your company starts paying for a catered deli lunch every day. You're a professional. You always have choices. You can be passive, or you can be smart. The company will always take what it can get.

Twenty-plus years and 200 columns and I am still standing. Pharmacists have asked for my help, told me their stories, and lambasted me. So many moments stand out in memory. Here are just a few.

January 23, 1989. Publication date of the first "JP at Large." My stomach did flips when a woman who suffered from bipolar disorder told me that she was going to jump off the Deception Pass Bridge. Life was just too tough. I just listened. That's all she wanted. She promised to go back on her meds.

1996. A woman asked me how she could help her mother kill herself. I was silent. She mentioned the 180 clonazepam and 240 APAP/codeine that had come from a mail-order outfit. "My Mom loves martinis," she said, giving me a look. The drugs plus martinis could be a deadly cocktail. I watched the obituaries for weeks after that.

"The people were the best part," he said. "Pharmacists don't seem to have time for people these days."

1990s. I thought I was a jazzman for a time. *I took my troubles down to Madame Ruth/You know that Gypsy with the gold-capped tooth/She's got a shop down at 34th and Vine/Selling little bottles of/Love Potion Number Nine.*

If you get your juju on, you can see how that song about Madame Ruth epitomizes what we do. *Rite-Aid's got a shop near a Pennsylvania mine/it sells Viagra and/cheap red Italian wine.*

1998. A store manager accused me of being *unprofessional* because I refused to refill an Rx for his friend. I told him to get a dictionary. I was on the *professional* train for the long ride.

Mid-1990s. I did a stealth interview with the produce manager at a local market. I asked him if the OTC famotidine was any good. Lettuce leaves started flying all over the place. "How the hell do I know?" He was red-faced from the cooler. "Ask a pharmacist!"

It was my first justification for a BTC class of drugs. A month earlier, famotidine had been Rx Only and too dangerous for self-use. All of a sudden, it could be sold at truck stops. Pathetic oversight from effete regulators. Profit rules!

1990. An elderly man who had been watching me work asked, "How long you been a registered man?" It was the old-fashioned distinction between a registered pharmacist and an apprentice. We talked and he told me about being paid in eggs, 2 dozen every week, by a cash-poor farm family.

"The people were the best part," he said. "I went to weddings and funerals. Pharmacists don't seem to have time for people these days." 1990 was 2 decades before the Prescription Mill Red Warning Timers of 2010.

2004. I did everything I could to shame a young mother because she had problems understanding how to dose her baby with the Prednisolone 15 mg/5 ml syrup. Then I realized that she did not know how to read. After that I did everything I could to help her, including sending her to the adult reading program at the local library. Months later, there were tears on my cheeks when she proudly showed me the first book she had read by herself: "Snuggle Piggy and the Magic Blanket."

A retail pharmacist today

I often wrote about the absurdity of working in a modern drugstore. You know you are a pharmacist when you are frequently referred to as "Hey" and one of the most common questions you are asked is "Hey, where are the lawn chairs for $9.99?"

You know you are a pharmacist when you get home at 10:30 p.m. and your spouse says, "I fed the kids. You can make your own dinner." Your spouse likes your money but isn't willing to dance the dance.

Pharmacists often complain that the profession is in the pits. I invite them to focus more closely. It's the job, stupid. The profession is just fine. DT

Jim Plagakis *is a community pharmacist in Galveston, Texas. You can e-mail him at jpgakis@hotmail.com and cc us at drugtopics@advanstar.com. You can also check out his website at jimplagakis.com.*

Website for providers, patients, focuses on chronic pain

Pharmacists working with chronic pain patients have a new tool. PainSAFE (Pain Safety & Access for Everyone), an initiative of the American Pain Foundation, has launched the website *www.painsafe.org* to educate patients and practitioners about pain-management therapies and their risks.


Kathy Hahn

In Portland, Ore., at a Bi-Mart Pharmacy that specializes in helping patients with chronic pain, pharmacy staff keeps files on such patients and "watches for all the things that go wrong, such as side effects and errant behavior," said Kathy Hahn, PharmD, owner of the pharmacy and Action Network Leader of the American Pain Foundation. "Some of our staff have become advocates. It's all about increasing access and trying to figure how we can work on the crisis of abusing pain medications," Hahn said.

PainSAFE organizers agree that the pharmacist's role is vital. "Pharmacists play a key role in preventing misuse and overuse of prescriptions. They are the last gate before a patient receives their medication," said Lynn Webster, MD, FACPM, and an advisor to PainSAFE.

Pharmacists can help prevent misuse of pain medication by monitoring initial drug doses. "Physicians often start patients on too high of a dose or increase the dose too rapidly. The pharmacist can see that and will hopefully contact the physician. This could save thousands of lives every year," Webster said.

Pharmacists can also help patients who switch or combine medications. "Pharmacists need to make sure that patients understand the higher risks of taking 2 together. There could be a substantial reduction in deaths immediately," Webster said.

At the website, simple tips include reminders to lock up pain medications to prevent misuse by the young or the elderly. "We have not been good at putting out the information that pain medications should be locked up," Hahn said.

— Christine Blank, Contributing Editor

***www.painsafe.org*: A new tool for chronic pain patients and healthcare providers**

NEW STUDY

More patients are abandoning prescriptions

Patients with health insurance are abandoning their prescriptions at higher rates than they did a year ago and far more frequently than they did 5 years ago, according to a recent study from healthcare data firm Wolters Kluwer Pharma Solutions, Bridgewater, N.J.

From 2006 to 2010, patient abandonment rates at retail pharmacies have soared 83.6%, according to the Wolters Kluwers study.

- In the first quarter of 2006, 5% of patients failed to pick up their brand prescriptions and 2.9% failed to pick up their generic prescriptions.
- In the first quarter of 2010, 9.4% abandoned their brand prescriptions and 5.1% abandoned their generics.

"It does seem to be tied to the economic climate right now, but we will see if it begins to flatten out or improve [when the economy improves]," said Mark Spiers, CEO of Wolters Kluwer Pharma Solutions.

As the United States entered recession in the third quarter of 2008, rates of prescription abandonment began to rise. "We really started to see a bump in 2009, which continued into 2010," Spiers said.

While prescription abandonment rates stayed the same for generic medications between the first and second quarter of 2010, the abandonment rates for brands rose from 9.4% to 9.6%.

Wolters Kluwer also tracks the abandonment rates by category of medication and found that adrenergic blocking prescriptions had the highest rate-of-abandonment increase from 2008 to 2009. In 2008, approximately 3% of patients abandoned adrenergic blocking medications; in 2009, the rate had risen to approximately 3.9%.

"We have also seen an increase in abandonment of maintenance medications such as those for diabetes and hypertension. Those are the areas that tend to become more concerning, because many of the drugs have demonstrated outcomes to prevent heart attack, stroke, and other conditions that put a greater cost on the healthcare system," Spiers said.

Approximately 4.8% of patients abandoned anti-ulcerant prescriptions in 2009, 4% abandoned diabetes prescriptions, 4.2% abandoned antidepressants, and approximately 3.7% failed to pick up cholesterol reducers.

— Christine Blank, Contributing Editor

Growth

Expanding product lines

Innovation

Technically complex products

125 years of *innovation*

125 Years of Impacting Tomorrow Right Now

Quality

The highest standards for safe and compliant manufacturing

Affordability

Accessible pharmaceuticals for all

Right Now, Roxane Laboratories is – *and always has been* – focused on the needs of our customers and their patients.

For more information, please visit www.roxane.com or call 800.520.1631.

Boehringer Ingelheim
Roxane Laboratories

GROWTH | INNOVATION | QUALITY | AFFORDABILITY | **Impacting Tomorrow Right Now.**

Up front
In Depth

Safety summit: Risk management gets its third checkup

BARBARA HESSELGRAVE

Since the 1999 publication of the Institute of Medicine (IOM) report "To Err is Human: Building a Safer Health System," both public and private interests have made patient safety a priority. Pharmacists can play a critical role in patient safety by ensuring that correct medications be dispensed appropriately. But necessary patient counseling, along with interaction with physicians and payors, often goes uncompensated. While recent FDA safety policies give the agency more authority to demand post-marketing accountability from manufacturers, they present an increasing burden for pharmacists.

Manufacturer risk reduction

Part of the 2007 FDA Amendment Act (FDAAA) was the Risk Evaluation and Mitigation Strategy (REMS) requirement for manufacturers, "to ensure that the benefits of a drug or biological product outweigh its risks."

FDA now publicly lists more than 160 REMS-approved drugs, detailing for each product the REMS components, which may include a medication guide, a communication plan, elements to assure safe use, and/or an implementation system.

At the Third Annual Risk Management and Drug Safety Summit, held October 18 and 19 in Bethesda, Md., attendees and presenters discussed the latest issues related to risk and safety, and examined how REMS and drug safety have been faring since 2007.


Annette Stemhagen

Annette Stemhagen, DrPH, FISPE, senior vice president of safety, epidemiology, registries, and risk management for United BioSource Corporation, a Summit sponsor, said that most REMS (70%) are "a medication-guide-only REMS."

Pharmacist fact-checking

"The pharmacist has the responsibility of dispensing the medication guide along with the prescription, but there's a bigger responsibility for the pharmacist when there's a REMS communication plan," Stemhagen said, explaining that when FDA requires a manufacturer to provide a communication plan, the pharmacist will have to confirm whether the patient is eligible to receive a specific product and whether certain tests are needed before the patient can obtain a drug or drug refill, as with Accutane, which requires a pregnancy test.

FDA now publicly lists more than 160 REMS-approved drugs.

Risk management

Before REMS legislation, manufacturers of Accutane and its generics operated iPLEDGE, a program designed to reduce risk of fetal exposure. On October 22, 2010, FDA approved the iPLEDGE program as an official REMS. The program has continued as before; the only change was in its official designation.

FDA representative Crystal Rice said that pharmacists could help communicate with physicians who are new to REMS and "help them complete the needed processes for a particular product," but that pharmacists should not be expected "to be the primary source of information regarding the correct prescribing choice for a physician's patients."

Summit keynote speaker Peter Pitts, co-founder and president of the Center for Medicine in the Public Interest (CMPI) and a Summit sponsor, said that "the REMS issue is part of the larger conversation of postmarket safety."

He added that he suspects pharmacists are probably much more knowledgeable about REMS than are physicians, whose "awareness of REMS is slim to none."

Education and technology

FDA is planning a number of projects to help pharmacists, Rice said, including a uniform REMS interface for prescribers, expanded pharmacy access to REMS, CE for pharmacists, and more.

"We are researching the possibilities presented by today's technology for using current or developing electronic systems to implement the registration and prescribing requirements of REMS," Rice said.

FDA is also "very involved in ongoing education for pharmacists and other stakeholders," Rice said, "to decrease the burden of the REMS process."

In her plenary remarks, Summit presenter Janet Woodcock, MD, Director of FDA's Center for Drug Evaluation and Research (CDER) said that "CDER promotes and protects public health by ensuring that safe and effective drugs are available to Americans, but 'safe' does not mean risk-free, and 'effective' does not mean equally for all."

In other words, Pitts said, the REMS program "doesn't tell physicians how to practice medicine, and it gives the FDA the route to keep higher-risk drugs on the market." DT

Barbara Hesselgrave *is a freelance writer based in Virginia.*

VIMOVO*– *the only prescription-strength NSAID therapy with a built-in PPI for

OA pain relief patients can stay with[1]

Compared with EC-naproxen – controlled studies did not extend beyond 6 months

As with all NSAIDs, use the lowest effective dose for the shortest duration of time consistent with individual patient treatment goals.

VIMOVO is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. VIMOVO is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products. Controlled studies do not extend beyond 6 months.

Cardiovascular Risk

- **Naproxen, a component of VIMOVO, may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.**
- **VIMOVO is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.**

Gastrointestinal Risk

- **NSAIDs, including naproxen, a component of VIMOVO, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal (GI) events.**

VIMOVO is contraindicated in patients with known hypersensitivity to any component of VIMOVO or substituted benzimidazoles; in patients with a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs; in patients during the perioperative period in the setting of coronary artery bypass graft (CABG) surgery; or in patients in the late stages of pregnancy.

The most commonly observed adverse events in clinical trials (experienced by >5% patients in the VIMOVO group) were erosive gastritis, dyspepsia, gastritis, diarrhea, gastric ulcer, upper abdominal pain, and nausea.

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

Reference: 1. VIMOVO™ Prescribing Information. Wilmington, DE: AstraZeneca; 2010.

Get the free app for your mobile smartphone at http://gettag.mobi

Take part in the VIMOVO experience

Scan the tag above to start now or visit www.VIMOVOtouchpoints.com to learn more

Vimovo™
(naproxen/esomeprazole magnesium)
375/20•500/20 mg delayed-release tablets

AstraZeneca

Vimovo™

naproxen/esomeprazole magnesium

delayed-release tablets

BRIEF SUMMARY of Prescribing Information.

Cardiovascular Risk

- **NonSteroidal Anti-inflammatory Drugs (NSAIDs), a component of VIMOVO, may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk [see *Warnings and Precautions*].**
- **VIMOVO is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see *Contraindications*, and *Warnings and Precautions*].**

Gastrointestinal Risk

- **NSAIDs, including naproxen, a component of VIMOVO, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events [see *Warnings and Precautions*].**

INDICATIONS AND USAGE

VIMOVO is a combination product that contains naproxen and esomeprazole. It is indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers. VIMOVO is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products. Controlled studies do not extend beyond 6 months.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of VIMOVO and other treatment options before deciding to use VIMOVO. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. VIMOVO does not allow for administration of a lower daily dose of esomeprazole. If a dose of esomeprazole lower than a total daily dose of 40 mg is more appropriate, a different treatment should be considered.

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis

The dosage is one tablet twice daily of VIMOVO 375 mg naproxen and 20 mg of esomeprazole or 500 mg naproxen and 20 mg of esomeprazole.

The tablets are to be swallowed whole with liquid. Do not split, chew, crush or dissolve the tablet. VIMOVO is to be taken at least 30 minutes before meals.

Geriatric Patients Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Use caution when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly use the lowest effective dose [see **Use in Specific Populations** and **Clinical Pharmacology** (12.3) in full Prescribing Information].

Patients With Moderate to Severe Renal Impairment Naproxen-containing products are not recommended for use in patients with moderate to severe or severe renal impairment (creatinine clearance <30 mL/min). [see **Warnings and Precautions** and **Use in Specific Populations**].

Hepatic Insufficiency Monitor patients with mild to moderate hepatic impairment closely and consider a possible dose reduction based on the naproxen component of VIMOVO.

VIMOVO is not recommended in patients with severe hepatic impairment because esomeprazole doses should not exceed 20 mg daily in these patients [see **Warnings and Precautions**, **Use in Specific Populations** and **Clinical Pharmacology** (12.3) in full Prescribing Information].

Pediatric Patients The safety and efficacy of VIMOVO in children younger than 18 years has not been established. VIMOVO is therefore not recommended for use in children.

CONTRAINDICATIONS

VIMOVO is contraindicated in patients with known hypersensitivity to naproxen, esomeprazole magnesium, substituted benzimidazoles, or to any of the excipients.

VIMOVO is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients [see **Warnings and Precautions**]. Hypersensitivity reactions, eg, angioedema and anaphylactic reaction/shock, have been reported with esomeprazole use.

VIMOVO is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see **Warnings and Precautions**].

VIMOVO is contraindicated in patients in the late stages of pregnancy [see **Warnings and Precautions** and **Use in Specific Populations**].

WARNINGS AND PRECAUTIONS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDS, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use.

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [see **Contraindications**].

Hypertension

NSAIDs, including naproxen, a component of VIMOVO, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy [see **Drug Interactions**].

Congestive Heart Failure and Edema

Fluid retention, edema, and peripheral edema have been observed in some patients taking NSAIDs and should be used with caution in patients with fluid retention, or heart failure.

Gastrointestinal Effects — Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including naproxen, a component of VIMOVO, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. While VIMOVO has been shown to significantly decrease the occurrence of gastric ulcers compared to naproxen alone, ulceration and associated complications can still occur.

These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months, and in about 2%–4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed.

VIMOVO should be prescribed with caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk of developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants or antiplatelets (including low-dose aspirin), longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients, and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID or NSAID-containing product, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Epidemiological studies of the case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of an NSAID, COX-2 inhibitor, or aspirin potentiated the risk of bleeding [see **Drug Interactions**]. Although these studies focused on upper gastrointestinal bleeding, bleeding at other sites cannot be ruled out.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

Gastrointestinal symptomatic response to therapy with VIMOVO does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long- term with omeprazole, of which esomeprazole is an enantiomer and a component of VIMOVO.

Active Bleeding

When active and clinically significant bleeding from any source occurs in patients receiving VIMOVO, the treatment should be withdrawn.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of VIMOVO in patients with advanced renal disease. Therefore, treatment with VIMOVO is not recommended in these patients with advanced renal disease. If VIMOVO therapy must be initiated, close monitoring of the patient's renal function is advisable [see **Dosage and Administration**, **Use in Specific Populations** and **Clinical Pharmacology** (12.3) in full Prescribing Information].

Anaphylactoid Reactions

Anaphylactoid reactions may occur in patients without known prior exposure to either component of VIMOVO. NSAIDs should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs [see **Contraindications**]. Emergency help should be sought in cases where an anaphylactoid reaction occurs. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

Skin Reactions

NSAIDs can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

Pregnancy Category C–In late pregnancy, as with other NSAIDs, naproxen, a component of VIMOVO should be avoided because it may cause premature closure of the ductus arteriosus [see **Contraindications** and **Use in Specific Populations**].

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including naproxen, a component of VIMOVO. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. These laboratory abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with VIMOVO.

If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg, eosinophilia, rash, etc), VIMOVO should be discontinued.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose for the shortest possible duration of adequate treatment.

VIMOVO is not recommended in patients with severe hepatic impairment because esomeprazole doses should not exceed 20 mg daily in these patients [see **Dosage and Administration**, and **Use in Specific Populations**].

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving VIMOVO who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants or antiplatelets, should be carefully monitored.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, VIMOVO should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Concomitant NSAID Use

VIMOVO contains naproxen as one of its active ingredients. It should not be used with other naproxen-containing products since they all circulate in the plasma as the naproxen anion.

The concomitant use of VIMOVO with any dose of a nonaspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

Corticosteroid Treatment

VIMOVO cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Bone Fracture

Several studies and literature reports indicate that proton pump inhibitor (PPI) therapy is associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. Those patients with the highest risk received high-dose or long-term PPI therapy (a year or longer). Patients should use the lowest effective dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to the established treatment guidelines. Adequate vitamin D and calcium intake is recommended.

Masking of Inflammation and Fever

The pharmacological activity of VIMOVO in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (eg, eosinophilia, rash, etc) or if abnormal liver tests persist or worsen, VIMOVO should be discontinued.

Patients with initial hemoglobin values of 10 g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

ADVERSE REACTIONS

Clinical Studies Experience

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

The adverse reactions reported below are specific to the clinical trials with VIMOVO. See also the full prescribing information for naproxen/esomeprazole magnesium products.

The safety of VIMOVO was evaluated in clinical studies involving 2317 patients (aged 27 to 90 years) and ranging from 3–12 months. Patients received either 500 mg/20 mg of VIMOVO twice daily (n=1157), 500 mg of enteric-coated naproxen twice daily (n=426), or placebo (n=246). The average number of VIMOVO doses taken over 12 months was 696±44.

The table below lists all adverse reactions, regardless of causality, occurring in >2% of patients receiving VIMOVO from two clinical studies (Study 1 and Study 2). Both of these studies were randomized, multi-center, double-blind, parallel studies. The majority of patients were female (67%), white (86%). The majority of patients were 50-69 years of age (83%). Approximately one quarter were on low-dose aspirin.

Table 1: Adverse Reactions Occurring in Patients >2% Study 1 and Study 2 (Endoscopic Studies)

Preferred Term (sorted by SOC)	VIMOVO 500 mg/20 mg twice daily (n=428) %	EC-Naproxen 500 mg twice daily (n=426) %
Gastrointestinal Disorders		
Gastritis Erosive	19	38
Dyspepsia	18	27
Gastritis	17	14
Diarrhea	6	5
Gastric Ulcer	6	24
Abdominal Pain Upper	6	9
Nausea	5	5
Hiatus Hernia	4	6
Abdominal Distension	4	4
Flatulence	4	3
Esophagitis	4	8
Constipation	3	3
Abdominal Pain	2	2
Erosive Duodenitis	2	12
Abdominal Pain Lower	2	3
Duodenitis	1	7
Gastritis Hemorrhagic	1	2
Gastroesophageal Reflux Disease	<1	4
Duodenal Ulcer	<1	5
Erosive Esophagitis	<1	6
Infections and Infestations		
Upper Respiratory Tract Infection	5	4
Bronchitis	2	2
Urinary Tract Infection	2	1
Sinusitis	2	2
Nasopharyngitis	<1	2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	1	2
Nervous System Disorders		
Headache	3	1
Dysgeusia	2	1
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2	3

In Study 1 and Study 2, patients taking VIMOVO had fewer premature discontinuations due to adverse reactions compared to patients taking enteric-coated naproxen alone (7.9% vs. 12.5% respectively). The most common reasons for discontinuations due to adverse events in the VIMOVO treatment group were upper abdominal pain (1.2%, n=5), duodenal ulcer (0.7%, n=3) and erosive gastritis (0.7%, n=3). Among patients receiving enteric-coated naproxen, the most common reasons for discontinuations due to adverse events were duodenal ulcer 5.4% (n=23), dyspepsia 2.8% (n=12), and upper abdominal pain 1.2% (n=5). The proportion of patients discontinuing treatment due to any upper gastrointestinal adverse events (including duodenal ulcers) in patients treated with VIMOVO was 4% compared to 12% for patients taking enteric-coated naproxen.

The table below lists all adverse reactions, regardless of causality, occurring in >2% of patients from 2 clinical studies conducted in patients with osteoarthritis of the knee (Study 3 and Study 4).

Table 2: Adverse Reactions Occurring in Patients >2% (Study 3 and Study 4)

Preferred Term (sorted by SOC)	VIMOVO 500 mg/20 mg twice daily (n=490) %	Placebo (n=246) %
Gastrointestinal Disorders		
Dyspepsia	8	12
Diarrhea	6	4
Abdominal Pain Upper	4	3
Constipation	4	1
Nausea	4	4
Nervous System Disorders		
Dizziness	3	2
Headache	3	5
General Disorders and Administration Site Conditions		
Peripheral Edema	3	1
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1	3
Infections and Infestations		
Sinusitis	1	2

The percentage of subjects who withdrew from the VIMOVO treatment group in these studies due to treatment-emergent adverse events was 7%. There were no preferred terms in which more than 1% of subjects withdrew from any treatment group.

The long-term safety of VIMOVO was evaluated in an open-label clinical trial of 239 patients, of which 135 patients received 500 mg/20 mg of VIMOVO for 12 months. There were no differences in frequency or types of adverse reactions seen in the long-term safety study compared to shorter-term treatment in the randomized controlled studies.

Postmarketing Experience

Naproxen The following adverse reactions have been identified during post-approval use of naproxen. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system. **Body as a Whole:** anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever); **Cardiovascular:** congestive heart failure, vasculitis, hypertension, pulmonary edema; **Gastrointestinal:** gastrointestinal bleeding and/or perforation, hematemesis, pancreatitis, vomiting, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease), nonpeptic gastrointestinal ulceration, ulcerative stomatitis, esophagitis, peptic ulceration; **Hepatobiliary:** jaundice, abnormal liver function tests, hepatitis (some cases have been fatal); **Hemic and Lymphatic:** eosinophilia, leucopenia, melena, thrombocytopenia, agranulocytosis, granulocytopenia, hemolytic anemia, aplastic anemia; **Metabolic and Nutritional:** hyperglycemia, hypoglycemia; **Nervous System:** inability to concentrate, depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, convulsions; **Respiratory:** eosinophilic pneumonitis, asthma; **Dermatologic:** alopecia, urticaria, skin rashes, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematosus, bullous reactions, including Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored. **Special Senses:** hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema; **Urogenital:** glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine; **Reproduction (female):** infertility.

Esomeprazole The following adverse reactions have been identified during post-approval use of esomeprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system. **Blood and Lymphatic:** agranulocytosis, pancytopenia; **Eye:** blurred vision; **Gastrointestinal:** pancreatitis, stomatitis; **Hepatobiliary:** hepatic failure, hepatitis with or without jaundice; **Immune System:** anaphylactic reaction/shock; **Infections and Infestations:** GI candidiasis; **Metabolism and Nutritional Disorders:** hypomagnesemia; **Musculoskeletal and Connective Tissue:** muscular weakness, myalgia; **Nervous System:** hepatic encephalopathy, taste disturbance; **Psychiatric:** aggression, agitation, depression, hallucination; **Renal and Urinary:** interstitial nephritis; **Reproductive System and Breast:** gynecomastia; **Respiratory, Thoracic, and Mediastinal:** bronchospasm; **Skin and Subcutaneous Tissue:** alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

DRUG INTERACTIONS

Several studies conducted with VIMOVO have shown no interaction between the two components, naproxen and esomeprazole.

ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking VIMOVO concomitantly with ACE-inhibitors.

Aspirin

VIMOVO can be administered with low-dose aspirin (≤325 mg/day) therapy. The concurrent use of aspirin and VIMOVO may increase the risk of serious adverse events. [see **Warnings and Precautions**, **Adverse Reactions**, and **Clinical Studies** (14) in full Prescribing Information].

When naproxen is administered with doses of aspirin (>1 gram/day), its protein binding is reduced. The clinical significance of this interaction is not known. However, as with other NSAIDs, concomitant administration of naproxen and aspirin is not generally recommended because of the potential of increased adverse effects.

Cholestyramine

As with other NSAIDs, concomitant administration of cholestyramine can delay the absorption of naproxen.

Diuretics

Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely both for signs of renal failure, as well as to monitor to assure diuretic efficacy [see **Warnings and Precautions**].

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Anticoagulants

Naproxen decreases platelet aggregation and may prolong bleeding time.

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. No significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants. However, caution is advised since interactions have been seen with other nonsteroidal agents of this class. The free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function.

Postmarketing reports of changes in prothrombin measures have been reported among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Selective Serotonin Reuptake Inhibitors (SSRIs)

There is an increased risk of gastrointestinal bleeding when selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs including COX-2 selective inhibitors. Caution should be used when NSAIDs are administered concomitantly with SSRIs [see **Warnings and Precautions**].

Other Information Concerning Drug Interactions

Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as sulphonylureas, hydantoins, and other NSAIDs. Patients simultaneously receiving VIMOVO and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Drug/Laboratory Test Interaction

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

Interactions Related to Absorption

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (eg, ketoconazole, iron salts, and digoxin).

Antiretroviral Agents

Concomitant use of atazanavir and nelfinavir with proton pump inhibitors such as esomeprazole is not recommended. Coadministration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Omeprazole, the racemate of esomeprazole, has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg once a day), AUC was decreased by 36% and 92%, C_{max} by 37% and 89% and C_{min} by 39% and 75% respectively for nelfinavir and main oxidative metabolite, hydroxy-t-butylamide (M8). Following multiple doses of atazanavir (400 mg, once a day) and omeprazole (40 mg, once a day, 2 hr before atazanavir), AUC was decreased by 94%, C_{max} by 96%, and C_{min} by 95%. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended. For other antiretroviral drugs, such as saquinavir, elevated serum levels have been reported with an increase in AUC by 82% in C_{max} by 75% and in C_{min} by 106% following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice a day for 15 days with omeprazole 40 mg once a day coadministered on days 11 to 15). Therefore, clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with esomeprazole. Dose reduction of saquinavir should be considered from the safety perspective for individual patients. There are also some anti-retroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

In vitro and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin.

However, postmarketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. Dose adjustment of esomeprazole is not normally required. Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in crossover study, increased C_{max} and AUC of cilostazol by 18% and 26% respectively. C_{max} and AUC of one of its active metabolites, 3,4-dihydrocilostazol, which has 4-7 times the activity of cilostazol, were increased by 29% and 69% respectively. Coadministration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its above-mentioned active metabolite. Therefore a dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered.

Other Pharmacokinetic-based Interactions

Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine does not seem to change the pharmacokinetic profile of esomeprazole.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C prior to 30 weeks gestation; Category D starting 30 weeks gestation.

Starting at 30 weeks gestation, VIMOVO, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. VIMOVO can cause fetal harm when administered to a pregnant woman starting at 30-weeks gestation. If this drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to a fetus. There are no adequate and well-controlled studies in pregnant women. Prior to 30-weeks gestation, VIMOVO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reproductive studies with naproxen have been performed in rats at 20 mg/kg/day (125 mg/m^2/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m^2/day, 0.27 times the human systemic exposure), and mice at 170 mg/kg/day (510 mg/m^2/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug [see **Animal Toxicology and/or Pharmacology** (13.2) in full Prescribing Information]. However, animal reproduction studies are not always predictive of human response.

Reproductive studies in rats and rabbits with esomeprazole and multiple cohort studies in pregnant women with omeprazole use during the first trimester do not show an increased risk of congenital anomalies or adverse pregnancy outcomes. There are no adequate and well-controlled studies of esomeprazole use in pregnancy. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Esomeprazole is the S-isomer of omeprazole. In four population-based cohort studies that included 1226 women exposed during the first trimester of pregnancy to omeprazole there was no increased risk of congenital anomalies.

Reproductive studies with esomeprazole have been performed in rats at doses up to 57 times the human dose and in rabbits at doses up to 35 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus. [see **Animal Toxicology and/or Pharmacology** (13.2) in full Prescribing Information].

Reproductive studies conducted with omeprazole on rats at oral doses up to 56 times the human dose and in rabbits at doses up to 56 times the human dose did not show any evidence of teratogenicity. In pregnant rabbits, omeprazole at doses about 5.5 to 56 times the human dose produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy loss. In rats treated with omeprazole at doses about 5.6 to 56 times the human dose, dose-related embryo/fetal toxicity and postnatal developmental toxicity occurred in offspring.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Naproxen-containing products are not recommended in labor and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage. The effects of VIMOVO on labor and delivery in pregnant women are unknown.

Nursing Mothers

VIMOVO should not be used in nursing mothers due to the naproxen component.

Naproxen The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

Esomeprazole The excretion of esomeprazole in milk has not been studied. It is not known whether this drug is excreted in human milk. However, omeprazole concentrations have been measured in breast milk of one woman taking omeprazole 20 mg per day. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for esomeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of VIMOVO has not been established in children younger than 18 years.

Geriatric Use

Of the total number of patients who received VIMOVO (n=1157) in clinical trials, 387 were ≥65 years of age, of which 85 patients were 75 years and over. No meaningful differences in efficacy or safety were observed between these subjects and younger subjects. [see **Adverse Reactions**].

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose [see **Dosage and Administration** and **Clinical Pharmacology** (12.3) in full Prescribing Information].

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of NSAIDs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population [see **Warnings and Precautions**].

Naproxen is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of NSAIDs [see **Warnings and Precautions**].

Hepatic Insufficiency

VIMOVO is not recommended for use in patients with severe hepatic impairment because esomeprazole doses should not exceed 20 mg daily in these patients [see **Dosage and Administration** and **Warnings and Precautions**].

Renal Insufficiency

Naproxen-containing products, including VIMOVO are not recommended for use in patients with advanced renal disease [see **Dosage and Administration** and **Warnings and Precautions**].

OVERDOSAGE

There is no clinical data on overdosage with VIMOVO.

Overdosage of Naproxen Significant naproxen overdosage may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening. The oral LD50 of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters, and greater than 1000 mg/kg in dogs.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.

Overdosage of Esomeprazole A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis) was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions.

The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - *Adverse Reactions*). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

If overexposure occurs, call the Poison Control Center at 1-800-222-1222.

Manufactured by: Patheon Pharmaceuticals Inc., Cincinnati, OH 45237
For: AstraZeneca LP, Wilmington, DE 19850
4/2010 301190

CHAINS & BUSINESS Kathryn Foxhall

Counterfeit drug war continues, threatens supply chain

The counterfeiters are winning the global counterfeit drug war, with counterfeit medications more abundant than ever before, according to Jeffrey Gren, director of the Office of Health and Consumer Goods in the U.S. Department of Commerce.

Gren spoke in October in Washington, D.C., at Interchange 2010, a conference sponsored by the Partnership for Safe Medicines, a coalition of individuals and groups working to protect consumers from counterfeit or contraband medications.

Along with counterfeit medications, substandard medications are also always on the rise. These are defined as products made primarily by manufacturers who do not comply with regulatory standards or U.S. Pharmacopeia requirements.

Although counterfeit drugs can contain anything from powdered drywall to highway paint, Gren said, he believes more counterfeit drugs include some actual ingredients, making them effective enough to bring the counterfeiters repeat business. He called this one of the most frightening potentials.

Although the counterfeit drug issue has received more government funding and attention in recent years, it has not received nearly enough, Gren told the meeting, which included the group's members, pharmaceutical professionals, government officials, and others.

Foreign drugs

According to FDA, Gren said, 80% of active pharmaceutical ingredients (API) in drugs consumed in the United States come from other countries, mostly from nations that don't have sophisticated regulatory regimes. An API, he said, "may come from China, it may be packaged in the Middle East, it may be sent through Brazil; ultimately it makes it to the United States or other parts of the world," making the problem difficult to solve.

Diplomatic efforts to address the issue include dialogues with countries such as China, India, and Brazil, and include Department of Commerce initiatives originated by the U.S.-China Joint Commission on Commerce and Trade. Also, a series of seminars and other projects continues under the aegis of Asia-Pacific Economic Cooperation, a forum for the Pacific Rim nations, Gren said.

A growing problem

Another speaker at the Interchange meeting, Nancy Kennedy, senior operations manager of drug investigations in FDA's Office of Criminal Investigations, said that some years ago imported, unapproved, and counterfeit drugs came into the United States addressed to individuals or packaged in small quantities. Then quantities increased, and counterfeits started going to drop-shippers and distributors working from online pharmacy operations.

"Now we see quantities of these drugs coming in and going directly to doctors, clinics, brick-and-mortar-pharmacies—and these are for use and distribution directly to patients," Kennedy said.

A question of resources

Asked at the meeting about resources allocated to the counterfeit drug problem, Kennedy said that for some time Congress and others have been saying, "Show us the bodies." But there may not be many bodies at one time, she said, unless an event occurs such as the mass poisonings that have happened in other countries.

Currently, she added, counterfeit drugs are more likely either to cause injuries or to cause patients to receive inappropriate doses of prescribed drugs without their realizing it.

Targeted enforcement

In another session at the partnership's forum, FDA Commissioner Margaret Hamburg said that her agency has now ranked more than 1,000 active pharmaceutical ingredients according to their vulnerability to economically motivated adulteration, so that enforcement can be better targeted.

To jump-start efforts to deal with supply-chain threats that include counterfeiting, economically motivated adulteration, diversion, and cargo thefts, Hamburg said, the agency is creating a new Drug Integrity and Security Program within the Office of Compliance of the FDA's Center for Drug Evaluation and Research.

Hamburg also said that FDA is developing standards for track-and-trace and authentication systems that would enable the identification of substandard prescription drugs as they move along the supply chain. The agency will help in efforts to recall these drugs.

However, asked when the requirement that drugs carry a pedigree will be enforced, as mandated by the 1987 Prescription Drug Marketing Act, Hamburg said she could not give a specific answer. That requirement, calling for wholesale distributors (or others not defined as "authorized distributors") to provide a statement of each prior sale, trade, or purchase of a prescription drug, has been held up by regulatory and legal wrangling for 2 decades. DT

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

Steady sailing for now

Drug Topics' 2011 business outlook survey

Jill Sederstrom

While the economy in many industries has yet to rebound, the pharmacy industry has remained strong and most pharmacists are hopeful about 2011. However, optimism isn't running as high as it was last year, and the pharmacy community is concerned about how competition, reimbursement, and healthcare reform will affect the industry.

These are just a few of the conclusions drawn from *Drug Topics*' annual business outlook survey, an online survey conducted in October that received more than 400 responses from community, hospital, and long-term-care (LTC) pharmacists.

Overall, respondents believe that the business climate looks positive for 2011. Of the 305 community pharmacists who responded to the survey, 77% believe that 2010 will be an excellent, very good, or good business year, and 68% predict that the trend will continue in 2011.

In addition, of the 96 hospital and LTC pharmacists who responded, 84% anticipate that 2010 will be an excellent, very good, or good business year, and 73% believe that will also be the case in 2011.


Thomas Menighan

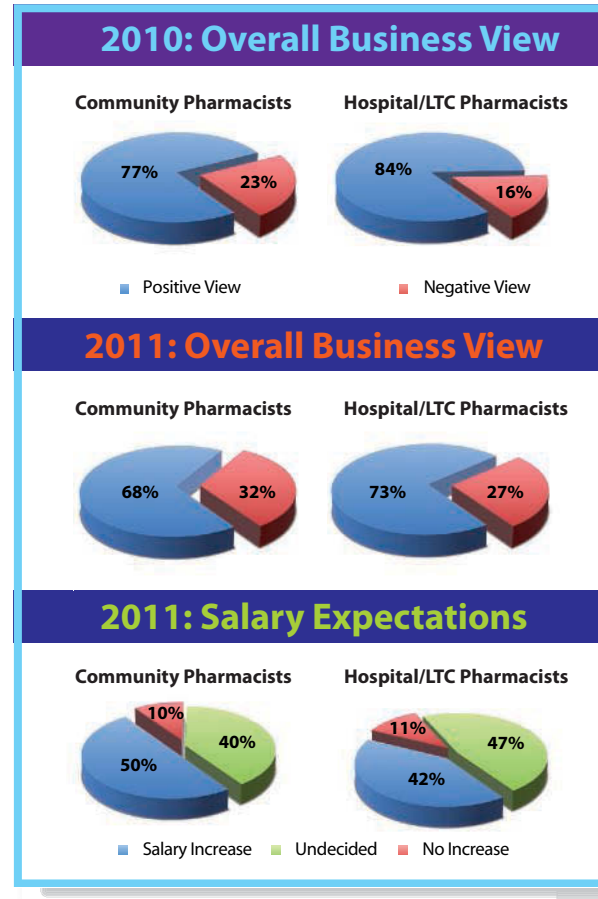
"I think there are a lot of very positive things going on in pharmacy, and so I think [pharmacists'] optimism is warranted, but it isn't going to get any easier," said Thomas Menighan, executive vice president and chief executive officer of the American Pharmacists Association (APhA). "Margins are not going to get larger. People are going to have to be more efficient. They are going to have to find ways to make the services that pharmacists can provide pay off rather than relying on buy low, sell high."

Community pharmacists' financial outlook

Pharmacists' financial expectations for 2011 are generally positive, but they aren't without their concerns.

Nearly half (45%) of community pharmacists surveyed believe that sales will increase in 2011. For those who anticipate rising sales figures, the average increase expected is 4.5%.

However, not everyone sees predicted sales in such a positive light. Survey findings indicate that 11% believe sales will decrease, and they predict an average decrease in 2011 of 2.3%.



Half of community pharmacists expect salaries to increase next year. More than 40% of hospital and LTC pharmacists believe their salaries will climb in 2011.

In addition, 56% anticipate an increase to operating expenses, while 6% expect a decrease. For those who believe there will be an increase, the average expected increase is 4.1%. For those who anticipate a decrease, the average expected decrease is 1.2%.

About a third, or 35%, expect net profits to increase in 2011 by an average of 2.6%.

Half of community pharmacists believe that in their pharmacies, pharmacist salaries will increase in 2011, while 40% do not expect an increase. For the 50% who expect an increase, the average expected increase is 3.6%.

Hospital pharmacists' financial outlook

Hospital and LTC pharmacists are less optimistic about sales expectations than are their counterparts in community pharmacy. According to the results, just 30% of hospital pharmacists expect an increase in sales in the coming year; the average increase they anticipate is 3.9%. However, only 6% predict a decrease in sales. For those who expected a decrease, the average expected decrease was 2.1%.

Most hospital pharmacists surveyed (51%) expect operating expenses to increase in the new year; they predict an average increase of 5.4%. On the other side of the spectrum, 6% of those surveyed believe operating expenses will decrease and expect an average decrease in 2011 of 0.6%.

Nearly a quarter, or 23%, of hospital pharmacists expect net profits to increase in 2011 by an average increase of 2.5%.

A significant percentage of hospital pharmacists do not believe a raise is in their future in 2011. According to the survey results, 47% do not expect a salary increase. However, 42% do believe that their pharmacies will be giving pharmacists a raise in 2011. The average increase anticipated is 3%.


Anna Garrett

Anna Garrett, PharmD, BCPS, manager of outpatient clinical pharmacy services for Mission Hospital in Asheville, N.C., believes that if pharmacists are expecting salary increases now, those increases will be more in line with cost-of-living adjustments, rather than being significant jumps in pay.

"It looks like the days when everybody is getting the huge raises are over," said Garrett, who is joining *Drug Topics*' editorial advisory board next month.

Challenges and opportunities

In any given year, the pharmacy industry will face challenges and opportunities, and 2011 is no exception. In one section of the survey, pharmacists identified the top 3 positive and top 3 negative factors that they believe will influence the industry in the coming year.

The most frequently cited positive factors expected to affect business are major brand-name drugs going off patent (cited by 62% of respondents), an increase of e-prescriptions (cited by 37% of respondents), and immunization certification (cited by 36% of respondents).

The most frequently mentioned negative factors affecting business for 2011 are expected to be the recession (cited by 77% of respondents), low reimbursement from third parties (cited by 66% of respondents), and mail-order programs (cited by 63% of respondents).


Charlie Mollien

Charlie Mollien, PharmD, a staff pharmacist with Meijer Pharmacy, Jenison, Mich., and a *Drug Topics* Frontline editorial advisory board member, said that he is optimistic about the future of pharmacy, although he does see some hurdles. While he believes that pharmacy utilization will continue to increase, he added that low reimbursement could translate into pharmacists filling more prescriptions for less profit.

To combat the problem, and to make up profits, Mollien said, pharmacists may need to look into other areas, such as adopting education programs for smoking cessation or chronic disease management. For the programs to be successful, however, pharmacists would need to be given the time, staff, and leadership support to run them.

The biggest challenges pharmacists will face in 2011 are said to be competition from chains offering generics at low or no cost (cited by 51% of respondents), competition from mail-order pharmacies (cited by 59%), and state Medicaid rates and Maximum Allowable Cost (MAC) and Federal Upper Limit (FUL) programs (cited by 53% of respondents).

To get ahead in the industry, Menighan believes, pharmacists will need to think creatively and reach out to the medical community to discuss new changes to healthcare.

"There are opportunities to partner with medicine in collaborative ways that are going to benefit everybody," he said.

One area that is not expected to be a challenge this year is the number of pharmacists in the market. While last year more than half of respondents believed that their states had a shortage of pharmacists, this year 74% of community pharmacists and 64% of hospital and LTC pharmacists said that they don't believe there is a pharmacist shortage in their states.


Cristina Medina

Cristina Medina, PharmD, manager of professional and college relations for CVS Caremark and a new member of *Drug Topics*' editorial advisory board, said that although the demand for pharmacists varies based on geographic region, most of the markets are now well staffed.

Medina attributes this change to an increase in pharmacy programs in the country and to the struggling economy.

The additional competition in the job market has not been lost on pharmacy students. Most students realize now that they may have to spend more time looking for a job, although Medina doesn't believe that the industry has become too diluted.

Continued on pg. 24

Continued from pg. 23

"I think there are definitely positions. I just think that in the major metropolitan areas students have to drive out further or go into different markets, but I think that supply is right with demand," she said.

Grading the associations

Pharmacy associations were established to serve the best interests of pharmacists, but how well they perform can be a matter of opinion. On the basis of responses to the *Drug Topics* survey, it appears that more than 40% of community, hospital, and LTC pharmacists are satisfied with the representation they've received.

According to the results, 43% of community pharmacists said they were satisfied with their pharmacy associations this year, while 27% were not and 30% did not know. Similarly, 42% of hospital and LTC pharmacists are satisfied with the way their associations have represented them, while 22% were not and 37% were not sure.

Mollien, who serves on both the Michigan Pharmacists Association and the APhA board, believes that associations can advocate for change that individual pharmacists may not have the time or power to effect on their own.

"One voice can be lost in a crowd," he said. "An association voice is more likely to be heard."


Edith Rosato

Edith Rosato, senior vice president of pharmacy affairs for the National Association of Chain Drug Stores (NACDS) and president of the NACDS Foundation, credited pharmacy associations with ushering in new industry changes, including the power pharmacists now have to administer immunizations in all 50 states, but, she said, not all pharmacists are sufficiently aware of the accomplishments achieved by associations.

"It's a fact that a lot of pharmacists out there really don't know who their associations are," she said.

Government programs

Medicare Part D received mixed reviews from community, hospital, and LTC pharmacists, although community pharmacists seemed to be more supportive overall of the program. According to the survey results, 43% of community pharmacists said that they believe Medicare Part D has had a positive impact on their pharmacy, while 23% believe it has had a negative impact. On the other hand, only 10% of hospital and LTC pharmacists cited a positive impact on their pharmacies, while 19% cited a negative impact, and 71% did not know.


Robert Greenwood

Robert J. Greenwood, RPh, is an independent pharmacy owner in Waterloo, Iowa, and president of the National Community Pharmacists Association (NCPA). When asked about Medicare Part D, he said that although prescription drug plans often offer recipients an economic incentive to use mail-order pharmacies, which can present its own set of challenges, overall he sees the Medicare Part D program as a positive aspect of business.

"The Medicare D program levels the playing field, [and] price is not part of the equation anymore," he said.

Pharmacists also had conflicting feelings about MTM services under Medicare Part D.

Drug Topics found that 38% of community pharmacists reported providing MTM services under Medicare Part D in 2010 and 26% of those who responded to the survey were paid an average of $1,536.90 for these services.

Furthermore, 17% of hospital and LTC pharmacists provided MTM services under Medicare Part D, and 6% of those survey respondents received an average of $1,791.70.

Garrett, who has had success with MTM services, said that she is able to provide additional counseling to Medicare surgical patients during preoperative visits for elective surgery. The hospital environment gives her more time to interact with patients and identify possible issues they may have before surgery.

One reason that MTM services have not been fully embraced by pharmacists may be the program's slow beginning, according to Rosato. She said that when the program began in 2003, many Medicare participants weren't eligible for it. Now, eligibility has increased and, Rosato believes, MTM services will gain momentum — possibly even beyond Medicare.

"One of the things that we're looking at as a profession is why not provide MTM services to patients who have chronic diseases?" she said.

While it's still unclear what effect the new Affordable Care Act will have on the industry, Greenwood said, he thinks the act will give pharmacists greater opportunities to demonstrate their value in the healthcare arena.

"Patients are going to be seen in a more ambulatory way than currently, and I see pharmacists being an extension of primary care delivery from the physician," he said. DT

Jill Sederstrom *is a freelance journalist based in Overland Park, Kansas.*

For additional information, visit www.PRADAXAPRO.com or call 1-866-395-1764.

NOW APPROVED

Boehringer Ingelheim

Pradaxa®

dabigatran etexilate

CAPSULES

Step up to a range of insulin delivery options.

As part of Eli Lilly and Company's ongoing commitment, we provide healthcare facilities with a choice of vial sizes.

Humalog® (insulin lispro injection [rDNA origin]), Humulin® R U-100 (regular insulin human injection, USP [rDNA origin]), and Humulin® N (NPH human insulin [rDNA origin] isophane suspension) are available in a smaller vial size.*

The smaller vials are designed to give healthcare facilities flexibility when evaluating insulin storage and distribution (floor stock vs individual patient supply), in addition to the 10 mL vial and Humalog® KwikPen™.

- Humalog NDC Number - 0002-7510-17
- Humulin R U-100 NDC Number - 0002-8215-17
- Humulin N NDC Number - 0002-8315-17

* Smaller vials contain 3 mL of insulin in a 5 mL vial.

Humalog Indication

Humalog (insulin lispro injection [rDNA origin]) is for use in patients with diabetes mellitus for the control of hyperglycemia. Humalog should be used with longer-acting insulin, except when used in combination with sulfonylureas in patients with type 2 diabetes.

Humalog Important Safety Information

Contraindications

Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or one of its excipients.

Warnings

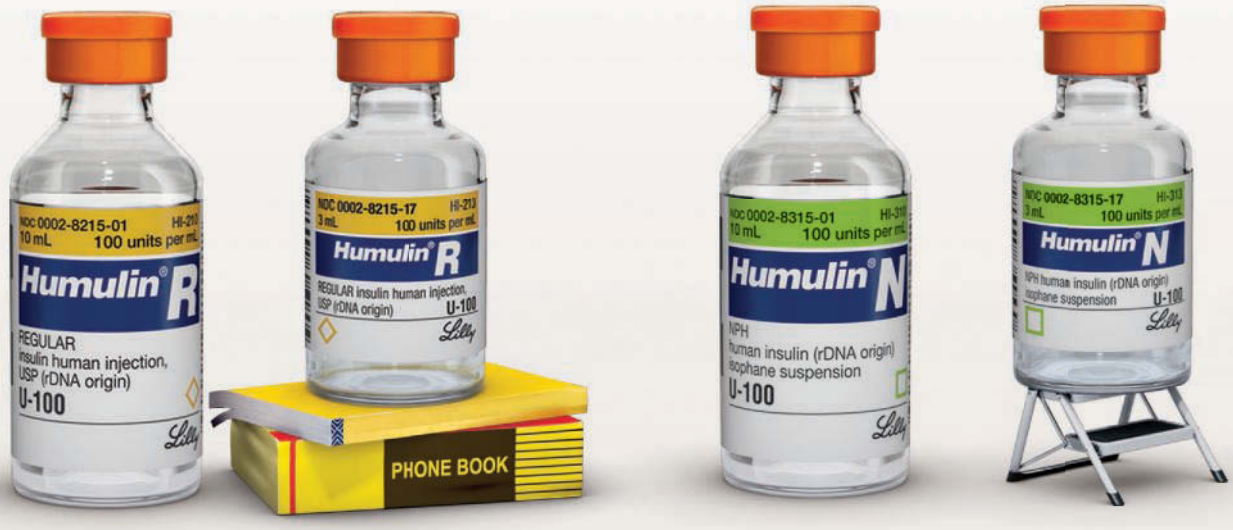
Humalog differs from regular human insulin by its rapid onset of action as well as a shorter duration of action. Therefore, when used as a mealtime insulin, Humalog should be given within 15 minutes before or immediately after a meal.

Due to the short duration of action of Humalog, patients with type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an insulin pump).

Glucose monitoring is recommended for all patients with diabetes.

The safety and effectiveness of Humalog in patients less than 3 years of age have not been established. There are no adequate and well-controlled clinical studies of the use of Humalog in pregnant or nursing women.

HI66337 0810 PRINTED IN USA



Humalog Important Safety Information, continued

Warnings, continued
Starting or changing insulin therapy should be done cautiously and only under medical supervision.

Hypoglycemia
Hypoglycemia is the most common adverse effect associated with insulins, including Humalog. Hypoglycemia can happen suddenly, and symptoms may be different for each person and may change from time to time. Severe hypoglycemia can cause seizures and may be life-threatening.

Other Side Effects
Other potential side effects associated with the use of insulins include: hypokalemia, weight gain, lipodystrophy, and hypersensitivity. Systemic allergy is less common, but may be life-threatening. Because of the difference

Humalog Important Safety Information, continued

Other Side Effects, continued
in action of Humalog, care should be taken in patients in whom hypoglycemia or hypokalemia may be clinically relevant (eg, those who are fasting, have autonomic neuropathy or renal impairment, are using potassium-lowering drugs, or taking drugs sensitive to serum potassium level).

Please see reverse side for Brief Summary of full Prescribing Information.

Please see full user manual that accompanies the pen.

Humalog®
insulin lispro injection (rDNA origin)

Humulin® R
REGULAR insulin
human injection, USP
(rDNA origin)

Humulin® N
NPH
human insulin (rDNA origin)
isophane suspension

Lilly

HUMALOG®

INSULIN LISPRO INJECTION (rDNA ORIGIN)

BRIEF SUMMARY: Consult package insert for complete prescribing information.

INDICATIONS AND USAGE: Humalog is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration of action than regular human insulin. Therefore, in patients with type 1 diabetes, Humalog should be used in regimens that include a longer-acting insulin. However, in patients with type 2 diabetes, Humalog may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents.

Humalog may be used in an external insulin pump, but should not be diluted or mixed with any other insulin when used in the pump. Humalog administration in insulin pumps has not been studied in patients with type 2 diabetes.

CONTRAINDICATIONS: Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or any of its excipients.

WARNINGS: This human insulin analog differs from regular human insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime insulin, the dose of Humalog should be given within 15 minutes before or immediately after the meal. Because of the short duration of action of Humalog, patients with type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an external insulin pump).

External Insulin Pumps: When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin. Patients should carefully read and follow the external insulin pump manufacturer's instructions and the "PATIENT INFORMATION" leaflet before using Humalog.

Physicians should carefully evaluate information on external insulin pump use in the Humalog physician package insert and in the external insulin pump manufacturer's instructions. If unexplained hyperglycemia or ketosis occurs during external insulin pump use, prompt identification and correction of the cause is necessary. The patient may require interim therapy with subcutaneous insulin injections (*see* PRECAUTIONS, *For Patients Using External Insulin Pumps, and* DOSAGE AND ADMINISTRATION).

Hypoglycemia is the most common adverse effect associated with the use of insulins, including Humalog. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using an external insulin pump.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (eg, regular, NPH, analog), species, or method of manufacture may result in the need for a change in dosage.

PRECAUTIONS: *General*—Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of Humalog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (eg, patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of Humalog action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

Hypoglycemia—As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment—The requirements for insulin may be reduced in patients with renal impairment.

Hepatic Impairment—Although impaired hepatic function does not affect the absorption or disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including Humalog, may be necessary.

Allergy—Local Allergy—As with any insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy—Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient. In Humalog-controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving Humulin R® (N=2969) and 30 patients receiving Humalog (N=2944) (*P*=.053).

Antibody Production—In large clinical trials, antibodies that cross-react with human insulin and insulin lispro were observed in both Humulin R- and Humalog-treatment groups. As expected, the largest increase in the antibody levels during the 12-month clinical trials was observed with patients new to insulin therapy.

Usage of Humalog in External Insulin Pumps—The infusion set (reservoir syringe, tubing, and catheter), Disetronic® D-TRON®[2,3] or D-TRONplus®[2,3] cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced and a new infusion site selected every 48 hours or less. Humalog in the external insulin pump should not be exposed to temperatures above 37°C (98.6°F).

In the D-TRON®[2,3] or D-TRONplus®[2,3] pump, Humalog 3 mL cartridges may be used for up to 7 days. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion site should be selected every 48 hours or less.

When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin (*see* INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, *For Patients Using External Insulin Pumps, Mixing of Insulins,* DOSAGE AND ADMINISTRATION, *and Storage*).

Information for Patients—Patients should be informed of the potential risks and advantages of Humalog and alternative therapies. Patients should also be informed about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic hemoglobin A1C testing, recognition and management of hypoglycemia and hyperglycemia, and periodic assessment for diabetes complications.

Patients should be advised to inform their physician if they are pregnant or intend to become pregnant.

Refer patients to the "PATIENT INFORMATION" leaflet for timing of Humalog dosing (≤15 minutes before or immediately after a meal), storing insulin, and common adverse effects.

For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read the "PATIENT INFORMATION" leaflet that accompanies the drug product and the User Manual that accompanies the delivery device. They should also reread these materials each time the prescription is renewed. Patients should be instructed on how to properly use the delivery device, prime the Pen to a stream of insulin, and properly dispose of needles. Patients should be advised not to share their Pens with others.

For Patients Using External Insulin Pumps: Patients using an external infusion pump should be trained in intensive insulin therapy and in the function of their external insulin pump and pump accessories. Humalog was tested in the MiniMed®[1] Models 506, 507, and 508 insulin pumps using MiniMed®[1] Polyfin®[1] infusion sets. Humalog was also tested in the Disetronic®[2] H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir), and the Disetronic D-TRON®[2,3] and D-TRONplus®[2,3] insulin pumps (with Humalog 3 mL cartridges) using Disetronic Rapid®[2] infusion sets.

The infusion set (reservoir syringe, tubing, catheter), D-TRON®[2,3] or D-TRONplus®[2,3] cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced, and a new infusion site selected every 48 hours or less. Humalog in the external pump should not be exposed to temperatures above 37°C (98.6°F).

A Humalog 3 mL cartridge used in the D-TRON®[2,3] or D-TRONplus®[2,3] pump should be discarded after 7 days, even if it still contains Humalog. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected.

Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

Laboratory Tests—As with all insulins, the therapeutic response to Humalog should be monitored by periodic blood glucose tests. Periodic measurement of hemoglobin A1C is recommended for the monitoring of long-term glycemic control.

Drug Interactions—Insulin requirements may be increased by medications with hyperglycemic activity, such as corticosteroids, isoniazid, certain lipid-lowering drugs (eg, niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy *(see* CLINICAL PHARMACOLOGY).

Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (eg, octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Mixing of Insulins—Care should be taken when mixing all insulins as a change in peak action may occur. The American Diabetes Association warns in its Position Statement on Insulin Administration, "On mixing, physiochemical changes in the mixture may occur (either immediately or over time). As a result, the physiological response to the insulin mixture may differ from that of the injection of the insulins separately." Mixing Humalog with Humulin® N or Humulin® U does not decrease the absorption rate or the total bioavailability of Humalog. Given alone or mixed with Humulin N, Humalog results in a more rapid absorption and glucose-lowering effect compared with regular human insulin.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies with insulin lispro have been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to Humalog. There are, however, no adequate and well-controlled studies with Humalog in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Although there are limited clinical studies of the use of Humalog in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Mothers—It is unknown whether Humalog is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when Humalog is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog dose, meal plan, or both.

Pediatric Use—In a 9-month, crossover study of prepubescent children (n=60), aged 3 to 11 years, comparable glycemic control as measured by A1C was achieved regardless of treatment group: regular human insulin 30 minutes before meals 8.4%, Humalog immediately before meals 8.4%, and Humalog immediately after meals 8.5%. In an 8-month, crossover study of adolescents (n=463), aged 9 to 19 years, comparable glycemic control as measured by A1C was achieved regardless of treatment group: regular human insulin 30 to 45 minutes before meals 8.7% and Humalog immediately before meals 8.7%. The incidence of hypoglycemia was similar for all 3 treatment regimens. Adjustment of basal insulin may be required. To improve accuracy in dosing in pediatric patients, a diluent may be used. If the diluent is added directly to the Humalog vial, the shelf life may be reduced (*see* DOSAGE AND ADMINISTRATION).

Geriatric Use—Of the total number of subjects (n=2834) in 8 clinical studies of Humalog, 12% (n=338) were 65 years of age or over. The majority of these were patients with type 2 diabetes. A1C values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of Humalog action have not been performed.

ADVERSE REACTIONS: Clinical studies comparing Humalog with regular human insulin did not demonstrate a difference in frequency of adverse events between the 2 treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole—allergic reactions (*see* PRECAUTIONS).

Skin and Appendages—injection site reaction, lipodystrophy, pruritus, rash.

Other—hypoglycemia (*see* WARNINGS *and* PRECAUTIONS).

OVERDOSAGE: Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION: Humalog is intended for subcutaneous administration, including use in select external insulin pumps (*see* DOSAGE AND ADMINISTRATION, *External Insulin Pumps*). Dosage regimens of Humalog will vary among patients and should be determined by the healthcare provider familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. Pharmacokinetic and pharmacodynamic studies showed Humalog to be equipotent to regular human insulin (ie, one unit of Humalog has the same glucose-lowering effect as one unit of regular human insulin), but with more rapid activity. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate from subcutaneous tissue. An adjustment of dose or schedule of basal insulin may be needed when a patient changes from other insulins to Humalog, particularly to prevent premeal hyperglycemia.

When used as a mealtime insulin, Humalog should be given within 15 minutes before or immediately after a meal. Regular human insulin is best given 30 to 60 minutes before a meal. To achieve optimal glucose control, the amount of longer-acting insulin being given may need to be adjusted when using Humalog.

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables. Humalog was absorbed at a consistently faster rate than regular human insulin in healthy male volunteers given 0.2 U/kg regular human insulin or Humalog at abdominal, deltoid, or femoral sites, the 3 sites often used by patients with diabetes. When not mixed in the same syringe with other insulins, Humalog maintains its rapid onset of action and has less variability in its onset of action among injection sites compared with regular human insulin (*see* PRECAUTIONS). After abdominal administration, Humalog concentrations are higher than those following deltoid or thigh injections. Also, the duration of action of Humalog is slightly shorter following abdominal injection, compared with deltoid and femoral injections. As with all insulin preparations, the time course of action of Humalog may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Humalog in a vial may be diluted with STERILE DILUENT for Humalog, Humulin N, Humulin R, Humulin 70/30, and Humulin® R U-500 to a concentration of 1:10 (equivalent to U-10) or 1:2 (equivalent to U-50). Diluted Humalog may remain in patient use for 28 days when stored at 5°C (41°F) and for 14 days when stored at 30°C (86°F). Do not dilute Humalog contained in a cartridge or Humalog used in an external insulin pump.

Parenteral drug products should be inspected visually before use whenever the solution and the container permit. If the solution is cloudy, contains particulate matter, is thickened, or is discolored, the contents must not be injected. Humalog should not be used after its expiration date. The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the cartridge or for the cartridge to be refilled with insulin.

External Insulin Pumps—Humalog was tested in MiniMed®[1] Models 506, 507, and 508 insulin pumps using MiniMed®[1] Polyfin®[1] infusion sets. Humalog was also tested in the Disetronic®[2] H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir) and the Disetronic D-TRON®[2,3] and D-TRONplus®[2,3] pumps (with Humalog 3 mL cartridges) using Disetronic Rapid®[2] infusion sets. Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

HOW SUPPLIED:

Humalog (insulin lispro injection, USP [rDNA origin]) is available in the following package sizes (with each presentation containing 100 units insulin lispro per mL [U-100]):

10 mL vials	NDC 0002-7510-01	(VL-7510)
3 mL vials	NDC 0002-7510-17	(VL-7533)
5 x 3 mL cartridges[3]	NDC 0002-7516-59	(VL-7516)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8725-59	(HP-8725)
5 x 3 mL prefilled insulin delivery devices (Humalog® KwikPen™)	NDC 0002-8799-59	(HP-8799)

[1] MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.
[2] Disetronic®, H-TRONplus®, D-TRON®, and Rapid® are registered trademarks of Roche Diagnostics GMBH.
[3] 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3 mL insulin delivery device, and Disetronic D-TRON® and D-TRONplus® pumps. Autopen® is a registered trademark of Owen Mumford, Ltd. HumaPen®, HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD are trademarks of Eli Lilly and Company.

Other product and company names may be the trademarks of their respective owners.

Storage—Unopened Humalog should be stored in a refrigerator (2° to 8°C [36° to 46°F]), but not in the freezer. Do not use Humalog if it has been frozen. Unrefrigerated (below 30°C [86°F]) 12 vials, cartridges, Pens, and KwikPens must be used within 28 days or be discarded, even if they still contain Humalog. Protect from direct heat and light.

Use in an External Insulin Pump—A Humalog 3mL cartridge used in the D-TRON®[2,3] or D-TRONplus®[2,3] should be discarded after 7 days, even if it still contains Humalog. Infusion sets, D-TRON®[2,3] and D-TRONplus®[2,3] cartridge adapters, and Humalog in the external insulin pump reservoir should be discarded every 48 hours or less.

Literature revised December 7, 2009

KwikPens manufactured by Eli Lilly and Company, Indianapolis, IN 46285, USA.
Pens manufactured by Eli Lilly and Company, Indianapolis, IN 46285, USA or Lilly France, F-67640 Fegersheim, France.
Vials manufactured by Eli Lilly and Company, Indianapolis, IN 46285, USA or Hospira, Inc., Lake Forest, IL 60045, USA or Lilly France, F-67640 Fegersheim, France.
Cartridges manufactured by Lilly France, F-67640 Fegersheim, France for Eli Lilly and Company, Indianapolis, IN 46285, USA.
www.humalog.com

RX CARE Fred Gebhart, Contributing Editor

Post–MI beta blocker doses too low

Care for patients with myocardial infarction (MI) may not be as good as quality measures suggest. New data show that while nearly all MI patients receive beta blockers, most patients receive suboptimal doses that are never increased.

"Beta blocker use is better than 93% at discharge," said Jeffrey Goldberger, MD, professor of medicine, Northwestern University Feinberg School of Medicine, Chicago. "We can attribute that to beta blockers post-MI becoming a quality measure. What we're not doing is ensuring that they are used at appropriate doses."

Pace-MI Trial

Dr. Goldberger is lead author of an analysis of data from the PACE-MI Trial, evaluating the survival impact of pacemaker-facilitated beta blocker therapy after MI in patients who have bradycardia contraindications to beta blockers. The study included a prospective registry of 1,971 consecutive MI patients across 19 centers admitted with MI between August 2007 and July 2008.

Registry data included beta blocker dose at discharge, Dr. Goldberger said. Physicians were queried 3 weeks after discharge for the current beta blocker dose. Researchers found that while 93.2% of patients were discharged on a beta blocker, only 17% of patients were receiving more than 50% of the recommended dose of metoprolol (Lopressor, Novartis), carvedilol (Coreg, GlaxoSmithKline), atenolol (Tenormin, AstraZeneca), propranolol (Inderal, Wyeth), or some other beta blocker.

If the resting heart rate is about 60 and does not spike dramatically during mild exercise such as walking, the patient is probably on an appropriate dose.

The right dose

"The question shouldn't be is the patient getting a beta blocker or not," Dr. Goldberger told *Drug Topics*. "The question should be is the patient getting the right dose of a beta blocker. For the majority of patients, the current answer is no."

Beta blocker dosing is a sticky issue, said Joseph Saseen, PharmD, FCCP, BCPS, CLS, professor of Clinical Pharmacy, University of Colorado Denver School of Pharmacy. Much of the data on appropriate dosing comes from heart-failure patients. Many MI patients progress to heart failure, but not all do so. Up-titrating beta blocker doses may be less important in patients who do not progress to heart failure.


Joseph Saseen

Older patients may also do well on lower doses of beta blockers. If the resting heart rate is about 60, Saseen noted, and does not spike dramatically during mild exercise such as walking, the patient is probably on an appropriate dose.

"This study is a good snapshot of beta blocker use post-MI, not the full picture," he said. "And there is good support for the notion that the beta blocker dose 3 weeks after discharge is a good indicator of dosage over the next year."

Short stays, less titration

Patients are traditionally started on a low dose of beta blocker and titrated up in the hospital, Dr. Goldberger said. But with shorter hospital stays, there is less time for managing dose titration. In many cases, it simply doesn't happen.

"Once you take a patient out of the post-MI setting, people tend to focus on absolutes like blood pressure and patient symptoms," he said. "They just don't think about beta blocker dosage. You don't need a physician to up the dose. You could just as easily use a pharmacist to follow up."

Quality systems

Tweaking existing quality systems can help, said Mary Andrawis, PharmD, MPH, director, clinical guidelines and quality improvement, American Society of Health-System Pharmacists. Most health systems evaluate beta blocker compliance with a simple yes/no question. Because dosing data are already captured, it should be possible to refine the quality measure to appropriate dose, not just any dose.


Mary Andrawis

"Beta blockers will be one of the first and easiest of these measures to take," she said. "Refining and evolving our quality measures is something we could implement in lipid dosing, anticoagulation therapy, and other areas."

Pharmacy could also play a role in discharge counseling, Andrawis said. Including beta blocker dosing as part of the medication reconciliation process when patients move into the community is a reasonable extension of care.

"Part of the discharge process is ensuring that the patient is seen again for appropriate follow-up," she said. "Checking a beta blocker dose is exactly what a pharmacist should be looking for." DT

AN ONGOING CE PROGRAM OF THE UNIVERSITY OF FLORIDA
COLLEGE OF PHARMACY AND *DRUG TOPICS*

An update on *Clostridium difficile* infection

Elias B. Chahine, PharmD, BCPS
ASSISTANT PROFESSOR OF PHARMACY PRACTICE
LLOYD L. GREGORY SCHOOL OF PHARMACY
PALM BEACH ATLANTIC UNIVERSITY
WEST PALM BEACH, FLORIDA

Allana J. Sucher, PharmD, BCPS
ASSOCIATE PROFESSOR OF PHARMACY PRACTICE
REGIS UNIVERSITY SCHOOL OF PHARMACY
DENVER, COLORADO

Clostridium difficile is an anaerobic, gram-positive spore-forming rod that exists in both a vegetative form and a resilient spore form. It was recognized as the cause of antibiotic-associated pseudomembranous colitis in 1978, and it remains the most common cause of healthcare-associated infectious diarrhea.[1,2]

C. difficile infection (CDI) refers to the presence in patients of clinical symptoms of disease (usually manifested as diarrhea) and either a stool test positive for the presence of *C. difficile* toxins or findings that reveal pseudomembranous colitis. CDI ranges in severity from asymptomatic colonization to fulminant disease characterized by severe diarrhea with intestinal complications. CDI is now recognized as a worldwide public health concern, as it is increasing in incidence, severity of disease, and associated mortality.

Clinical practice guidelines for treating CDI in adults have recently been updated through a collaboration of the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA).[3] This article focuses on these guidelines and reviews the current terminology, etiology, pathogenesis, and treatment recommendations for CDI.

Epidemiology

Between 1% and 3% of healthy adults and up to 50% of patients residing in hospitals and nursing homes are colonized with and asymptomatically carry *C. difficile* in their stool. Interestingly, the rates of colonization are higher in neonates, with reported ranges between 5% and 70%, although this population is less likely to develop the disease than adults. It is believed that the lower rates of disease in neonates are due to the immaturity of their intestinal cells, which lack receptors for one of the organism's disease-producing toxins.[4] *C. difficile* is currently recognized as the most common cause of nosocomial infectious diarrhea in nursing homes, and overall mortality associated with CDI is estimated to be more than 17% in the older adult population.[5]

CDI occurs in up to 8% of hospitalized patients and results in an estimated $1.3 billion annually in healthcare costs in the United States.[6,7] As previously mentioned, CDI is increasing in frequency and severity of disease. During the 1990s, the incidence of CDI in U.S. hospitals was approximately 30 to 40 cases per 100,000 persons; this number increased to 84 per 100,000 in 2005. The number of fatal CDI cases has also increased over this time.

A new strain of *C. difficile*, which has caused disease outbreaks in the United States, Canada, Europe, and Asia, was reported by the Centers for Disease Control and Prevention (CDC) in 2004.[8] This hypervirulent strain produces toxins A and B in quantities 16-fold to 20-fold higher than seen in other strains, and produces an additional third toxin, as well. This strain has been referred to by several different names: "North American pulsed-field gel electrophoresis type 1 (NAP-1)"; "restriction endonuclease pattern BI"; or "PCR ribotype 027." It is now commonly referred to as "NAP1/BI/027." Overall, the NAP1/BI/027 strain is considered to be easier to transmit, more virulent, and more difficult to treat than previously identified strains.[9]

Transmission

Transmission of *C. difficile* occurs via the fecal-oral route, through ingestion of either the vegetative form or the spore form of the microorganism. The spore form of *C. difficile* may survive on inanimate surfaces and is resistant to alcohol and routine disinfectants.[10] Transmission of the microorganism occurs in healthcare facilities via the fecal-oral route either directly from person to person (particularly from the spore-contaminated hands of healthcare workers) or from a contaminated environment, especially in institutions with improper hygiene practices, isolation precautions, or environmental cleaning practices.[11]

Pathogenesis

Disease pathogenesis of CDI involves the following factors: disruption of normal enteric flora; colonization with *C. difficile*; production by the microorganism of toxins A and B; and mucosal injury and inflammation. In general, disease progresses from a patient in an uncolonized state becoming colonized with *C. difficile* to the organism producing its toxins, ultimately resulting in CDI. The host's immune

GETTY IMAGES/ROB LEWINE

CE CREDIT: 2.0

EARN CE CREDIT FOR THIS ACTIVITY AT WWW.DRUGTOPICS.COM

EDUCATIONAL OBJECTIVES

Goal: To provide pharmacists with the knowledge necessary to appropriately treat and prevent *Clostridium difficile* infection.

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

- **Identify the most common risk factors for *Clostridium difficile* infection.**
- **Recommend the most appropriate therapeutic regimen, including pharmacologic and nonpharmacologic agents, for the prevention and treatment of *C. difficile* infection.**
- **List common adverse effects and drug interactions of medications used to treat *C. difficile* infection.**
- **Discuss infection-control strategies to prevent the spread of *C. difficile*.**

The University of Florida College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education

ACPE # 0012-9999-10-106-H01-P (K)

This lesson is not valid for CE credit after 12/31/2012.

To obtain immediate CE credit, take the test online at ***www.drugtopics.com***. Click on the "Continuing Education" box on the *Drug Topics* home page, which will take you to the CE site. Log in, find and click on this lesson, and follow the three simple steps. Test results will be displayed immediately and you can print the certificate showing your earned CE credits.

For questions concerning PRINT CEs, call 352-273-6275.
For questions concerning ONLINE CEs, call 877-252-7711.

system helps protect an individual from the progression of colonization to symptomatic disease. Those who are unable to produce antitoxin antibodies are more likely to develop severe disease and experience disease recurrence.[1]

The spore form of *C. difficile* is resistant to stomach acid and, once ingested, is able to survive passage through the stomach into the intestine, where it changes into its active vegetative form. If normal enteric flora are disrupted (as may occur in the presence of antimicrobial agents), the vegetative form can reproduce within intestinal crypts. The bacteria then release toxins key to the development of disease. Toxin A has proinflammatory activity, attracting neutrophils and monocytes, and has enterotoxic activity, loosening tight junctions between cells that line the colon. This allows the cytotoxic toxin B to enter into and degrade epithelial cells of the colon. The effect of both toxins causes colitis and may cause the formation of pseudomembranes on the intestinal wall that impair the normal process of reabsorption, ultimately producing watery diarrhea.[4]

NAP1/BI/027 strains of *C. difficile* have an altered repressor gene, which normally inhibits toxin production. These isolates produce 16 to 20 times more quantities of toxins A and B than other strains and also produce a unique third toxin, referred to as binary toxin, which acts synergistically with toxins A and B to produce more severe forms of disease.[4]

TABLE 1

Risk factors associated with CDI

Exposure risk factors	Host risk factors
Exposure to antimicrobial agents	Advanced age
Duration of hospitalization	Comorbidities
GI procedures (including feeding tubes)	Compromised immune system (cancer chemotherapy, other immunosuppressive agents, HIV)
Proximity to patients with CDI	

Abbreviations: CDI, Clostridium difficile *infection; GI, gastrointestinal; HIV, human immunodeficiency virus*
Source: Refs 1,3,7,9,12,13

Risk factors

The most important modifiable risk factor for acquiring CDI is receipt of an antimicrobial agent. Although longer exposure, exposure to multiple agents, or exposure to broader-spectrum agents may increase a patient's risk, even a single dose of an antimicrobial agent increases the risk for *C. difficile* colonization and symptomatic disease. In addition to use of antimicrobial agents, there are several other risk factors for CDI as indicated in **Table 1.**[1,3,7,9,12,13] It is not clear whether the use of acid-suppressing medications such as histamine-2 blockers or proton pump inhibitors increase a patient's risk for CDI; some studies have shown an epidemiologic association, but others have found that the association is due to confounding factors such as severity of illness and duration of hospitalization. In addition to previously established risk factors for disease, an increased incidence of CDI has been reported in otherwise healthy individuals ("community-associated" infection) and in women during the peripartum period.[1,3,7,9,12,13]

TABLE 2

Criteria for determining severity of illness resulting from CDI

Definition	Supportive data
Mild or moderate infection	WBC count ≤15,000 cells/μL and SCr <1.5 times the level prior to illness
Severe infection	WBC count ≥15,000 cells/μL and SCr >1.5 times the level prior to illness
Severe, complicated infection	Hypotension or shock, ileus, megacolon

Abbreviations: CDI, Clostridium difficile *infection; SCr, serum creatinine; WBC, white blood cell*
Source: Ref 3

Clinical presentation

Although the median incubation period between the ingestion of *C. difficile* and the development of CDI is 2 to 3 days, this varies greatly among individuals. Patients may become symptomatic soon after starting antimicrobial therapy or several weeks after completion of an antimicrobial regimen.[1,13]

Clinical manifestations of CDI range from asymptomatic carriage of the organism to mildly or moderately acute watery diarrhea, to severe disease characterized by pseudomembranous colitis. About 50% of patients will also have fever, cramping, lower abdominal pain, and leukocytosis. Complications of severe colitis include sepsis, toxic megacolon (characterized by colonic dilation >6 cm), colonic ileus, or bowel perforation. Patients who develop toxic megacolon or an ileus usually have abdominal pain and distension but may not develop diarrhea.[1,12]

The updated guidelines include proposed criteria for the definitions of mild or moderate, severe, and complicated CDI. The 3 main criteria that are recommended for consideration when choosing treatment include age (older patients may have a decreased immune response to *C. difficile* toxins); peak white blood cell (WBC) count (this may reflect the severity of colonic inflammation and potential for complications); and elevated serum creatinine level (this may indicate dehydration or inadequate renal perfusion from severe diarrhea). These criteria for severity of CDI, based on expert opinion, are included in **Table 2.**[3] Because treatment recommendations vary according to the patient's severity of illness, the clinician should be familiar with these definitions. However, the guidelines acknowledge that these

criteria may need to be adjusted in the future as further data become available.

Recurrent CDI is common, with some sources estimating that up to 50% of patients experience recurrent infection within 2 weeks after completion of therapy. Mechanisms of recurrence include relapse of infection from the original strain of *C. difficile* or re-infection with a new bacterial strain. Identified risk factors for recurrent CDI include exposure to antimicrobials during or after initial treatment for CDI and an impaired immune response against *C. difficile* toxins. A recently identified potential risk factor for recurrence may be the use of metronidazole as treatment for CDI, particularly in patients aged ≥65 years.

Diagnosis

Unless the clinician suspects that a patient has an ileus due to CDI, it is recommended that only patients with diarrhea (defined as 3 or more unformed stools in ≤24 hr) be tested for the presence of *C. difficile*. This is because of the high rate of persons with asymptomatic colonization with *C. difficile*. As previously stated, the diagnosis of CDI includes both clinical symptoms of diarrhea and either a positive stool test for *C. difficile* toxins or the presence of pseudomembranous colitis.[1]

In the United States, the most commonly used method for diagnosis of CDI is an enzyme immunoassay (EIA) testing for *C. difficile* toxins A and B. EIA testing is relatively easy to use and is associated with low labor costs. In addition, it has a rapid turnaround time of within 1 day, a high specificity, and an estimated sensitivity of 63% to 94%.[3]

Other testing methods that are more sensitive for detection of *C. difficile* but are less commonly used, due to higher cost and slower turnaround time, include a cell cytotoxin assay (to detect toxin activity in stools) and stool culture. It is recommended that stool cultures be performed for molecular typing of strains for the purpose of epidemiologic studies. Another testing strategy recently studied is a 2-step testing method that uses EIA detection of glutamate dehydrogenase (GDH), an enzyme produced by *C. difficile*, as an initial screening tool. A negative result is considered negative, while a positive assay requires additional testing to determine whether the strain of *C. difficile* is toxin-producing. This additional testing is performed with the cell cytotoxin assay or stool culture. The 2-step GDH testing method has a sensitivity of 85% to 95% and a specificity of 89% to 99%.[3]

Direct visualization of pseudomembranes on the colonic mucosa via endoscopy or histopathologic examination definitively establishes the diagnosis of pseudomembranous colitis. However, because of its cost, the potential risk of colonic perforation, and the availability of other tests for diagnosis, it is usually reserved for times when a rapid diagnosis is needed, as in the case of a patient with severe disease, or when other tests are insensitive or the results are delayed.[3,13]

Treatment

The goals of treatment for CDI are to stop the production of toxins, eradicate the microorganism, attenuate signs and symptoms of the disease, decrease disease recurrence, and prevent associated morbidity and mortality.

TABLE 3

Antimicrobial dosing recommendations for treatment of CDI

Antibiotics	Usual dosing regimen[c]
Vancomycin[a]	125 mg PO q 6 hr[a] 250 mg – 500 mg PO q 6 hr 500 mg dissolved in 100 mL normal saline via retention enema[b] q 6 hr
Metronidazole[a]	250 mg PO q 6 hr 500 mg PO q 8 hr[a] 500 mg IV q 8 hr
Nitazoxanide	500 mg PO q 12 hr
Bacitracin	25,000 U PO q 6 hr
Rifaximin	400 mg PO q 12 hr 200 mg PO q 8 hr
Rifampin[b]	300 mg – 600 mg PO q 12 hr
Tigecycline	100 mg IV loading dose, followed by 50 mg IV q 12 hr

Abbreviations: CDI, Clostridium difficile *infection; IV, intravenous; PO, by mouth; q, every*

[a] *Widely used*

[b] *No data support its use as monotherapy*

[c] *Dosages are for patients with normal renal and hepatic function*

Source: Ref 14

The newly released guidelines recommend treating CDI on the basis of disease severity.[3] In cases of mild CDI, early discontinuation of a precipitating antimicrobial will resolve symptoms in 15% to 23% of patients. Most cases, however, will require antimicrobial therapy directed against *C. difficile* in addition to routine fluid and electrolyte replacement as needed. Definitions of disease severity are included in **Table 2** (page 32), and adult dosages of antimicrobial agents used for the treatment of CDI are listed in **Table 3**.[3,14]

First episode of CDI. For mild-to-moderate cases of CDI, metronidazole 500 mg orally 3 times daily for 10 to 14 days is recommended. If the patient has a comorbidity or drug interaction that prohibits the use of metronidazole, oral vancomycin may be used instead. For severe cases of CDI, vancomycin 125 mg orally 4 times daily for 10 to 14 days is recommended. For severe, complicated cases, vancomycin 500 mg orally or by nasogastric tube in a liquid form 4 times daily plus metronidazole 500 mg intravenously every 8 hours is recommended for 10 to 14 days at the discretion

of the clinician. No evidence supports the routine use of oral metronidazole and oral vancomycin in combination. If a patient has a complete ileus, adding vancomycin 500 mg in 100 mL of normal saline administered per rectum as a retention enema may be considered. For critically ill patients, colectomy may be considered.[3] Vancomycin may be administered as capsule, or the reconstituted intravenous formulation may be administered orally after dilution in 1 ounce of water. The intravenous formulation may also be used to prepare an enema.

Recurrent CDI. The updated guidelines recommend treating the first recurrence of CDI with the same antibiotic used for the initial episode as long as the recurrence occurs at the severity level of the initial episode. The guidelines recommend against the use of metronidazole beyond the first recurrence of CDI, because of increased potential for cumulative neurotoxicity and because stool concentration of metronidazole tends to wane during recovery. For patients with a second recurrence of infection, vancomycin should be given via a tapered or pulsed regimen, such as the following example: at the end of the traditional vancomycin regimen, continue with vancomycin 125 mg twice daily for a week, then 125 mg once daily for a week, and 125 mg every 2 to 3 days for 2 to 8 weeks.[3]

A closer look at antibiotic treatment options

Vancomycin. Vancomycin is currently the only antibiotic that has been approved by FDA for the treatment of CDI. Oral vancomycin achieves high concentrations in the intestinal lumen and has little systemic absorption, which may explain the rapid response to its use. The administration of 2 g of oral vancomycin daily results in a mean fecal concentration of 3,100 µg/g of stool, which far exceeds the minimum inhibitory concentration (MIC) needed to inhibit 90% of strains of *C. difficile* (MIC_{90} 0.75 – 2 µg/mL).[15] Intravenous vancomycin should never be used for the treatment of CDI, as subtherapeutic levels reach the gastrointestinal (GI) tract when given via this route of administration. Higher dosing of vancomycin is recommended for cases complicated by an ileus to ensure that adequate therapeutic concentrations of drug are reached within the lumen of the colon.[16]

Due to concerns regarding the emergence of vancomycin-resistant enterococci (VRE), the use of vancomycin has historically been limited to patients with multiple episodes of CDI, patients intolerant to metronidazole, patients who had not responded to 2 to 5 days of treatment with metronidazole, or patients who were pregnant or breastfeeding. The recent emergence of the more toxic epidemic NAP1/BI/027 strain of *C. difficile* has caused a marked increase in the use of vancomycin as a first-line antibiotic.

In addition, a recent prospective, randomized, double-blind, placebo-controlled trial comparing vancomycin to metronidazole in the treatment of 172 patients with CDI stratified by disease severity showed that vancomycin was superior to metronidazole for severe cases.[17] The clinical cure rate was 97% with vancomycin and 76% with metronidazole (*P*=.02). Severe CDI was defined as endoscopic evidence of pseudomembranous colitis, treatment in the intensive care unit (ICU), or the presence of 2 or more of the following conditions within 48 hours of enrollment into the study: patient aged >60 years; temperature >38.3°C; albumin level <2.5 mg/dL; or WBC count >15,000 cells/mm^3.

Factors associated with treatment failure of metronidazole in patients with severe disease included a low albumin level, pseudomembranous colitis, or admission to the ICU. It is hypothesized that superiority of vancomycin over metronidazole for the treatment of severe disease may be due not to drug resistance but to decreased blood flow to the colon, and therefore lower local concentrations of metronidazole in patients with severe disease. For patients who meet criteria for severe CDI, use of vancomycin for treatment of a first episode or for disease recurrence is recommended.

Metronidazole. Metronidazole, although not FDA-approved for treatment of CDI, is widely used for that purpose. Both oral and intravenous metronidazole achieve sufficient concentrations in watery or semiformed stools. The administration of 1.2 g of oral metronidazole daily results in a mean fecal concentration of 0.4 to 14.9 µg/g of stool, and the administration of 1.5 g of intravenous metronidazole per day results in a mean fecal concentration of 5.1 to 24.2 µg/g of stool. This exceeds the MIC needed to inhibit 90% of existing strains of *C. difficile* (MIC_{90} 0.2 – 2 µg/mL).

Historically, metronidazole has been preferred to vancomycin because it is less expensive, it is less likely to induce the development of VRE, and it can be given by IV to patients who are unable to tolerate oral medications or to those with an ileus.[18,19] Even though a recent study questioned its efficacy, oral metronidazole has been proven to be as efficacious as oral vancomycin in patients with mild-to-moderate CDI.[20]

In a recent prospective, randomized, double-blind, placebo-controlled trial comparing vancomycin to metronidazole in the treatment of 172 patients with CDI stratified by disease severity, the clinical cure rate was 90% with metronidazole and 98% with vancomycin (*P*=.36).[17] However, when compared to vancomycin, metronidazole is associated with a slightly delayed response. It is also important for the clinician to be aware that the NAP1/BI/027 strain of *C. difficile* may not respond well to metronidazole therapy. In addition, vancomycin is preferred over metronidazole in patients with severe episodes of CDI, patients with complicated courses of CDI, patients with more than one recurrence of CDI, and patients who are pregnant or breastfeeding.

Nitazoxanide. Nitazoxanide is an antiparasitic agent that has been shown to be active against *C. difficile*. In a small prospective, double-blind, randomized controlled trial comparing nitazoxanide with vancomycin for the treatment of 50 patients with CDI, the initial response rates were 77% with nitazoxanide and 74% with vancomycin (95% confidence interval [CI], -24% to 28%) and the sustained response rates were 89% with nitazoxanide and 78% with vancomy-

cin (95% CI, -18% to 35%).[21] Although results of this small study suggest that nitazoxanide may be as effective as vancomycin for the treatment of patients with CDI, the authors acknowledge that larger studies are needed before definitive conclusions about its place in therapy can be drawn.

In a prospective, randomized, double-blind study comparing nitazoxanide with metronidazole for the treatment of 110 patients with CDI, the initial response rates were 89.5% with nitazoxanide and 82.4% with metronidazole (95% CI, -7.1% to 25.5%) and the sustained response rates were 65.8% with nitazoxanide given for 7 days, 74.3% with nitazoxanide given for 10 days, and 57.6% with metronidazole for 10 days (*P*=.34).[22] The authors concluded that nitazoxanide is at least as effective as metronidazole in the treatment of patients with CDI.

In an open-label study, nitazoxanide was also shown to be effective in 26 (74%) of 35 patients who did not respond to treatment with metronidazole for CDI; however, 7 patients later had recurrent disease yielding an estimated overall cure rate of 54%.[23] Although it is not currently recommended in the updated guidelines for routine use, nitazoxanide may represent an alternative option for the treatment of initial and recurrent CDI.

Bacitracin. Bacitracin, a commonly used topical antibiotic for the treatment of staphylococcal infections, has been shown to be active against *C. difficile* when given in an oral formulation.[24] The injection formulation is extemporaneously prepared and flavored to improve palatability. Although parenteral bacitracin therapy is associated with renal failure, oral administration achieves low, nontoxic serum concentrations. Studies conducted in the 1980s showed that oral bacitracin was as effective as oral vancomycin in resolving the symptoms of CDI, but that it was less effective in eradicating *C. difficile* and its toxin from the stools of patients.[24,25] The fact that some patients still had detectable toxins in stools did not affect the number of clinical recurrences in one study.

Rifaximin. Rifaximin, a rifamycin antibiotic with limited oral bioavailability, is approved by FDA for the treatment of travelers' diarrhea and for prophylaxis against hepatic encephalopathy. As it is active in vitro against *C. difficile* and achieves a high concentration in the colon, rifaximin is currently under investigation for the treatment of CDI. In a recent uncontrolled case series, 4 of 6 patients with multiple recurrences of CDI responded to rifaximin therapy immediately after completing their last course of vancomycin therapy.[26]

In another uncontrolled case series, 8 women who each experienced 4 to 8 episodes of diarrhea due to *C. difficile* were given a 2-week course of rifaximin therapy immediately after completing their last course of vancomycin therapy. Seven of the 8 patients experienced no further recurrence of diarrhea. However, resistance of *C. difficile* to this agent has already been reported, so its use is not recommended until further clinical trials have been performed.[27,28]

Rifampin. Rifampin has been used as adjunctive therapy with either vancomycin or metronidazole for the treatment of CDI, as it has been shown to have potent in vitro activity against *C. difficile* and anecdotal reports have shown success with its use.[29] A small prospective, randomized, single-blinded study was performed to compare metronidazole monotherapy versus metronidazole plus rifampin for the treatment of 39 patients with a primary episode of CDI.[29] After 10 days of treatment, no difference was observed between treatment groups in terms of time to symptom improvement (6.5 days vs 9 days; *P*=.74), proportion of patients with relapse (38% vs 42%; *P*=1.0), or time to first relapse (16 days vs 26 days; *P*=.23). The authors concluded that rifampin does not have a role for use as routine adjunctive therapy with metronidazole for the treatment of CDI.

Tigecycline. Tigecycline is a parenteral glycylcycline antibiotic approved by FDA for the treatment of complicated skin and skin-structure infections, complicated intra-abdominal infections, and community-acquired pneumonia. Tigecycline is active in vitro against *C. difficile* and has been reported successful in the treatment of CDI in an uncontrolled case series of 4 patients with severe CDI, including patients with ileus and patients refractory to vancomycin and metronidazole.[30-32] None of the tigecycline-treated patients relapsed within 3 months of therapy, which makes tigecycline an attractive potential addition to the arsenal of antibiotics directed against *C. difficile*.

Antibiotic agents available outside the U.S.

Teicoplanin. Teicoplanin, a glycopeptide similar to vancomycin but not available in the United States, has been shown to have excellent activity against *C. difficile* and similar efficacy to oral vancomycin in prospective randomized studies.[33-35]

Fusidic acid. Fusidic acid is a commonly used topical antibiotic in Europe and Canada for the treatment of skin infections due to gram-positive bacteria. Although oral fusidic acid is effective for the treatment of CDI, its use is associated with a higher rate of relapse when compared to vancomycin or metronidazole.[35,36]

Investigational antibiotic agents

Fidaxomicin. Fidaxomicin, also known by several other names including OPT-80 or difimicin, is a novel macrocyclic antibiotic that exhibits potent *in vitro* activity against *C. difficile*. It has a narrow spectrum of activity and lacks activity against Gram-negative bacteria, thus potentially limiting its effect on GI flora. Studies have shown that oral fidaxomicin achieves high concentrations in stool while maintaining low plasma concentrations. Preliminary results from phase 2 and 3 clinical trials involving patients with CDI showed favorable outcomes for difimicin when compared to oral vancomycin.[37]

Ramoplanin. Ramoplanin, a novel glycolipodepsipeptide nonabsorbable antibiotic, showed a potential benefit against *C. difficile* in both *in vitro* studies and an *in vivo* hamster model. One study showed that all isolates of *C. difficile*, independent of their levels of susceptibility to vancomycin or metronidazole, were susceptible to ramoplanin.[38] The

results of a second study suggested that ramoplanin may be more effective than vancomycin at eradicating *C. difficile* spores and preventing spore recrudescence.[39] The FDA approved a Special Protocol Assessment non-inferiority trial against vancomycin for phase 3.

Nonantibiotic treatment options

Anion-binding resins. The anion-binding resins include cholestyramine and colestipol. Cholestyramine is theoretically useful for the treatment of CDI because it binds to the disease-producing toxins secreted by *C. difficile* without altering GI flora. However, although there are some reports of patients with disease relapses responding to cholestyramine, not enough clinical evidence supports its routine use for CDI. In addition, cholestyramine may bind to an oral vancomycin, thus potentially decreasing its effect. It is important for the clinician to note that other medications must be given 1 hour before or 4 to 6 hours after an anion-binding resin to maintain therapeutic efficacy.[4,14,40]

One randomized, placebo-controlled trial of colestipol in 38 patients with postoperative diarrhea showed no difference in fecal excretion of *C. difficile* toxins as compared to placebo. Therefore the use of colestipol for the treatment of CDI is not justified.[41]

Toxin-binding polymer. Tolevamer is a nonantimicrobial toxin-binding polymer that has been studied for the treatment of CDI. Although it showed early promise from *in vitro*, animal, and phase 2 studies, a randomized, double-blind, phase 3 clinical trial showed that tolevamer was less effective than either vancomycin or metronidazole for CDI.[42,43] Interestingly, among patients who did achieve clinical success with tolevamer, use of this agent was associated with significantly lower rates of disease recurrence.

Probiotics. Probiotics, which are live microorganisms that confer a potential health benefit when administered in adequate amounts, have been used in practice for the treatment and prevention of CDI.[44] Examples of probiotics used for this purpose include *Bifidobacterium spp., Lactobacillus rhamnosus* GG, and *Saccharomyces spp.*[45] Although some small studies and meta-analyses have provided data suggesting that prophylactic use of probiotics may decrease the incidence of CDI, no large, prospective, randomized trials have been designed to assess the benefits of probiotics for the prevention or treatment of CDI.

One small open-label trial assessing the effect of *S. boulardii* added to oral vancomycin in patients with recurrent CDI showed that 11 of 13 patients had no further recurrences of infection with this combination.[46]

In addition to a lack of data, product dosages of probiotics are not standardized, and there have been reports of fungemia resulting from *Saccharomyces spp.* and bacteremia resulting from *Lactobacillus spp.*, especially in patients who are critically ill or immunocompromised. Thus, the guidelines recommend against using probiotics to prevent primary CDI until further, larger trials are conducted. The guidelines acknowledge that adjunctive *S. boulardii* may be useful for treatment of recurrent CDI, but caution against its use in those who are immunocompromised or critically ill.

Immunomodulators. Intravenous immunoglobulin (IVIG) has been used in the treatment of CDI with variable success.[47] IVIG is formed through pooling immunoglobulin (containing antitoxin A and B antibodies) from donors and providing this passive immunization to a host who is unable to form an adequate protective immune response. Because low levels of IgG antitoxin are associated with increased disease severity, IVIG may compensate for this failed host immune response to *C. difficile* toxins.

Although there are no prospective, randomized, controlled clinical trials of IVIG, case reports and case series suggest that it may be efficacious for patients with severe or recurrent CDI.[48] There is conflicting evidence, however, as published retrospective reviews showed no clinical benefit with the use of IVIG in patients with severe disease. Additional drawbacks to IVIG therapy include its unknown optimal dose, high cost, limited supply, and adverse effect profile. The updated guidelines refer to IVIG as a potential option for the treatment of recurrent disease.

Recently, a phase 2 randomized, double-blind, placebo-controlled trial of 2 human monoclonal antibodies against *C. difficile* toxins A and B was performed.[49] This study showed a significantly decreased rate of recurrence of CDI when the simultaneously administered monoclonal antibodies were added to antibiotic agents. No significant difference was seen in the incidence of adverse effects between the monoclonal antibody and placebo groups. The ultimate role of monoclonal antibodies for the treatment of CDI is yet to be determined.

Corticosteroids. Given that *C. difficile* can cause diarrhea and colitis from an inflammatory reaction to its toxins, and that corticosteroids have been shown to be effective in inflammatory bowel disease, clinicians may try these agents in patients with refractory CDI. A preliminary report describing the use of intravenous methylprednisolone followed by oral prednisone in a child with severe CDI refractory to treatment with metronidazole and vancomycin suggests that corticosteroids may be effective.[50] The steroid dosing regimen used in this study was IV methylprednisolone 2 mg/kg/day in 2 divided doses for 16 days, followed by oral prednisone 2 mg/kg/day in 2 divided doses, with a gradual taper over the course of 1 month. Further studies are necessary to confirm this case-report observation.

Stool transplantation. Fecal bacteriotherapy is defined as the transfer of stool from one person to another. Also known as fecal transplant, this process seeks to recolonize the normal bacterial flora of the intestines.[51] In the largest retrospective review of patients who received donor stool by nasogastric tube for recurrent CDI, 15 of 18 patients were cured, 1 patient experienced a single recurrence, and 2 patients died of unrelated illnesses.[52] No adverse effects were associated with stool treatment. Several other published re-

ports have attested to positive results from the use of fecal bacteriotherapy for recurrent episodes of CDI.[53] The updated guidelines list fecal transplant as a potential option for recurrent CDI if the donor is properly screened for potentially transmissible agents and if the logistical issues of collection and administration can be adequately addressed.

Vaccines. A *C. difficile* vaccine containing toxoids A and B is currently under development for prevention of infection in high-risk individuals. Preliminary results demonstrated safety and immunogenicity in healthy volunteers as well as in patients with recurrent CDI.[54,55] These results must still be validated in large randomized controlled trials, because there is concern that the vaccine may not be effective in those who are unable to develop an adequate immune response to *C. difficile* toxins, as is common in patients with recurrent disease. The vaccine manufacturer is currently recruiting U.S. patients with CDI for a phase 2 randomized, double-blind, placebo-controlled dose-ranging study of the vaccine.[56]

Antiperistaltics. Drugs that inhibit intestinal peristasis, including loperamide, diphenoxylate, and narcotics, should generally be avoided in patients with infectious diarrhea. These agents may hinder the flushing of GI bacteria such as *C. difficile* and its associated toxins. It is hypothesized that these agents may prolong the mucosal exposure to toxins, possibly predisposing patients to complications such as toxic megacolon.[57]

A recently published literature review challenges this long-standing hypothesis.[58] The authors found that all cases of CDI treated with an antimotility agent that subsequently developed complications also failed to receive an appropriate anti-*C. difficile* antimicrobial agent. This review concluded that further controlled studies are needed to determine the role of antiperistaltics (because these agents may assist with faster resolution of diarrhea) for the treatment of CDI. Until the results of a prospective clinical trial are available, most practitioners would withhold antiperistaltic agents from a patient with CDI.

Evaluation of therapeutic outcomes

Efficacy. When treating patients with CDI, clinicians should closely monitor them for resolution of signs and symptoms of infection. A patient's temperature and WBC count should normalize within 48 to 72 hours of start of effective therapy, and diarrhea should improve within 48 hours and resolve by day 6 to day 7 of treatment. In light of the risk that infection may recur, close follow-up of patients is warranted. If a patient's disease progresses after the start of treatment, a complication may be present, and additional or alternative therapeutic options, including surgery, may need to be considered.[12,13]

Safety. The common side effects of antimicrobial agents available in the United States for the treatment of CDI are listed in **Table 4**.[14] More serious but less commonly encountered side effects are discussed below.

Although ***oral vancomycin*** is not systemically absorbed to a significant extent in patients with an intact intestinal mucosa, there may be some systemic absorption when the intestinal mucosa is severely altered, as is common in severe CDI. Monitoring for nephrotoxicity is therefore recommended in patients taking oral vancomycin who have a severely damaged intestinal mucosa.

TABLE 4

Common side effects of antimicrobials used to treat CDI

Antibiotics	Side effects
Vancomycin	Bitter taste, nausea/vomiting, fever/chills
Metronidazole	Metallic taste, GI upset, disulfiram-like reaction with alcohol, discoloration of urine, confusion
Nitazoxanide	Abdominal pain, diarrhea, nausea/vomiting, headache
Bacitracin	Nausea/vomiting, hypotension
Rifaximin	Headache, dizziness, peripheral edema, hypersensitivity reactions
Rifampin	Red-orange discoloration of body fluids, GI upset, increased liver function tests
Tigecycline	Nausea/vomiting, diarrhea, increased liver function tests

Abbreviations: CDI, Clostridium difficile *infection; GI, gastrointestinal*
Source: Ref 14

Metronidazole carries a black-box carcinogenicity warning based on animal data. Its prolonged use may cause neuropathy and seizures. In addition, metronidazole inhibits CYP3A4 and displaces warfarin from protein-binding sites, thus potentially increasing a patient's international normalized ratio (INR) and risk for bleeding. Close monitoring of INR is highly recommended in patients receiving both metronidazole and warfarin.

Parenteral bacitracin may cause renal failure resulting from tubular and glomerular necrosis. Although nephrotoxicity is not expected when bacitracin is used orally, one might consider monitoring renal function in patients with severe CDI.

A***nion-binding resins.*** When using these as adjunctive therapy, the clinician should take into account the fact that these agents have been shown to bind to oral vancomycin and have the potential to bind to other oral antibiotics and drugs, and thus compromise their efficacy.

Tigecycline has the potential to cause permanent discoloration of teeth and is not recommended in pregnant patients and in patients aged <8 years. Rare cases of pancreatitis have also been reported with this agent.

Prevention. CDI often occurs after administration of antimicrobials, so judicious and appropriate use of antimicrobials is extremely important to reduce the risk of CDI. Implementation of formal antimicrobial stewardship programs targeted at reducing the frequency and duration of antimicrobial therapy and restriction of certain high-risk antimicrobials such as clindamycin and broad-spectrum agents have been shown to reduce outbreaks of *C. difficile*.[3] Discon-

tinuation of unnecessary acid-suppressing medications may also be helpful. Prophylactic use of anti-CDI therapy such as metronidazole or vancomycin, also known as early preventive therapy, has been used in certain patients considered to be at high risk for the development of disease, despite the absence of supporting literature for this routine practice. Administration of probiotics is not recommended to prevent primary CDI because of lack of supporting evidence and because of increased risk of bacteremia and fungemia, particularly in severely ill and immunocompromised patients.[3]

Close attention to personal hygiene such as the use of a dedicated commode for each patient, isolation precautions such as the use of single rooms, barrier precautions such as the use of gloves and gowns, and appropriate hygiene and environmental cleaning are also very important in preventing transmission of healthcare-associated infections, including CDI. Oral and particularly rectal thermometers should be replaced with single-use disposable thermometers to minimize potential spread of this microorganism.

As mentioned previously, the spore form of *C. difficile* may survive on inanimate surfaces for long periods of time and is resistant to alcohol and routine disinfectants. Thus, healthcare professionals should wash their hands using soap and water instead of alcohol-based hand rubs. Chlorine-based solutions such as hypochlorite and isocyanuric acid are preferred for environmental cleaning over traditional quaternary ammonium-based agents, as the latter are not sporicidal. A recent study showed that aerosolization of *C. difficile* occurs in patients with symptomatic CDI.[10] Therefore the necessity for isolation of patients in single rooms as soon as possible after the onset of diarrhea cannot be overemphasized.

Role of the pharmacist

CDI is an emerging threat to patient safety. Pharmacists play a vital role in managing the disease by educating patients and healthcare professionals about risk factors for CDIs. Pharmacists are in a key position to refer patients with symptoms consistent with CDI to a clinician for further work-up. Pharmacists are also well positioned to recommend appropriate antimicrobial treatment regimens, as well as to monitor and counsel patients about drug therapy to achieve optimal outcomes, while minimizing side effects and unnecessary toxicity. Pharmacists trained in infectious diseases are essential for the establishment of antimicrobial stewardship programs targeted at reducing outbreaks of *C. difficile*. Finally, pharmacists may also serve on infection control committees and emphasize the importance of hygiene and environmental cleaning in reducing transmission of *C. difficile*. DT

References

1. Poutanen SM, Simor AE. *Clostridium difficile*-associated diarrhea in adults. *CMAJ*. 2004;171:51–58.

2. Vasa CV, Glatt AE. Effectiveness and appropriateness of empiric metronidazole for *Clostridium difficile*-associated diarrhea. *Am J Gastroenterol*. 2003;98:354–358.

3. Cohen SH, Gerding DN, Johnson S, Kelly CP, et al; Society for Healthcare Epidemiology of America; Infectious Disease Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol.* 2010;31:431–455.

4. McMaster-Baxter NL, Musher DM. *Clostridium difficile*: Recent epidemiologic findings and advances in therapy. *Pharmacotherapy*. 2007;27:1029–1039.

5. Crogan NL, Evans BC. *Clostridium difficile*: An emerging epidemic in nursing homes. *Geriatr Nurs*. 2007;28:161–164.

6. Dubberke ER, Wertheimer AI. Review of current literature on the economic burden of *Clostridium difficile* infection. *Infect Control Hosp Epidemiol*. 2009;30:57–66.

7. Leffler DA, Lamont JT. Treatment of *Clostridium difficile*-associated disease. *Gastroenterology*. 2009;136:1899–1912.

8. Centers for Disease Control and Prevention. Information about the current epidemic strain of *Clostridium difficile*. http://www.cdc.gov/ncidod/dhqp/id_CdiffFAQ_newstrain.html. Accessed November 17, 2010.

9. Kelly CP, LaMont JT. *Clostridium difficile* – more difficult than ever. *N Engl J Med*. 2008;359:1932–1940.

10. Best EL, Fawley WN, Parnell P, Wilcox MH. The potential for airborne dispersal of *Clostridium difficile* from symptomatic patients. *Clin Infect Dis.* 2010;50:1450–1457.

11. Sunenshine RH, McDonald LC. *Clostridium difficile*-associated disease: New challenges from an established pathogen. *Cleve Clin J Med*. 2006;73:187–197.

12. Stanley JD, Burns RP. *Clostridium difficile* and the surgeon. *Am Surg.* 2010;76:235–244.

13. Efron PA, Mazuski JE. *Clostridium difficile* colitis. *Surg Clin North Am*. 2009;89:483–500.

14. Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. *Drug Information Handbook 2009-2010.* 18th ed. Hudson, OH: Lexi-Comp Inc; 2009.

15. Shannon-Lowe J, Matheson NJ, Cooke FJ, Aliyu SH. Prevention and medical management of *Clostridium difficile* infection. *BMJ*. 2010;340:c1296.

16. Fekety R, Silva J, Kauffman C, Buggy B, Deery HG. Treatment of antibiotic-associated *Clostridium difficile* colitis with oral vancomycin: Comparison of two dosage regimens. *Am J Med.* 1989;86:15–19.

17. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis.* 2007;45:302–307.

18. Teasley DG, Gerding DN, Olson MM et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium difficile*-associated diarrhoea and colitis. *Lancet*. 1983;2:1043–1046.

19. Johnson S, Peterson LR, Gerding DN. Intravenous metronidazole and *Clostridium difficile*-associated diarrhea or colitis. *J Infect Dis.* 1989;160:1087–1088.

20. Johnson S, Homann SR, Bettin KM et al. Treatment of asymptomatic *Clostridium difficile* carriers (fecal excretors) with vancomycin or metronidazole. A randomized, placebo-controlled trial. *Ann Intern Med*. 1992;117:297–302.

21. Musher DM, Logan N, Bressler AM, Johnson DP, Rossignol JF. Nitazoxanide versus vancomycin in *Clostridium difficile* infection: a randomized, double-blind study. *Clin Infect Dis.* 2009;48:e41–e46.

22. Musher DM, Logan N, Hamill RJ, et al. Nitazoxanide for the treatment of *Clostridium difficile* colitis. *Clin Infect Dis.* 2006;43:421–427.
23. Musher DM, Logan N, Mehendiratta V et al. *Clostridium difficile* colitis that fails conventional metronidazole therapy: Response to nitazoxanide. *J Antimicrob Chemother.* 2007;59:705–710.
24. Dudley MN, McLaughlin JC, Carrington G, et al. Oral bacitracin vs vancomycin therapy for *Clostridium difficile*-induced diarrhea. A randomized double-blind trial. *Arch Intern Med.* 1986;146:1101–1104.
25. Young GP, Ward PB, Bayley N, et al. Antibiotic-associated colitis due to *Clostridium difficile*: Double-blind comparison of vancomycin with bacitracin. *Gastroenterology*. 1985;89:1038–1045.
26. Johnson S, Schriever C, Patel U, et al. Rifaximin redux: Treatment of recurrent *Clostridium difficile* infections with rifaximin immediately post-vancomycin treatment. *Anaerobe*. 2009;15:290–291.
27. Johnson S, Schriever C, Galang M, Kelly CP, Gerding DN. Interruption of recurrent *Clostridium difficile*-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. *Clin Infect Dis.* 2007;44:846–848.
28. O'Connor JR, Galang MA, Sambol SP, et al. Rifampin and rifaximin resistance in clinical isolates of *Clostridium difficile. Antimicrob Agents Chemother.* 2008;52:2813–2817.
29. Lagrotteria D, Holmes S, Smieja M, Smaill F, Lee C. Prospective, randomized inpatient study of oral metronidazole versus oral metronidazole and rifampin for treatment of primary episode of *Clostridium difficile*-associated diarrhea. *Clin Infect Dis*. 2006;43:547–552.
30. Herpers BL, Vlaminckx B, Burkhardt O, et al. Intravenous tigecycline as adjunctive or alternative therapy for severe refractory *Clostridium difficile* infection. *Clin Infect Dis.* 2009;48:1732–1735.
31. Lu CL, Liu CY, Liao CH, et al. Severe and refractory *Clostridium difficile* infection successfully treated with tigecycline and metronidazole. *Int J Antimicrob Agents*. 2010;35:311–312.
32. Hawser SP. Activity of tigecycline against recent European clinical isolates of *Clostridium difficile*. *Int J Antimicrob Agents.* 2010;35:97–98.
33. Nelson R. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. *Cochrane Database Syst Rev*. 2007;(3):CD004610.
34. de Lalla F, Nicolin R, Rinaldi E, et al. Prospective study of oral teicoplanin versus oral vancomycin for therapy of pseudomembranous colitis and *Clostridium difficile*-associated diarrhea. *Antimicrob Agents Chemother.* 1992;36:2192–2196.
35. Wenisch C, Parschalk B, Hasenhündl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. *Clin Infect Dis*. 1996;22:813–818.
36. Wullt M, Odenholt I. A double-blind randomized controlled trial of fusidic acid and metronidazole for treatment of an initial episode of *Clostridium difficile*-associated diarrhea. *J Antimicrob Chemother.* 2004;54:211–216.
37. Sullivan KM, Spooner LM. Fidaxomicin: A macrocyclic antibiotic for the management of *Clostridium difficile* infection. *Ann Pharmacother.* 2010;44:352–359.
38. Peláez T, Alcalá L, Alonso R, et al. In vitro activity of ramoplanin against *Clostridium difficile*, including strains with reduced susceptibility to vancomycin or with resistance to metronidazole. *Antimicrob Agents Chemother.* 2005;49:1157–1159.
39. Freeman J, Baines SD, Jabes D, Wilcox MH. Comparison of the efficacy of ramoplanin and vancomycin in both in vitro and in vivo models of clindamycin-induced *Clostridium difficile* infection. *J Antimicrob Chemother.* 2005;56:717–725.
40. Parmar M. Treating *C. difficile* (author reply). *CMAJ*. 2005;172:448.
41. Mogg GA, George RH, Youngs D, et al. Randomized controlled trial of colestipol in antibiotic-associated colitis. *Br J Surg.* 1982;69:137–139.
42. Baines SD, Freeman J, Wilcox MH. Tolevamer is not efficacious in the neutralization of cytotoxin in a human gut model of *Clostridium difficile* infection. *Antimicrob Agents Chemother.* 2009;53:2202–2204.
43. Louie T, Gerson M, Grimard D, et al. Results of a phase III trial comparing tolevamer, vancomycin and metronidazole in patients with *Clostridium difficile*-associated diarrhea (CDAD) [abstract K-425a]. In: Program and abstracts of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Washington, DC: American Society for Microbiology; 2007:219.
44. Williams NT. Probiotics. *Am J Health-Syst Pharm.* 2010;67:449–458.
45. Segarra-Newnham M. Probiotics for *Clostridium difficile*-associated diarrhea: Focus on *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii. Ann Pharmacother.* 2007;41:1212–1221.
46. Surawicz CM, McFarland LV, Elmer G, Chinn J. Treatment of recurrent *Clostridium difficile* colitis with vancomycin and *Saccharomyces boulardii. Am J Gastroenterol.* 1989;84:1285–1287.
47. Juang P, Skledar SJ, Zgheib NK, et al. Clinical outcomes of intravenous immune globulin in severe *Clostridium difficile*-associated diarrhea. *Am J Infect Control.* 2007;35:131–137.
48. Abougergi MS, Broor A, Cui W, Jaar BG. Intravenous immunoglobulin for the treatment of severe *Clostridium difficile* colitis: An observational study and review of the literature. *J Hosp Med.* 2010;5:E1–E9.
49. Lowy I, Molrine DC, Leav BA, et al. Treatment with monodonal antibodies against *Clostridium difficile* toxins. *N Engl J Med.* 2010;362:197–205.
50. Cavagnaro C, Berezin S, Medow MS. Corticosteroid treatment of severe, non-responsive *Clostridium difficile*-induced colitis. *Arch Dis Child*. 2003;88:342–344.
51. Bakken JS. Fecal bacteriotherapy for recurrent *Clostridium difficile* infection. *Anaerobe*. 2009;15:285–289.
52. Aas J, Gessert CE, Bakken JS. Recurrent *Clostridium difficile* colitis: Case series involving 18 patients treated with donor stool administered via a nasogastric tube. *Clin Infect Dis.* 2003;36:580–585.
53. You DM, Franzos MA, Holman RP. Successful treatment of fulminant *Clostridium difficile* infection with fecal bacteriotherapy. *Ann Intern Med*. 2008;148:632–633.
54. Sougioultzis S, Kyne L, Drudy D, et al. *Clostridium difficile* toxoid vaccine in recurrent *C. difficile*-associated diarrhea. *Gastroenterology*. 2005;128:764–770.
55. Kotloff K, Wasserman SS, Losonsky GA, et al. Safety and immunogenicity of increasing doses of a *Clostridium difficile* toxoid vaccine administered to healthy adults. *Infect Immun*. 2001;69:988–995.
56. U.S. National Institutes of Health. Study of a *Clostridium difficile* toxoid vaccine (ACAM-CDIFF™) in subjects with *Clostridium difficile* infection. http://clinicaltrials.gov/ct2/show/study/NCT00772343. Accessed September 19, 2010.
57. Gerding D. Antimotility agents for the treatment of *Clostridium difficile* infection: Is the juice worth the squeeze? *Clin Infect Dis.* 2009;48:606–608.
58. Koo HL, Koo DC, Musher DM, DuPont HL. Antimotility agents for the treatment of *Clostridium difficile* diarrhea and colitis. *Clin Infect Dis.* 2009;48:598–605.

TEST QUESTIONS

Write your answers on the form appearing on page 41 (photocopies of the answer form are acceptable) or on a separate sheet of paper. Mark the most appropriate answer.

1. *Clostridium difficile* (*C. difficile*) is classified as an:
a. Aerobic, gram-negative coccus **c.** Anaerobic, gram-negative rod
b. Aerobic, gram-positive coccus **d.** Anaerobic, gram-positive rod

2. Which of the following statements is TRUE?
a. Roughly 70% of healthy adults asymptomatically carry *C. difficile* in their stool.
b. *C. difficile* is more likely to cause disease in neonates than in adults.
c. *C. difficile* infections are decreasing in frequency and severity of disease.
d. The newly identified NAP1/BI/027 strain of *C. difficile* is more virulent than previously identified strains.

3. Which of the following statements correctly identifies the pathogenesis of CDI?
a. If normal enteric flora are disrupted, the spore form of the microorganism reproduces within the intestinal crypts and releases toxins.
b. If normal enteric flora are disrupted, the spore form of the microorganism reproduces within the stomach and degrades its epithelial cells.
c. If normal enteric flora are disrupted, the vegetative form of the microorganism reproduces within intestinal crypts and releases toxins.
d. If normal enteric flora are disrupted, the vegetative form of the microorganism reproduces within the stomach and degrades its epithelial cells.

4. Which of the following is a risk factor for the development of CDI?
a. Genitourinary procedure **c.** Receipt of cancer chemotherapy
b. Receipt of an antiplatelet agent **d.** Schizophrenia

5. Which of the following would be classified as having severe, complicated CDI?
a. 47-year-old woman with white blood cell (WBC) count = 15,000 and serum creatinine increase from 1 mg/dL to 1.6 mg/dL
b. 48-year-old woman with WBC = 16,000, serum creatinine increase from 1 mg/dL to 1.5 mg/dL, and ileus
c. 50-year-old man with WBC = 16,000, serum creatinine increase from 1 mg/dL to 1.3 mg/dL, and diabetes mellitus
d. 55-year-old man with WBC = 20,000 and serum creatinine increase from 1 mg/dL to 2 mg/dL

6. What is the most commonly used test for the diagnosis of CDI?
a. Endoscopy to visualize pseudomembranes
b. Enzyme-linked immunoassay for *C. difficile* toxins A and B
c. Presence of WBC in stool
d. Stool culture

7. What is the recommended length of treatment of metronidazole for a 58-year-old man who was recently diagnosed with a mild first-time case of CDI?
a. 5 to 7 days **b.** 7 to 10 days **c.** 10 to 14 days **d.** 14 to 17 days

8. A 55-year-old man recently diagnosed with CDI has a medical history that includes alcohol and cocaine abuse. He refuses to undergo alcohol detoxification. His pre-infection laboratory values include: WBC 10,000 cells/µL; serum creatinine (SCr) 0.8 mg/dL; temperature (T) 37.4° C. His laboratory values after *C. difficile* include: WBC 13,500 cells/µL; SCr 1 mg/dL; T 37.6°C. Which of the following treatment regimens is the MOST appropriate for this patient?
a. Metronidazole 500 mg PO q 8 hours **c.** Rifaximin 400 mg PO q 12 hours
b. Metronidazole 500 mg IV q 8 hours **d.** Vancomycin 125 mg PO q 6 hours

9. After receiving antibiotics for healthcare-associated pneumonia, a 73-year-old woman is diagnosed with a severe CDI. She has no known drug allergies and can tolerate oral medications. Which treatment regimen would be first-line for her?
a. Metronidazole 500 mg PO q 8 hours
b. Metronidazole 500 mg IV q 8 hours
c. Rifaximin 400 mg PO q 12 hours
d. Vancomycin 125 mg PO q 6 hours

10. A 70-year-old male patient is transferred from the medical ward to the ICU for management of severe, complicated CDI associated with hypotension and acute renal failure. What treatment would you recommend?
a. Metronidazole 500 mg IV q 8 hours plus metronidazole 500 mg PO every 6 hours
b. Metronidazole 500 mg IV q 8 hours plus vancomycin 500 mg PO every 6 hours
c. Rifaximin 400 mg IV q 12 hours plus vancomycin 500 mg PO every 6 hours
d. Vancomycin 1 g IV q 12 hours

11. Which of the following antibiotics has FDA approval for treatment of CDI?
a. Bacitracin **b.** Metronidazole **c.** Nitazoxanide **d.** Vancomycin

12. When used to treat CDI, by which route is vancomycin most commonly given?
a. Intramuscular **b.** Intravenous **c.** Oral **d.** Retention enema

13. Which treatment is recommended for a 30-year-old pregnant woman diagnosed with CDI after receiving antimicrobial therapy for community-acquired pneumonia?
a. Metronidazole 250 mg PO q 6 hours
b. Metronidazole 500 mg IV q 6 hours
c. Tigecycline 100 mg IV x 1 dose, then 50 mg IV q 12 hours
d. Vancomycin 125 mg PO q 6 hours

14. Which of the following statements is CORRECT?
a. A vaccine to prevent *C. difficile* is currently under development.
b. Cholestyramine may be administered at the same time as oral vancomycin.
c. Corticosteroids may be useful because they bind to disease-producing toxins.
d. Probiotics are safe for use in immunocompromised patients.

15. Which of the following agents may prolong mucosal exposure to *C. difficile*'s toxins and predispose patients to toxic megacolon?
a. Cholestyramine **c.** Loperamide
b. Intravenous immunoglobulin (IVIG) **d.** Nitazoxanide

16. When treating patients with *C. difficile* infection, a patient's temperature should normalize within _____ and diarrhea should resolve within _____ of effective therapy.
a. 12 hours; 2 days **b.** 48 hours; 7 days **c.** 96 hours; 12 days **d.** 5 days; 17 days

17. Which adjunctive treatment may cause red-orange discoloration of body fluids?
a. Bacitracin **b.** Metronidazole **c.** Nitazoxanide **d.** Rifampin

18. A 63-year-old man with a history of atrial fibrillation and diabetes mellitus takes amiodarone 200 mg PO daily, glipizide 10 mg PO daily, and warfarin 2.5 mg PO daily. Following a recent diagnosis of CDI, he is prescribed oral metronidazole therapy. Which of the drug interactions below may occur?
a. Metronidazole may decrease amiodarone levels and increase arrhythmia risk.
b. Metronidazole may decrease warfarin levels and increase risk of clot formation.
c. Metronidazole may increase warfarin levels and increase risk of bleeding.
d. Metronidazole does not interact with any of his medications.

19. Which of the following strategies has NOT been shown to control CDI effectively?
a. Antimicrobial stewardship programs
b. Cleaning rectal thermometers with alcohol
c. Isolation precautions
d. Restriction of high-risk antimicrobials

20. Which of the following will reduce the risk of transmission of *C. difficile* in a healthcare facility?
a. The use of alcohol-based hand rubs
b. The use of quaternary ammonium-based agents for cleaning
c. The use of rectal thermometers
d. The use of soap and water to wash hands

EVALUATION OF CE

Drug Topics is conducting an evaluation of this CE article. Please check the box that best reflects your opinion of the evaluation questions. Please keep this evaluation attached to your answer form.

	Strongly Agree	Agree	Disagree	Strongly Disagree
1. The objectives listed on page 31 were met. If not, please describe:				
2. The author wrote an article of value.				
3. The information was clear and presented well.				
4. The learning activity (quiz) was effective.				
5. The article content was useful and relevant.				
6. The article was educational and not promotional.				

2010 CEU CREDIT REQUEST

To obtain immediate CE credit, take the test online at www.drugtopics.com. Just click on the "Continuing Education" box on the *Drug Topics* home page, which will take you to the CE site. Log in, find and click on this lesson, and follow the three simple steps. Test results will be displayed immediately and you can print the certificate showing your earned CE credits. The cost of the online test for this lesson is $6.

ANSWER FORM

ACPE # 0012-9999-10-106-H01-P (K)

***C. Difficile* CE Quiz Answers** December 2010

Test questions start on page 40

1. a. b. c. d.	**5.** a. b. c. d.	**9.** a. b. c. d.	**13.** a. b. c. d.	**17.** a. b. c. d.
2. a. b. c. d.	**6.** a. b. c. d.	**10.** a. b. c. d.	**14.** a. b. c. d.	**18.** a. b. c. d.
3. a. b. c. d.	**7.** a. b. c. d.	**11.** a. b. c. d.	**15.** a. b. c. d.	**19.** a. b. c. d.
4. a. b. c. d.	**8.** a. b. c. d.	**12.** a. b. c. d.	**16.** a. b. c. d.	**20.** a. b. c. d.

Not valid for CE credit after 12/31/2012

Amount enclosed:
- ☐ $6.00 for this lesson
- ☐ $54.00 for any 12 lessons you take over the next year, starting from the date you sign up
- ☐ Already series-enrolled for 2010

Submit your check (payable to The University of Florida) and form to:
University of Florida College of Pharmacy
P.O. Box 113195, Gainesville, FL 32611-3195

E-mail address: continuinged@cop.ufl.edu
Fees not refundable or transferable

For questions concerning PRINT CEs, call 352-273-6275.
For questions concerning ONLINE CEs, call 877-252-7711.

Are you employed by a chain? If so, which one?

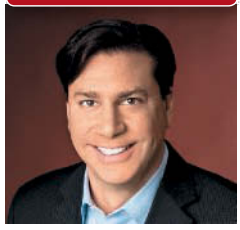
REGISTRANT INFORMATION

Name:
(Last) (First) (M.I.) Phone

Address: **E-mail address:**
(Street)

City: **State:** **ZIP:**

Florida pharmacists: Please provide your license number _____



FDA loses preliminary injunction case against vet-compounding pharmacy

Ned Milenkovich, PharmD, JD

A compounding pharmacy in Florida, Franck's Lab, Inc., which engages in veterinary compounding, has been embroiled in a struggle with the FDA since it compounded a vitamin supplement for administration to 21 polo ponies during the U.S. Open Polo Championships in April 2009. When they were injected with the compounded vitamin supplement, all 21 ponies collapsed and died.

As a result, FDA sought to obtain a preliminary injunction against the pharmacy to prevent it from engaging in further veterinary compounding.

FDA makes its case

The agency argued that the pharmacy was violating a compliance policy guidance issued by FDA in 2003 for purposes of clarifying its interpretation of the Animal Medicinal Drug Use Clarification Act. FDA asserted that any "compounding from bulk substances," such as the Florida pharmacy had done, "or unapproved drugs renders the compounded drugs unsafe as a matter of law, and thus adulterated in violation of 21 USC § 351(a)(5)." FDA argued that the bulk drugs constitute new drugs and therefore require FDA regulatory approvals before they may be introduced in interstate commerce.

The pharmacy responds

The pharmacy responded by asserting that FDA has no authority to ban veterinary drug compounding from bulk product. In its defense, the pharmacy stated that the "use of bulk ingredients to compound commercially unavailable preparations is a core part of the traditional pharmacy practice" which is left for purposes of oversight to the individual states and not to the federal government and FDA.

The pharmacy did not dispute that FDA may have regulatory authority over the manufacturing of veterinary pharmaceuticals if it can show that the pharmacy is truly engaged in the "manufacturing" process. But, the pharmacy pointed out, FDA is not permitted "to override state law and impose a blanket ban on traditional pharmacy compounding practices."

The pharmacy also noted that the legislative history of the Federal Food, Drug, and Cosmetic Act (FDCA) proves that Congress intentionally left regulation of compounding to state regulatory oversight as part of pharmacy practice, while preserving regulatory oversight of manufacturing as a task of the federal government.

If FDA can demonstrate that a compounding pharmacy was in fact engaged in manufacturing, then it will be able to exercise its authority over the pharmacy, and state regulatory oversight would not apply.

Finally, the defendant pharmacy stated that even if the FDCA provided FDA with the right to regulate veterinary compounding, FDA would need to promulgate regulations through formal rule-making procedures that would include a notice-and-comment period, rather than through the issuance of an informal compliance policy guide.

Motion denied

In summary, the judge denied FDA's motion for preliminary injunction without issuing an opinion. However, the court is currently reviewing the request for permanent injunction.

This case illustrates the important point that legal tension arises when pharmacy compounding is alleged by FDA to reach the level of manufacturing. FDA regulates manufacturing, while state laws and regulations govern pharmacy compounding. If FDA is able to demonstrate that a compounding pharmacy was in fact engaged in manufacturing, then it will be able to exercise its authority over the pharmacy, and state regulatory oversight would not apply.

Other cases have analyzed this matrix, and this body of law continues to evolve as different parties and efforts — including by the federal government through the FDA; by state governments and boards of pharmacy; and through the various pharmacy practice acts — attempt to draw the fine line whereby compounding and manufacturing are defined. DT

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

Ned Milenkovich *is a member at McDonald Hopkins, LLC, and chairs its Drug & Pharmacy Practice Group. He is also a member of the Illinois State Board of Pharmacy. Contact him at 312-642-1480 or at nmilenkovich@mcdonaldhopkins.com.*

See the effect of LEXAPRO

Proven efficacy in MDD in adolescents aged 12 to 17, and in MDD and GAD in adults[1-5]

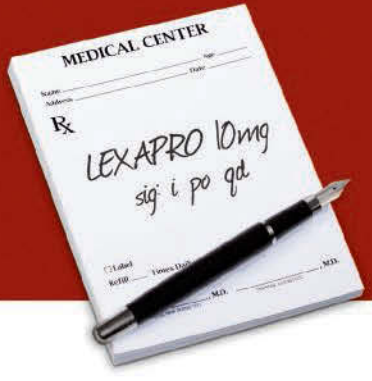
In adolescents aged 12 to 17 with Major Depressive Disorder (MDD)*[1]

In adults with MDD and Generalized Anxiety Disorder (GAD)[1]

LEXAPRO and citalopram are not the same[1,6,7]

- LEXAPRO is approved for MDD and GAD[1]; citalopram is not approved for GAD.[6]
- LEXAPRO is approved for MDD in adolescents aged 12 to 17 years[1]; citalopram is not.[6]

There is no generic available for LEXAPRO



*LEXAPRO is indicated as an integral part of a total treatment program for MDD. Drug treatment may not be indicated for all adolescents with this syndrome.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients less than 12 years of age.

Contraindications

- Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). There have been reports of serious, sometimes fatal, reactions with some cases resembling neuroleptic malignant syndrome (NMS) and serotonin syndrome. Features may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Serotonin syndrome was reported for two patients who were concomitantly receiving linezolid, an antibiotic which has MAOI activity. Lexapro should not be used in combination with an MAOI or within 14 days of discontinuing an MAOI. MAOIs should not be initiated within 14 days of discontinuing Lexapro.
- Lexapro is contraindicated in patients taking pimozide or with hypersensitivity to escitalopram or citalopram.

Please see additional Important Safety Information on adjacent page.

Lexapro® escitalopram oxalate

Visit the LEXAPRO website at www.lexapro.com

There is no generic available for LEXAPRO

Lexapro (escitalopram oxalate) is indicated for the acute and maintenance treatment of major depressive disorder (MDD) in adults and adolescents aged 12-17 years. Lexapro is also indicated for the acute treatment of generalized anxiety disorder (GAD) in adults.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality and unusual changes in behavior, especially within the first few months of treatment or when changing the dose. Consideration should be given to changing the therapeutic regimen, including discontinuing medication, in patients whose depression is persistently worse, who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Families and caregivers of patients treated with antidepressants should be alerted about the need to monitor patients daily for the emergence of agitation, irritability, unusual changes in behavior, or the emergence of suicidality, and report such symptoms immediately. Prescriptions for Lexapro should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.
- A major depressive episode may be the initial presentation of bipolar disorder. In patients at risk for bipolar disorder, treating such an episode with an antidepressant alone may increase the likelihood of precipitating a mixed/manic episode. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. Lexapro should be used cautiously in patients with a history of mania or seizure disorder. Lexapro is not approved for use in treating bipolar depression.
- The concomitant use of Lexapro with other SSRIs, SNRIs, triptans, tryptophan, antipsychotics or other dopamine antagonists is not recommended due to potential development of life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. Reactions have been reported with SNRIs and SSRIs alone, including Lexapro, but particularly with drugs that impair metabolism of serotonin (including MAOIs). Management of these events should include immediate discontinuation of Lexapro and the concomitant agent and continued monitoring.
- Patients should be monitored for adverse reactions when discontinuing treatment with Lexapro. During marketing of Lexapro and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation, including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias), anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania. A gradual dose reduction rather than abrupt cessation is recommended whenever possible.
- SSRIs and SNRIs have been associated with clinically significant hyponatremia. Elderly patients and patients taking diuretics or who are otherwise volume-depleted appear to be at a greater risk. Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.
- SSRIs (including Lexapro) and SNRIs may increase the risk of bleeding. Patients should be cautioned that concomitant use of aspirin, NSAIDs, warfarin or other anticoagulants may add to the risk.
- Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro does not affect their ability to engage in such activities.
- Lexapro should be used with caution in patients with severe renal impairment or with diseases or conditions that alter metabolism or hemodynamic responses. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day.
- For pregnant or nursing mothers, Lexapro should be used only if the potential benefit justifies the potential risk to the fetus or child.

Adverse Reactions

- In clinical trials of MDD, the most common adverse reactions in adults treated with Lexapro (approximately 5% or greater and at least twice the incidence of placebo) were nausea (15% vs 7%), insomnia (9% vs 4%), ejaculation disorder (9% vs <1%), fatigue (5% vs 2%), somnolence (6% vs 2%), and increased sweating (5% vs 2%). In pediatric patients, the overall profile of adverse reactions was similar to that seen in adults; however, the following additional adverse reactions were reported at an incidence of at least 2% for Lexapro and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion.
- In clinical trials of GAD, the most common adverse reactions in adults treated with Lexapro (approximately 5% or greater and at least twice the incidence of placebo) were nausea (18% vs 8%), ejaculation disorder (14% vs 2%), insomnia (12% vs 6%), fatigue (8% vs 2%), decreased libido (7% vs 2%) and anorgasmia (6% vs <1%).

References: 1. LEXAPRO [package insert]. St. Louis, Mo: Forest Pharmaceuticals, Inc.; 2009. **2.** Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry.* 2009;48:721-729. **3.** Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry.* 2002;63:331-336. **4.** Davidson JRT, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety.* 2004;19:234-240. **5.** Wade A, Lemming OM, Hedegaard KB. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol.* 2002;17:95-102. **6.** Celexa [package insert]. St. Louis, Mo: Forest Pharmaceuticals, Inc.; 2009. **7.** Mork A, Kreilgaard M, Sanchez C. The R-enantiomer of citalopram counteracts escitalopram-induced increase in extracellular 5-HT in the frontal cortex of freely moving rats. *Neuropharmacology.* 2003;45:167-173.

Please see accompanying brief summary of Prescribing Information for LEXAPRO, including Boxed Warning.

Forest Pharmaceuticals, Inc.
Pharmaceuticals • Therapeutics • Healthcare • Ethicare • Managed Care • Specialty Sales

 Printed in U.S.A. 41-1017601r 5/10

Lexapro® escitalopram oxalate

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION **Rx Only**

Brief Summary: For complete details, please see full Prescribing Information for Lexapro.

WARNINGS: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients less than 12 years of age. *[See Warnings and Precautions: Clinical Worsening and Suicide Risk, Patient Counseling Information: Information for Patients, and Used in Specific Populations: Pediatric Use]*.

INDICATIONS AND USAGE: Major Depressive Disorder-Lexapro (escitalopram) is indicated for the acute and maintenance treatment of major depressive disorder in adults and in adolescents 12 to 17 years of age [*see Clinical Studies*]. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation. **Generalized Anxiety Disorder**-Lexapro is indicated for the acute treatment of Generalized Anxiety Disorder (GAD) in adults [*see Clinical Studies*]. Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance.

CONTRAINDICATIONS: Monoamine oxidase inhibitors (MAOIs)-Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated [*see Warnings and Precautions*]. **Pimozide**-Concomitant use in patients taking pimozide is contraindicated [*see Drug Interactions*]. **Hypersensitivity to escitalopram or citalopram**-Lexapro is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in Lexapro.

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk-Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

TABLE 1

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

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Dosage and Administration*]. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers [*see also Patient Counseling Information*]. Prescriptions for Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Screening Patients for Bipolar Disorder**-A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Lexapro is not approved for use in treating bipolar depression. **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions**-The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Lexapro treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. The concomitant use of Lexapro with MAOIs intended to treat depression is contraindicated. If concomitant treatment of Lexapro with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Lexapro with serotonin precursors (such as tryptophan) is not recommended. Treatment with Lexapro and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated. **Discontinuation of Treatment with Lexapro**-During marketing of Lexapro and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Lexapro. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [*see Dosage and Administration*]. **Seizures**-Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Lexapro, cases of convulsion have been reported in association with Lexapro treatment. Like other drugs effective in the treatment of major depressive disorder, Lexapro should be introduced with care in patients with a history of seizure disorder. **Activation of Mania/Hypomania**-In placebo-controlled trials of Lexapro in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Lexapro and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Lexapro treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro should be used cautiously in patients with a history of mania. **Hyponatremia**-Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Lexapro. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Lexapro was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [*see Geriatric Use*]. Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. **Abnormal Bleeding**-SSRIs and SNRIs, including Lexapro, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Lexapro and NSAIDs, aspirin, or other drugs that affect coagulation. **Interference with Cognitive and Motor Performance**-In a study in normal volunteers, Lexapro 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. **Use in Patients with Concomitant Illness**-Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day [*see Dosage and Administration*]. Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Lexapro, however, it should be used with caution in such patients [*see Dosage and Administration*]. **Potential for Interaction with Monoamine Oxidase Inhibitors**-In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.

ADVERSE REACTIONS: Clinical Trials Experience-Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. **Clinical Trial Data Sources; Pediatrics (6 -17 years)**-Adverse events were collected in 576 pediatric patients (286 Lexapro, 290 placebo) with major depressive disorder in double-blind placebo-controlled studies. Safety and effectiveness of Lexapro in pediatric patients less than 12 years of age has not been established. **Adults**-Adverse events information for Lexapro was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Lexapro in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Associated with Discontinuation of Treatment; Major Depressive Disorder; Pediatrics (6 -17 years)**-Adverse events were associated with discontinuation of 3.5% of 286 patients receiving Lexapro and 1% of 290 patients receiving placebo. The most common adverse event (incidence at least 1% for Lexapro and greater than placebo) associated with discontinuation was insomnia (1% Lexapro, 0% placebo). **Adults**-Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder; Adults**-Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Reactions in Placebo-Controlled Clinical Trials; Major Depressive Disorder; Pediatrics (6 -17 years)**-The overall profile of adverse reactions in pediatric patients was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse reactions (excluding those which appear in Table 2 and those for which the coded terms were uninformative or misleading) were reported at an incidence of at least 2% for Lexapro and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion. **Adults**-The most commonly observed adverse reactions in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence. Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients.

TABLE 2

Treatment-Emergent Adverse Reactions Observed with a Frequency of ≥ 2% and Greater Than Placebo for Major Depressive Disorder

Adverse Reaction	Lexapro (N=715)	Placebo (N=592)
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder[1,2]	9%	<1%
Impotence[2]	3%	<1%
Anorgasmia[3]	2%	<1%

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=225 Lexapro; N=188 placebo).
[3]Denominator used was for females only (N=490 Lexapro; N=404 placebo).

Generalized Anxiety Disorder; Adults-The most commonly observed adverse reactions in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia. Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients.

TABLE 3

Treatment-Emergent Adverse Reactions Observed with a Frequency of ≥ 2% and Greater Than Placebo for Generalized Anxiety Disorder

Adverse Reactions	Lexapro (N=429)	Placebo (N=427)
Autonomic Nervous System Disorders		
Dry Mouth	9%	5%
Sweating Increased	4%	1%
Central & Peripheral Nervous System Disorders		
Headache	24%	17%
Paresthesia	2%	1%
Gastrointestinal Disorders		
Nausea	18%	8%
Diarrhea	8%	6%
Constipation	5%	4%
Indigestion	3%	2%
Vomiting	3%	1%
Abdominal Pain	2%	1%
Flatulence	2%	1%
Toothache	2%	0%
General		
Fatigue	8%	2%
Influenza-like Symptoms	5%	4%
Musculoskeletal System Disorder		
Neck/Shoulder Pain	3%	1%
Psychiatric Disorders		
Somnolence	13%	7%
Insomnia	12%	6%
Libido Decreased	7%	2%
Dreaming Abnormal	3%	2%
Appetite Decreased	3%	1%
Lethargy	3%	1%

TABLE 3 Treatment-Emergent Adverse Reactions Observed with a Frequency of ≥ 2% and Greater Than Placebo for Generalized Anxiety Disorder (continued)		
Adverse Reactions	**Lexapro (N=429)**	**Placebo (N=427)**
Respiratory System Disorders		
Yawning	2%	1%
Urogenital		
Ejaculation Disorder[1,2]	14%	2%
Anorgasmia[3]	6%	<1%
Menstrual Disorder	2%	1%

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=182 Lexapro; N=195 placebo).
[3]Denominator used was for females only (N=247 Lexapro; N=232 placebo).

Dose Dependency of Adverse Reactions-The potential dose dependency of common adverse reactions (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse reactions that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group.

TABLE 4 Incidence of Common Adverse Reactions in Patients with Major Depressive Disorder			
Adverse Reaction	**Placebo (N=311)**	**10 mg/day Lexapro (N=310)**	**20 mg/day Lexapro (N=125)**
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

Male and Female Sexual Dysfunction with SSRIs-Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

TABLE 5 Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials		
Adverse Event	**Lexapro**	**Placebo**
	In Males Only	
	(N=407)	(N=383)
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Libido Decreased	6%	2%
Impotence	2%	<1%
	In Females Only	
	(N=737)	(N=636)
Libido Decreased	3%	1%
Anorgasmia	3%	<1%

There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes**-Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes**-Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes**-Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes**-Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Reactions Observed During the Premarketing Evaluation of Lexapro**-Following is a list of treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. The listing does not include those events already listed in Tables 2 & 3, those events for which a drug cause was remote and at a rate less than 1% or lower than placebo, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. Events are categorized by body system. Events of major clinical importance are described in the Warnings and Precautions section. Cardiovascular - hypertension, palpitation. Central and Peripheral Nervous System Disorders - light-headed feeling, migraine. Gastrointestinal Disorders - abdominal cramp, heartburn, gastroenteritis. General - allergy, chest pain, fever, hot flushes, pain in limb. Metabolic and Nutritional Disorders - increased weight. Musculoskeletal System Disorders - arthralgia, myalgia jaw stiffness. Psychiatric Disorders - appetite increased, concentration impaired, irritability. Reproductive Disorders/Female - menstrual cramps, menstrual disorder. Respiratory System Disorders - bronchitis, coughing, nasal congestion, sinus congestion, sinus headache. Skin and Appendages Disorders - rash. Special Senses - vision blurred, tinnitus. Urinary System Disorders - urinary frequency, urinary tract infection. **Post-Marketing Experience; Adverse Reactions Reported Subsequent to the Marketing of Escitalopram**-The following additional adverse reactions have been identified from spontaneous reports of escitalopram received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to escitalopram and have not been listed elsewhere in labeling. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include: Blood and Lymphatic System Disorders: anemia, agranulocytis, aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Ear and Labyrinth Disorders: vertigo Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma, mydriasis, visual disturbance. Gastrointestinal Disorders: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait, asthenia, edema, fall, feeling abnormal, malaise. Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction, anaphylaxis. Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia. Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis. Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, seizures, syncope, tardive dyskinesia, tremor. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency. Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention. Reproductive System and Breast Disorders: menorrhagia, priapism. Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn. Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

DRUG INTERACTIONS: Serotonergic Drugs-Based on the mechanism of action of SNRIs and SSRIs including Lexapro, and the potential for serotonin syndrome, caution is advised when Lexapro is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort [*see Warnings and Precautions*]. The concomitant use of Lexapro with other SSRIs, SNRIs or tryptophan is not recommended. **Triptans**-There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Lexapro with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions*]. **CNS Drugs**- Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs. **Alcohol**-Although Lexapro did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Lexapro is not recommended. **Monoamine Oxidase Inhibitors (MAOIs)**-[*see Contraindications and Warnings and Precautions*]. **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)**-Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Lexapro is initiated or discontinued. **Cimetidine**-In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. **Digoxin**-In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. **Lithium**-Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Lexapro and lithium are coadministered. **Pimozide and Celexa**-In a controlled study, a single dose of pimozide 2 mg coadministered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known. **Sumatriptan**-There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised. **Theophylline**-Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. **Warfarin**-Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. **Carbamazepine**-Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered. **Triazolam**-Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. **Ketoconazole**-Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. **Ritonavir**-Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram. **CYP3A4 and -2C19 Inhibitors**-*In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance. **Drugs Metabolized by Cytochrome P4502D6**-*In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6. **Metoprolol**-Administration of 20 mg/day Lexapro for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Lexapro and metoprolol had no clinically significant effects on blood pressure or heart rate. **Electroconvulsive Therapy (ECT)**-There are no clinical studies of the combined use of ECT and escitalopram.

USE IN SPECIFIC POPULATIONS: Pregnancy; Pregnancy Category C-In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥ 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis). When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was also seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis. In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses. In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit. When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day. A no-effect dose was not determined in that study. There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy-Nonteratogenic Effects Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions*]. Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment [*see Dosage and Administration*]. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **Labor and Delivery**-The effect of Lexapro on labor and delivery in humans is unknown. **Nursing Mothers**-Escitalopram is excreted in human breast milk. Limited data from women taking 10-20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when Lexapro is administered to a nursing woman. **Pediatric Use**-Safety and effectiveness of Lexapro has not been established in pediatric patients (less than 12 years of age) with Major Depressive Disorder. Safety and effectiveness of Lexapro has been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder [*see Clinical Studies*]. Although maintenance efficacy in adolescent patients with Major Depressive Disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients. Safety and effectiveness of Lexapro has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder. **Geriatric Use**-Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Lexapro in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out. SSRIs and SNRIs, including Lexapro, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Hyponatremia*]. In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged [*see Clinical Pharmacology*]. 10 mg/day is the recommended dose for elderly patients [*see Dosage and Administration*]. Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

DRUG ABUSE AND DEPENDENCE: Abuse and Dependence; Physical and Psychological Dependence-Animal studies suggest that the abuse liability of racemic citalopram is low. Lexapro has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Lexapro did not reveal any drug-seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate Lexapro patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE: Human Experience-In clinical trials of escitalopram, there were reports of escitalopram overdose, including overdoses of up to 600 mg, with no associated fatalities. During the postmarketing evaluation of escitalopram, Lexapro overdoses involving overdoses of over 1000 mg have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of escitalopram has been rarely reported. Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose. **Management of Overdose**-Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Lexapro. In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045 USA
Licensed from H. Lundbeck A/S

Rev. 05/09

Zegerid OTC is the only nonprescription PPI with 2 active ingredients.

FiberChoice Weight Management: The chewable tablets offer 4g of fiber in each 2-tablet dose.

Digest Gold + Probiotics combines digestive enzymes and probiotics.

OTC

For those who dine not wisely but too well

DANA K. CASSELL

In this season of gustatory indulgence, it can't hurt to prepare for the occasional upset stomach. According to reports, more than 100 million Americans are affected by some form of digestive disorder, including gas, heartburn, indigestion, vomiting, bloating, constipation, diarrhea, and worse. Fortunately, OTC manufacturers have been hard at work preparing new and improved digestive and gastrointestinal aids.

PPI

Schering-Plough HealthCare Products has introduced **Zegerid OTC**, a proton pump inhibitor (PPI), the most potent class of acid-reducing drugs currently available.

The only nonprescription PPI product with 2 active ingredients, Zegerid OTC combines the PPI omeprazole with sodium bicarbonate, which protects the medication from being broken down by acid in the stomach prior to absorption. Zegerid OTC is approved for use by adults 18 and over for the treatment of frequent heartburn (defined as occurring 2 or more days a week).

Fiber

Dietary fiber not only aids digestion, it can help control weight, because it makes one feel full faster and longer. From GlaxoSmithKline comes an addition to its **FiberChoice** line: a new strawberry-flavored **Weight Management** formula containing chromium picolinate, a naturally occurring compound that aids in metabolism.

Enzymes and probiotics

When the category is digestives and gastrointestinal agents, increasingly popular elements are enzymes and probiotics. Enzymedica has combined the 2 in its new **Digest Gold + Probiotics**, offering "complete digestive care in a single capsule."

Enzymedica's **Digest Gold** is an enzyme product formulated to assist in digestion of proteins, fats, carbohydrates, and fiber.

Digest Gold + Probiotics combines that enzyme formula with 500 million cultures of specially coated probiotics that release in the alkaline pH of the lower intestines, guaranteeing potency.

Bayer HealthCare's **Phillips' Colon Health** now offers a larger, 60-count package to give customers 2 months of daily probiotic support. The product's 3 strains of good bacteria are derived from the 2 most common groups of good bacteria, *Lactobacillus* and *Bifidobacterium*.

According to Bayer, "Scientific evidence demonstrates that *Lactobacillus* and *Bifidobacterium* help relieve occasional gas, constipation, diarrhea, and other common GI issues while also helping to support a healthy immune system. Probiotics work to rebalance the bacteria in your colon to support overall digestive health and to help defend against occasional digestive symptoms." DT

Dana K. Cassell, *a frequent contributor to* Drug Topics, *lives in North Stratford, N.H.*

PHOTOS COURTESY OF SCHERING-PLOUGH HEALTHCARE PRODUCTS/GLAXO-SMITH-KLINE/ENZYMEDICA

RX & OTC

New products

PHOTOS COURTESY OF ISTA/BOEHRINGER INGELHEIM/ECO LIPS

RX CARE

New drugs

FDA has approved Warner Chilcott's bisphosphonate **Atelvia** (risedronate sodium delayed-release tablets) for the treatment of postmenopausal osteoporosis. The product is a delayed-release formulation of Actonel, which is approved to prevent and treat postmenopausal osteoporosis and glucocorticoid-induced osteoporosis (in men and women), to increase bone mass in men with osteoporosis, and to treat Paget's disease of the bone. **(www.wcrx.com/800-521-8813)**

Bristol-Myers Squibb's **Baraclude** (entecavir tablets), a nucleoside analog, is approved for the treatment of chronic hepatitis B (CHB) in adult patients with decompensated liver disease. Baraclude is already indicated for the treatment of CHB infection in adults with evidence of active viral replication and evidence of either persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. **(www.baraclude.com/800-321-1335)**

FDA has approved ISTA's **Bromday** [1] (bromfenac ophthalmic solution 0.09%), a nonsteroidal anti-inflammatory drug (NSAID), for the treatment of postoperative inflammation and reduction of ocular pain after cataract surgery. **(www.istavision.com/949-788-6000)**.

Pradaxa [2] (dabigatran etexilate) capsules from Boehringer Ingelheim are approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AFib). An oral direct thrombin inhibitor, Pradaxa is the first new oral anticoagulant approved in the United States in more than 50 years. **(www.pradaxa.com/800-542-6257)**

Fera has launched a preservative-free formulation of **Garamycin** (gentamicin sulfate ophthalmic ointment), indicated for the treatment of susceptible ocular bacterial infections, including conjunctivis, keratitis, keratoconjunctivitis, corneal ulcers, blepharitis, blepharoconjunctivitis, acute meibomianitis, and dacryocystitis. **(www.ferapharma.com/414-434-6604)**

New generics

FDA approved Teva's ANDA to market **lansoprazole**, a generic version of Takeda's Prevacid SoluTab. The product, a proton pump inhibitor, suppresses gastric acid production and is often prescribed for use in gastroesophageal reflux disease. **(888-838-2872)**

Dr. Reddy's Laboratories will launch **lansoprazole delayed-release capsules (15 mg and 30 mg)**, a bioequivalent generic version of Prevacid Delayed-Release Capsules, in the U.S. market. **(www.drreddys.com)**

Tris Pharma announced that FDA has approved **hydrocodone polistirex and chlorpheniramine polistirex in extended-release suspension**, the first-ever generic version of Tussionex (UCB Manufacturing). **(www.trispharma.com)**

OTC

Chestal, a natural cough syrup free of dextromethorphan, has been made available by Boiron. A blend of homeopathic medicines and honey, Chestal helps loosen chest congestion for dry and productive coughs. **(www.childrenschestal.com/800-266-7661)**

Eco Lips announces new colors in its **Eco Tints** [3] line: Moonstone, Sugar Plum, and Coralyte. With more than 90% certified organic ingredients, Eco Tints are free of carmine, lead, gluten, lanolin, petroleum, hydrogenated oils, and nanoparticles. **(www.ecolips.com/866-326-5477)**

From Smith & Nephew comes **No-Sting Skin Prep** spray, a liquid dressing that leaves a clear, waterproof, and breathable film barrier for up to 4 days, protecting skin from irritation due to digestive secretions, exudate, adhesives, frictional forces, and skin trauma during tape and adhesive removal. **(www.smith-nephew.com/800-876-1261)**

Vitalah has introduced **Prenatal Oxylent**, a digestible effervescent vitamin formulated for needs of preconception, pregnancy, and lactation. It is naturally sweetened with stevia; no sugar is added and it has no artificial color, flavor, gluten, lactose, or caffeine. **(www.vitalah.com)** DT

Products & Services

Books/Publications

Brokers

See More Brokers on next page

Business For Sale

Continuing Education

Products & Services

Brokers

Financing

Education

Legal Services

Pharmacy Technicians

A glimpse into the world of retail pharmacy through the eyes of JP

Julia Talsma, Editor-in-Chief

This issue is a milestone for *Drug Topics*, with the publication of the 200th column by Jim Plagakis to appear under the heading "JP at Large." In this issue (page 13), he takes us on a journey that began in 1989 with the publication of his first column, about a patient with bipolar disorder who needed someone to listen. That someone was Jim.

Jim has been listening and counseling as a pharmacist for almost 45 years. At his first job, in a downtown drugstore that still had a lunch counter, patients received a coupon for a free cup of coffee to drink while they waited for their prescriptions. Jim would join patients for a sip of coffee and ask whether they had any questions about their medications. He called it "stealth counseling in the 1960s."

Fast-forward to 1993. Jim explained in a column that he took "3 focused minutes" to listen to a father's grief for his 9-year-old son, who was near death from brain cancer. He wrote, "I was his sponge. He released the poison, and I sucked it up. Not required by law, but I think it's part of my job, even if the next person up for an Rx had to wait 3 extra minutes."

Today counseling on every new prescription is mandatory in Texas, where Jim practices. When the technician rings up the prescriptions, including new ones, the whole process stops. Jim usually asks the patient whether he has used the prescription before. If the patient says yes, Jim asks whether he has any questions. If there are none, Jim sends the patient on his way. When the prescription is a new one for the patient, Jim either sticks to the basic facts or counsels in greater depth.

"If the drug really needs extensive counseling, I move the patient over to the counseling window and we really talk," he told *Drug Topics*. "I have serious issues with benzodiazepines, because they are a dangerous class of drugs if used for a long period of time. Patients hardly even know that they are taking that stuff, because it works so well. However, for most people, a certain part of their personality is lost to them, and it can be the best part of their personality — the passion, the anger, stuff that normal human beings have."

In fact, Jim recently told one of his patients, a young medical student who had been taking a benzodiazepine regularly for 6 months, that she was too young to continue with this drug for so long. He warned her of the risks of terrible withdrawal and the need to manage the stress of medical school differently.

"This is the kind of extensive counseling that pharmacists can do, although most don't. Younger pharmacists don't give themselves permission to do that. I'm older, so I actually can intrude like that. It helps a lot to make eye contact and let patients know that you are serious," Jim said. "I love it. It's the best part of my job."

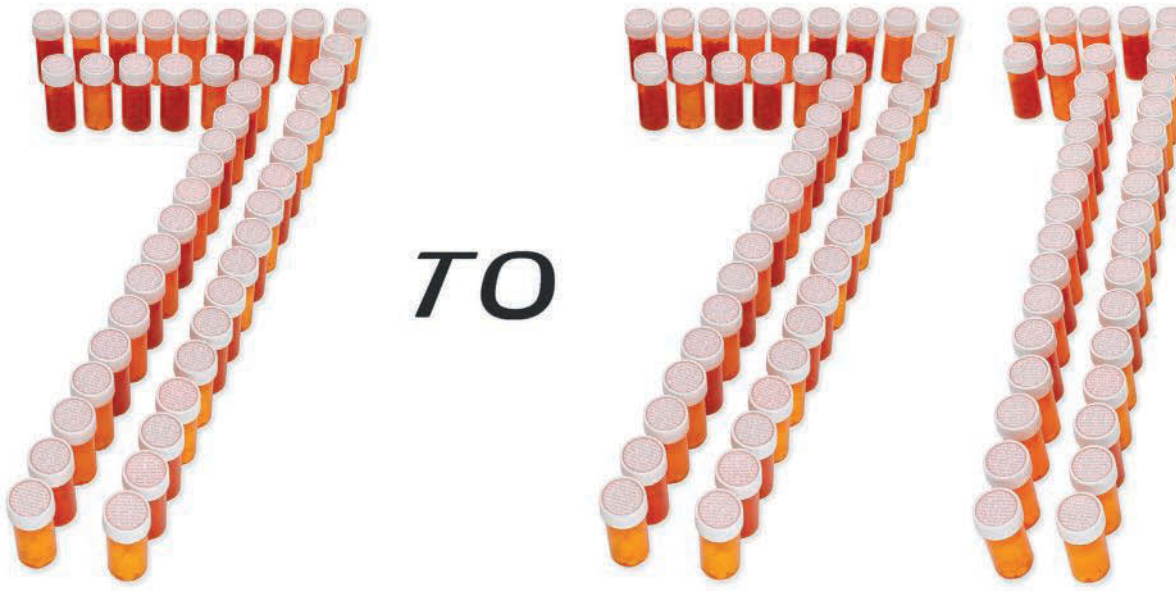
"This is the kind of extensive counseling that pharmacists can do, although most don't... It helps a lot to make eye contact and let patients know that you are serious. I love it. It's the best part of my job."

Jim also believes in taking the time to counsel patients about over-the-counter medications. He works part-time, approximately 2 to 3 days per week, as a relief pharmacist for a national chain. While some pharmacists direct all their attention to the "prescription mill" behind the counter, Jim's patients know that if they come in on Tuesday or Friday, he is accessible and knowledgeable about the OTC products that look so benign on the drugstore shelves.

With the need to fill ever-growing numbers of prescriptions, pharmacists may be worried that technicians will take over their jobs, Jim said. "Qualified technicians will be legally empowered to do more of the filling tasks. The idea is to allow the pharmacist more time for counseling and MTM, as well as the various professional tasks that will define us in the 21st century. We must, however, be ever watchful. It's our profession. We will have it our way."

Thank you, Jim, for sharing your perspective and insight. DT

Counts



top-selling drugs, making hand-counting a thing of the past.

The RxMedic ACS™ counting system makes pinpoint accuracy affordable for any pharmacy. The ACS simultaneously counts and pre-counts pills. It's available in four standard configurations or can be customized to fit your individual needs. The ACS includes the added safety of digitally imaging vial contents for more complete records.

For higher-volume needs, experience fully-automated dispensing with the RxMedic ADS™ robotic system.

Ready to count less and do more for your patients? Visit **www.rxmedic.com** or call **800-882-3819**.

RxMedic
count less...do more

Happy Holidays!

**In the spirit of the holiday season,
we send our thanks
and best wishes for the New Year.**

Mylan® Pharmaceuticals

Proven Medicine. Just More Affordable.™