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Drug Topics®

VOL. 157 NO. 5

Voice of the Pharmacist DrugTopics.com May 2013

2013 ANNUAL SALARY SURVEY

NEW REALITY

Salaries, benefits strong, yet work environment complex

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Pharmacology and therapeutics of pain medications: Part 1 PAGE 42

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Available in Pharmacies

Quillivant XR™ (methylphenidate HCl) is the **first and only** extended-release methylphenidate **oral suspension** for ADHD treatment

Quillivant XR™ (methylphenidate HCl) CII demonstrated efficacy at its primary endpoint of 4 hours and at all time points measured from 45 minutes to 12 hours post-dosing.

Quillivant XR contains approximately **20%** immediate-release and **80%** extended-release methylphenidate, which contributes to its pharmacokinetic profile characterized by a rapid initial absorption followed by a continuous release of methylphenidate.

INDICATION

Quillivant XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Quillivant XR was established in a 2-week, placebo-controlled trial in children aged 6 to 12 years with a diagnosis of ADHD. Accumulated efficacy data from other methylphenidate products were also considered.

IMPORTANT SAFETY INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including Quillivant XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

- Quillivant XR is contraindicated:
  - In patients known to be hypersensitive to methylphenidate or other components of Quillivant XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported.
  - During treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days following discontinuation of treatment with an MAOI because of the risk of hypertensive crisis.
- Stroke and myocardial infarction have occurred in adults treated with CNS stimulants at recommended doses. Sudden death has occurred in children and adolescents with structural cardiac abnormalities and other serious cardiac problems, and in adults taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with Quillivant XR.
- CNS stimulants cause an increase in blood pressure (mean increase approximately 2-4 mm Hg) and heart rate (mean increase approximately 3-6 bpm). Some individuals may have larger increases. Monitor all patients for hypertension and tachycardia.
- Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to Quillivant XR use.
- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Growth should be monitored during treatment with stimulants, including Quillivant XR. Patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

The Quillivant XR $20 Co-pay Card* may help eligible patients save up to $1200 per year!

*Terms and Conditions apply. Please see full Terms and Conditions at www.QuillivantXRPro.com/Terms-and-Conditions. **This co-pay card is not health insurance. The co-pay card is only accepted at participating pharmacies.** For any questions, please call 1-800-932-4371, or write: Pfizer, ATTN: Quillivant XR, PO Box 2249, Morrisville, PA 19067-8049. **No membership fees required.** Savings limited to $100 per 30 days for up to 12 uses within the program term. Card may be used once every 30 days. The maximum limit is $1200 per year or the amount of the co-pay you paid, whichever is less.

IMPORTANT SAFETY INFORMATION (cont'd)

- Based on accumulated data from other methylphenidate products, the most common (≥5% and twice the rate of placebo) expected adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. There is limited experience with Quillivant XR in controlled trials. Based on this limited experience, the adverse reaction profile of Quillivant XR appears similar to other methylphenidate extended-release products. The most common (≥2% in the Quillivant XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 45 ADHD patients (aged 6-12 years) were affect lability (9%), excoriation (4%), initial insomnia (2%), tic (2%), decreased appetite (2%), vomiting (2%), motion sickness (2%), eye pain (2%), and rash (2%).
- Based on animal data, use of Quillivant XR during pregnancy may cause fetal harm. Quillivant XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing mothers should be advised to discontinue drug or discontinue nursing, taking into consideration the importance of the drug to the mother.

For more information, please visit www.QuillivantXRPro.com

Quillivant XR™ CII
methylphenidate HCl | 25 mg/5 mL
for extended-release oral suspension

*Please see Brief Summary of Prescribing Information, including **BOXED WARNING** regarding Abuse and Dependence, on the following page.*

Pfizer

Quillivant XR™ (methylphenidate HCl) for extended-release oral suspension, CII Rx only
BRIEF SUMMARY: Consult Full Prescribing Information for Complete Product Information.

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including Quillivant XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Warnings and Precautions, Drug Abuse and Dependence].*

INDICATIONS AND USAGE

Quillivant XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Quillivant XR was established in a 2-week, placebo-controlled, laboratory classroom, crossover study in children aged 6-12 years with a diagnosis of ADHD. Patients in the trial met DSM-IV-TR® criteria for ADHD. Accumulated efficacy data from other methylphenidate products were also considered.

CONTRAINDICATIONS

Hypersensitivity to Methylphenidate or other Components of Quillivant XR. Quillivant XR is contraindicated in patients known to be hypersensitive to methylphenidate, or other components of Quillivant XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products.

Monoamine Oxidase Inhibitors Quillivant XR is contraindicated during treatment with monoamine oxidase inhibitors, and also within 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (MAOI), because of the risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS

Potential for Abuse and Dependence CNS stimulants, including Quillivant XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [*see Drug Abuse and Dependence*].

Serious Cardiovascular Reactions Stroke and myocardial infarction have occurred in adults treated with CNS stimulants at recommended doses. Sudden death has occurred in children and adolescents with structural cardiac abnormalities and other serious cardiac problems, and in adults taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with Quillivant XR.

Blood Pressure and Heart Rate Increases CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

Psychiatric Adverse Reactions Exacerbation of Pre-Existing Psychosis CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing Quillivant XR. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0 in placebo-treated patients.

Long-Term Suppression of Growth CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Quillivant XR. Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or nonmedication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth; however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

ADVERSE REACTIONS

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. *Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD* Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia. *Clinical Trials Experience with Quillivant XR in Children and Adolescents with ADHD*. There is limited experience with Quillivant XR in controlled trials. Based on this limited experience, the adverse reaction profile of Quillivant XR appears similar to other methylphenidate extended-release products. The most common (≥2% in the Quillivant XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 45 ADHD patients (ages 6-12 years) were affect lability, excoriation, initial insomnia, tic, decreased appetite, vomiting, motion sickness, eye pain, and rash.

Table 2. Common Adverse Reactions occurring in ≥2% of subjects on Quillivant XR and greater than placebo during the controlled cross-over phase

Adverse reaction	Quillivant XR (N=45)	Placebo (N=45)
Affect lability	9%	2%
Excoriation	4%	0%
Initial Insomnia	2%	0%
Tic	2%	0%
Decreased appetite	2%	0%
Vomiting	2%	0%
Motion sickness	2%	0%
Eye pain	2%	0%
Rash	2%	0%

Postmarketing Experience The following adverse reactions have been identified during post approval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are as follows:

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura

Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole

Eye Disorders: Diplopia, Mydriasis, Visual impairment

General Disorders: Chest pain, Chest discomfort, Hyperpyrexia

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC

Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching

Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia

Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Mania

Urogenital System: Priapism

Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

Vascular Disorders: Raynaud's phenomenon

DRUG INTERACTIONS

MAO Inhibitors Do not administer Quillivant XR concomitantly with monoamine oxidase inhibitors or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C Risk Summary There are no adequate or well-controlled studies with Quillivant XR in pregnant women. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in mothers dependent on other stimulant products such as amphetamines. Methylphenidate showed some potential for teratogenicity when pregnant animals were treated during organogenesis: an increased incidence of fetal spina bifida in rabbits at 40 times the maximum recommended human dose (MRHD), on a mg/m^2 basis, and an increased incidence of fetal skeletal variations in rats at 7 times the MRHD. A decrease in body weight gain was seen in the offspring of rats treated with methylphenidate throughout pregnancy and lactation at 4 times the MRHD. Quillivant XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Clinical Considerations Stimulant medications, such as Quillivant XR, cause vasoconstriction and thereby decrease placental perfusion. Infants born to amphetamine dependent mothers have an increased risk of premature delivery and low birth weight. Monitor infants for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness. Animal Data In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m^2 basis), but no other effects on postnatal

Voices

Been there, left that

My thanks to Dennis Miller for speaking out about the atrocious way chain pharmacists are treated ["Why I wrote Pharmacy Exposed," March 2013]. I have been a pharmacist for 27 years, and pharmacy is in my blood; my father owned his pharmacy for almost 50 years.

Over the years, I have worked for chain pharmacies, hospital pharmacies, and independents. Only in the chain pharmacies have I been treated as a "nonprofessional."

In fact, in November of 2011, after 15 years, I decided to abandon retail pharmacy and make the move back to hospital pharmacy. It was the scariest, yet best, career choice I have ever made. That is really saying a lot for a woman who was literally born to be a retail pharmacist.

I say shame on the collective state boards of pharmacy for allowing us to be treated as "nonprofessionals." If we were doctors, we might be protected against these kinds of working conditions.

I hope the powers that be will eventually realize this is an extremely dangerous way to practice pharmacy.

Jill M. Sande, RPh
SIGOURNEY, IOWA

The days of Doc

I too am a retired chain-store pharmacist. I started way back in my early teens, making deliveries on that bike with the big basket and small wheel in the front. I worked my way up to the soda fountain, and eventually, after finishing college, I became a registered pharmacist.

I chose pharmacy because of what I saw working in a neighborhood drugstore, where people of all ages came in seeking assistance from "their pharmacist" — or as they called him, "Hey Doc!"

The young PharmDs as well as most of their professors have no idea what the profession was like then. There were drugstores on most major corners in many neighborhoods. What brought the customers into any particular drugstore was the customer service that they received. Your current chain pharmacies have no idea what those two words mean, because it affects their bottom line.

I really enjoyed all those years that I was a practicing RPh. I actually had FUN. But now, since it's no longer fun, I'm done.

Fred Tanenbaum, RPh
EVANSTON, ILL.

To each according to his needs

Every time a customer asks me ahead of time, "What is the copay for this Rx?" I

Continued on pg. 17

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 pharmacists to share practical ideas for better pharmacy management and patient care.

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MAY 2013 **Drug Topics** Voice of the Pharmacist DrugTopics.com VOL. 157 NO. 5

COVER STORY

2013 Salary Survey

The good news: Satisfaction with salaries and benefits is high. The bad news: Ever-increasing workloads and more on-the-job stress. Overall job satisfaction? Your point of view depends on where you're standing.

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Caffeine acts as an adjuvant, enabling a lower amount of analgesic without compromising efficacy[1-3]

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- **Aspirin** (250 mg)
- **Caffeine** (65 mg)

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THE GO-TO HEADACHE MEDICINE.

*Versus acetaminophen monotherapy for headaches.

Do not recommend for use with any other acetaminophen-containing products.

References: 1. Laska EM, Sunshine A, Mueller F, Elvers WB, Siegel C, Rubin A. Caffeine as an analgesic adjuvant. *JAMA*. 1984;251(13):1711-1718. **2.** Echeverri D, Montes FR, Cabrera M, Galán A, Prieto A. Caffeine's vascular mechanisms of action. *Int J Vasc Med*. 2010;2010:834060. **3.** Diener HC, Pfaffenrath V, Pageler L, Peil H, Aicher B. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia*. 2005;25(10):776-787.

NOVARTIS

May 2013 **Drug Topics** Voice of the Pharmacist Vol. 157 No. 5

CPE **CONTINUING EDUCATION**

Pharmacology and therapeutics of pain medications: Part 1

An overview of non-opioid analgesics, including acetaminophen, selective and nonselective NSAIDs, and adjuvant analgesics. **PAGE 42**

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DT BLOG

More for the toolbox
Following up on the April issue's management tips for supervising pharmacists, reader Christina Pereira outlines five crucial factors that every team leader should bear in mind. Find them at *www.drugtopics.com*.

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IMAGE: THINKSTOCK / ISTOCKPHOTO


Introducing a
NEW approach in
type 2 diabetes
treatment...

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

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS and PRECAUTIONS

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

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.

NOW AVAILABLE

In adults with type 2 diabetes,

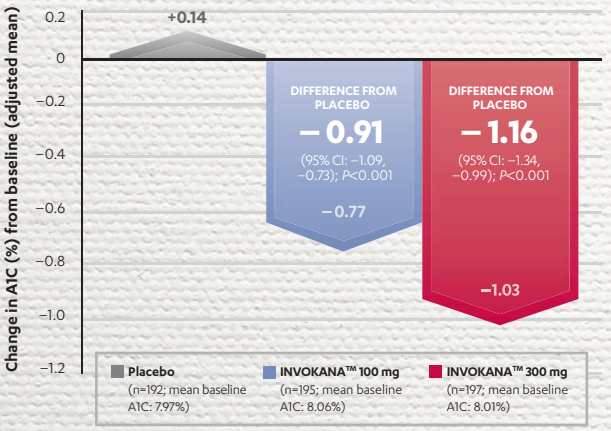
ENVISION NEW POSSIBILITIES

Introducing INVOKANA™—the first and only treatment option approved in the United States that reduces the reabsorption of glucose in the kidneys via sodium glucose co-transporter-2 (SGLT2) inhibition[1]

A1C Reductions as Monotherapy

INVOKANA™ monotherapy provided statistically significant A1C reductions vs placebo at 26 weeks[1]

A1C Change From Baseline With INVOKANA™ Monotherapy[1]



Effect on Weight*

Statistically significant weight reductions vs placebo at 26 weeks (*P*<0.001)[1]

» Difference from placebo†:
100 mg: −2.2%; 300 mg: −3.3%

Impact on Systolic Blood Pressure (SBP)*

Statistically significant SBP lowering vs placebo at 26 weeks (*P*<0.001)[2]

» Difference from placebo†:
100 mg: −3.7 mm Hg; 300 mg: −5.4 mm Hg

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

***Prespecified secondary endpoint.**

†Adjusted mean.

A1C Reductions vs Sitagliptin

INVOKANA™ 300 mg demonstrated greater A1C reductions vs sitagliptin 100 mg, in combination with metformin + a sulfonylurea, at 52 weeks (*P*<0.05)[1]

» Difference from sitagliptin†: −0.37%

Incidence of Hypoglycemia

Monotherapy over 26 weeks:
100 mg: 3.6%; 300 mg: 3.0%; placebo: 2.6%[1]

With metformin and a sulfonylurea over 52 weeks:
INVOKANA™ 300 mg: 43.2%; sitagliptin 100 mg: 40.7%[1]

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

Convenient Once-Daily Dosing[1]

» Recommended starting dose: INVOKANA™ 100 mg

» Dose can be increased to 300 mg in patients tolerating 100 mg, who have an eGFR of ≥60 mL/min/1.73 m^2 and require additional glycemic control

The most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.

References: 1. Invokana [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013. **2.** Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15(4):372-382.

Learn more at INVOKANAhcp.com/journal

Invokana™
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IMPORTANT SAFETY INFORMATION *(continued from first page)*

WARNINGS and PRECAUTIONS *(cont'd)*

- **Impairment in Renal Function:** INVOKANA™ (canagliflozin) increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.
- **Genital Mycotic Infections:** INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.
- **Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

  These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing

human kidney. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.

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

»**Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in nine clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years of age. Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA™ 100 mg and -0.74% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).

»**Renal Impairment:** The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m^2); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

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

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

OVERDOSAGE

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

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

ADVERSE REACTIONS

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

K02CAN13149

Please see Brief Summary of full Prescribing Information on the following pages.

Invokana™
canagliflozin tablets

Janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

April 2013 K02CAN13075

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA

100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator.

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

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

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

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

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

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

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

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

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

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

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

***** Week 26 in mITT LOCF population

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

INVOKANA™ (canagliflozin) tablets

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

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

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

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

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

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

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

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

Voices

Continued from pg. 3

get on my soapbox and say, "Well, this is the U.S.A. Everyone has a different plan. We are told by your insurer what the copay is, and the only way we can tell is to run it, so give us a few minutes and we will let you know."

When people complain that their copay is high, I say the same thing.

I too want a single-payer system. And I think copays should be set based on the income level of the family. For example: $5, $10, $20 for incomes $40-$50,000; $2, $5, $10 for lower incomes; and for people over $50,000, maybe $10, $20, $30, etc. This sets a copay based on the scale of income.

I have a very wealthy customer who owns a large business. His copays are ZERO because he owns the company, but his employees have regular copays. Is that right or fair?

Mike Saija, RPh, CIP
SHARON, MASS.

On a happier note

I can relate to everything "Goose" Rawlings says in his article ["Here's to the Flyboys," March 2013]. Our daughters were told in med school, "People don't care how much you know until they know how much you care." Thankfully, grateful patients still exist, and when we communicate with them in a professional and caring manner, they often show their appreciation.

What "Goose" describes is everything that keeps me going, too. I graduated in '71 and have worked in five different states, following my husband's career. These 42 years have involved a lot of change, from manual typewriters to robotics, but the occasional heartwarming message from a patient is the same, and it makes my day.

Healthcare may have changed, but patients are still people. I continue working because I still feel like I'm helping people, and that's good for me. Being a pharmacist gives me a sense of purpose, and I am content.

Rita Smith, RPh
MANHATTAN, KS

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DISPENSED AS WRITTEN B. Douglas Hoey, RPH, MBA

NCPA addresses compounding

In response to last year's tragic fungal meningitis outbreak, the National Community Pharmacists Association (NCPA) is actively working with healthcare leaders in Congress who are considering new drug-compounding legislation. The deaths and sickness caused by tainted injectable methylprednisolone have forced the reexamination of existing authority and caused intense pressure for Congressional legislation.

NCPA is dedicated to advocating for sufficient patient access to customized, pharmacist-compounded medications and has made it a top priority; it is included as a plank in NCPA's 2013 "Independent Community Pharmacy Checklist" for federal and state policymakers.

A vital service

NCPA continues to affirm two key points with lawmakers.

First, every day thousands of patients benefit from the services of medications compounded by pharmacists, whose practice is regulated by the state Boards of Pharmacy. Without these services, many patients would not have access to needed medications.

- Compounded medications provide solutions to patients who have few or no options. They provide alternative medication delivery routes, help avert allergic reactions, and fill gaps in demand not fulfilled by mass-produced medications. They also meet countless veterinary needs for companion animals and livestock.
- FDA itself has endorsed the role of compounding pharmacists in alleviating drug shortages, as with Tamiflu during the 2009 H1N1 flu outbreak. The liquid version used by children was in short supply, so compounding pharmacists converted Tamiflu capsules into liquid for dispensing.
- According to some estimates, 40% of intravenous medications used in hospitals are pharmacist-compounded.

In March, NCPA sent a letter to FDA about the role of compounding pharmacists in mitigating drug shortages. We asserted that "Compounding pharmacists have filled gaps in patient care during drug shortages in the past and should be allowed, through compounding and under existing rules and authorities, to continue to fill these gaps in these critical times of drug shortages to preserve access to medications."

NECC not typical

Second, federal and state policies should reflect the fact that the actions of the New England Compounding Center (NECC) were vastly out of step with compounding as practiced by community pharmacists. The allegations of NECC's misconduct include failure to adhere to standard practice for compounding, sterility procedures, and record-keeping requirements. Existing state and federal authority could have prevented the tragic events that unfolded. Why that authority was not exercised should be examined as the first step in determining whether new oversight is needed. If it is needed, the type of oversight and who should conduct it must also be addressed.

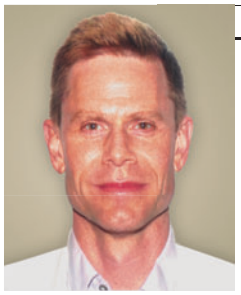
A November 2012 NCPA survey of more than 400 community pharmacists provides a snapshot of the role of compounding in a traditional community pharmacy. While 85.5% of respondents said they offer compounding services, 62% of those pharmacists said sales of traditionally compounded medications make up 5% or less of their pharmacy practice. Survey respondents also said that 70% of pharmacists participate in training/educational courses related to compounding techniques beyond what the state already requires to sustain their pharmacist license. In other words, most independent community pharmacists readily offer compounding in response to specific patient needs and do so with a seriousness of purpose.

Our goal

Some in Congress are pushing for sweeping federal legislation regulating all forms of compounding, which could compromise the state's role in overseeing pharmacy practice. NCPA believes that states should continue to oversee the practice of pharmacy. If certain activities go beyond the practice of pharmacy, only then should another regulating body have oversight.

While our messages — the preservation of patient access to traditional compounding and the more forceful exercise of existing powers — are being delivered to lawmakers, we continue to address these issues. Finding solutions for patients through the appropriate use of compounded medications is foundational to our profession. Whether or not you compound products, robust advocacy for the art of compounding is a must. We encourage concerned pharmacists to contact their U.S. senators and representatives and make their voices heard. DT

B. Douglas Hoey *is CEO of the National Community Pharmacists Association (www.ncpanet.org).*



STUDENT CORNER Jim Ober, PharmD Candidate

Why do drugstores sell products that kill?

According to the 2012 "U.S. Surgeon General's Report," approximately 80% of those who start smoking as teenagers will continue to smoke into adulthood. According to the 2008 "National Survey on Drug Use," each day in America, almost 4,000 young people between 12 and 17 years of age start smoking, and of these, about 1,000 become daily smokers.

Target the young

New marketing campaigns and packaging strategies have been developed to appeal to younger consumers. Many of these new products have candy flavors. Their brightly colored packages are featured in attractive point-of-sale displays meant to appeal to younger consumers. Fashion magazines present integrated marketing campaigns that contain color-coordinated dresses, shoes, and accessories — including the properly color-coordinated cigarette appropriate to an exciting night on the town.

An entire new line of products has emerged to tempt young consumers or ease their transition into chronic use of tobacco. Some of these new products include snus, orbs, energy dips, and electronic cigarettes (e-cigarettes). Snus is a spit-free and smoke-free tobacco product that comes in a small pouch and is placed under the upper lip. Orbs are dissolvable flavored pellets similar to Tic Tacs and made from finely ground tobacco meant to dissolve within 15 minutes. Energy dip is a blend of chewing

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VIEW FROM THE ZOO David Stanley, RPh

Shining a light into the dark places

When I graduated from pharmacy school in 1992 and started counseling patients, I felt really good about doing my part to bring the federal budget deficit under control. I'll admit I was a little skeptical at first that I could talk this nation into fiscal responsibility, but as the patients rolled in and I explained their prescriptions, I'll be darned if each year those deficits didn't get smaller and smaller, resulting in 1998 in the first federal balanced budget in a generation. What was perhaps the biggest change in the practice of pharmacy in our lifetime had paid off. OBRA-mandated counseling was a success.

OBRA

I'm kidding, of course. I've never thought my gift of gab so powerful that it could turn the fiscal course of a colossus like the federal government.

It is true, though, that a sea change in our profession began with an attempt to manage the government's monetary affairs.

OBRA stands for the Omnibus Budget Reconciliation Act of 1990. Along with revenue increases and other tweaks of the tax code that would achieve the main aims of the bill's authors, OBRA included such items as the creation of the Walter B. Jones Memorial Excellence Awards for Coastal and Ocean Resource Management.

That wasn't all it included. Not by a long shot. Deep, deep in the entrails of this document was the provision that changed pharmacy forever, the requirement that pharmacists offer to counsel patients with each new prescription filled.

Interestingly enough, OBRA was sponsored by recently departed Secretary of Defense Leon Panetta during his tenure in the U.S. House of Representatives as Congressman for California's central coast. Which makes me wonder whether the death of Osama Bin Laden might not have been the result of something like a new policy to evaluate the air quality on nuclear submarines, as it would seem that what Washington says and what Washington does can be dramatically different things.

HIPAA

If you need further proof, look no further than the passage of HIPAA in1996. If OBRA's afterthought was the biggest change in pharmacy in our lifetimes, than it's a safe bet that HIPAA would rank in a list of the Top 5.

You might be surprised to learn, however, that the "P" in that law's title does not stand for "privacy." The full title is "The Health Insurance Portability and Accountability Act," and while its privacy provisions weren't quite the footnote pharmacy counseling was to OBRA, once again a law's biggest legacy appears nowhere in its title.

If you were counting on monitoring seismic changes in healthcare law and pharmacy practice by looking at the actual titles of laws, you would have been burned twice, and I'm betting other examples wouldn't be very hard to find.

By the way, Title II of the HIPAA law, the one in which its patient privacy provisions appear, includes the words "administrative simplification" right up front in its heading.

I'll leave it to you to decide how much HIPAA has simplified things around your pharmacy.

Call it what it is

I suppose it would be too much to expect the level of honesty that changing the title of HIPAA to "The Paper Provider and Shredder Manufacturer Stimulus Act" would provide, but is it really unrealistic to ask for some sort of connection between a law's title and what the law actually does?

Is this really how things were designed to work? Can you imagine Thomas Jefferson creating the Louisiana Purchase by inserting a provision into an Omnibus Tariff Bill? I can't.

Evidently though, I can make my effort to keep on top of changes in the profession a little easier by just ignoring anything coming out of Congress with the word "pharmacy" in the title.

My decision not to go to law school looks better each day. DT

David Stanley *is a pharmacist, blogger, and professional writer in northern California. He can be reached at dstan93940@gmail.com.*

Why do drugstores sell products that kill?

Continued from pg. 19

tobacco touted to provide an energized sensation without the crashes associated with many energy drinks.

Like giving candy to a baby

These products are meant to tempt teenagers as fun and innovative analogues to products they already know. Products such as the electronic cigarette and flavored cigars are touted as less addictive and harmful. They are also less expensive and easier to rationalize, which helps to keep current smokers addicted and to attract new and younger tobacco users.

These products often act as "gateway" items, introducing teenagers to tobacco use and making it easier for them to move into use of a broader array of tobacco products, and they encourage lifelong habits. Some of these items are even marketed as smoking cessation aids, when in reality they only strengthen the addiction.

Pharmacists' role

According to the Centers for Disease Control and Prevention, tobacco-related deaths in the United States outnumber all deaths from HIV, illegal drug use, alcohol, motor vehicle injuries, suicides, and murders combined.

Lung cancer is the leading cause of cancer death in the United States for both men and women.

Tobacco use is the single most preventable cause of death.

As pharmacists we must consider that we are giving consumers mixed messages about tobacco products. On the one hand, we sell these products; on the other, we sell products intended to help stop tobacco use or treat the illnesses brought on by tobacco products.

We also should bear in mind that the sale of cigarettes in pharmacies may breed mistrust for pharmacists, who are still regarded as among the most trusted and accessible healthcare professionals.

They did it in S.F.

Activists in San Francisco lobbied the city council and achieved passage of an ordinance prohibiting cigarette sales in pharmacies.

It is the responsibility of pharmacists to inform all members of the public, regardless of their age, of the dangers of tobacco products, as well as to dispel any glamorous myths that the tobacco industry might have created. And it is the pharmacists' responsibility to stop selling these products in their pharmacies.

San Francisco did it. All pharmacists should consider following suit. DT

Jim Ober *is a 2014 PharmD candidate at Touro University College of Pharmacy. Contact him at jober601@yahoo.com.*

Up front » In Depth

Allen Nichol, PharmD

Patient-centered medical homes: Clinical pharmacy joins the team

The role of a clinical pharmacist at the patient-centered medical home (PCMH) where I practice in Columbus, Ohio, is to assist in the design of drug therapy regimens as they apply to patients with chronic disease.

Disease states

Disease states in this category include:

- Diabetes
- Hypertension
- Hyperlipidemia
- Weight loss
- Chronic kidney disease, stages 3 and 4 (CKD-3&4), as it relates to vitamin D deficiency and secondary hyperparathyroidism (SHPT)
- Non-narcotic chronic pain management

Collaborative visits

As an employee of the practice, I engage in what is termed a scheduled collaborative visit, a three-party activity that includes the patient, the physician, and the pharmacist.

A clinical pharmacist's role: Assist in design of drug therapy regimens for chronic disease.

As the team pharmacist, I am listed just as the physicians and physician assistants are in the practice's electronic scheduling program, which shows the days of the week and the hourly schedule for seeing patients at the site.

I schedule new visits with patients for 30 minutes and follow-up visits for 15 minutes. I meet with patients in the PCMH patient care room, just as if the visit were with a regular physician.

During my initial visit with the patient, I identify potential modification or continuation of current drug therapy, based upon current lab work, vital signs, and other patient-related information such as self-monitoring of blood glucose.


Allen Nichol

Then I leave the patient care room and, in the outer area, I review my suggestions with the physician for concurrence, rejection of suggested changes, or continuation of the drug therapy for the patient with no changes.

The physician and I then return to the patient care room. The physician explains to the patient why the current drug therapy needs modification. The physician invites the patient to ask questions and assures the patient that any proposed changes are for the betterment of the treatment process for the health problems from which the patient suffers.

I may then assist the physician with changes to the medication order or continuation of the current regimen (refills).

Each week, in "sitting rounds" with the pharmacy student assigned to me, I review and discuss strategy for patients we will see the following week.

Electronic evaluation

Through the CeutiCare computer software program, algorithms have been developed for the following disease states and comorbid conditions: Diabetes; hypertension; hyperlipidemia; CKD-3&4, with vitamin D 25OH deficiency and SHPT; and non-narcotic pain management.

The CeutiCare software system evaluates patient information stored in the patient's specific and individualized health record. It then offers a best evidence-based clinical suggestion for any necessary drug therapy change.

After being presented the information in a mini-grand-rounds fashion, the physician may either accept the suggestion and implement it; reject the initial change and continue into the algorithm until an acceptable modification of therapy is found; or choose to hold any therapy changes until new lab values have been processed.

For each suggestion, the software also lists clinical reference points that may be shared with the managing physician, if the physician wishes to evaluate the pharmacist's suggestion further.

As new medications come to market, the CeutiCare program continues to apply modifications that we evaluate in our practice with patients.

The CeutiCare program was developed over a five-year period and evaluated for ease of use and clinical effectiveness through a process conducted in 2012 by the Department of Family Medicine at the Cleveland Clinic.

The software is available for commercial use. It can be adapted to interface with commercial electronic medical record (EMR) systems (it has its own internal mini-EMR) through a standard HL-7 connection. DT

Allen Nichol *is COO/VP, clinical operations, CeutiCare LLC. E-mail allennichol@aol.com or k.bachmann@ceuticare.com for more info.*

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*Generic prescriptions. IMS Health NPA data on file at Teva.

Up front
In Depth

Valerie DeBenedette

MTM: Centering the pharmacist in healthcare

Call it cognitive services, pharmaceutical care, or pharmacy professional services, medication therapy management (MTM) is starting to come into its own. MTM programs enable pharmacists to help both patients and other healthcare providers stay on top of any medication issues, which in turn may improve the cost effectiveness of prescriptions.

MTM includes patient assessment and comprehensive medication reviews, the creation of a medication treatment plan, the tracking of medication safety and effectiveness, patient medication adherence, and pharmacist-prescriber communications.


Patty Kumbera

"MTM leverages the local pharmacist to serve as the patient advocate — and to work with patients and their various prescribers — to ensure they are on the right medications in right combination, taking them at appropriate time, and getting the right outcome from their prescriptions," said Patty Kumbera, BS Pharm, RPh, chief operating officer with OutcomesMTM, West Des Moines, Iowa. Patients and other healthcare providers see pharmacists as the medication experts, she said. "Let's utilize them and leverage their value to mend this broken healthcare system."

Medicare Part D includes a mandate requiring Part D prescription plans to include MTM programs. "The rules and regulations for the first several years were quite broad and anything counted," Kumbera said. "But the requirements MTM plans had to meet have become stronger in recent years."

Medical home

One growing role for MTM programs is connected with the patient-centered medical home (PCMH), which the federal Agency for Healthcare Research and Quality calls a way to improve healthcare by transforming how primary care is organized and delivered. PCMH, also known as primary care medical home, uses local and regional care coordinators to oversee the care received by patients who may have issues with their medications.

One PCMH, CareFirst BlueCross BlueShield in Maryland, uses the OutcomesMTM pharmacist network to work with local care coordinators to provide comprehensive medication reviews for patients who need them, Kumbera said. Local care coordinators identify patients who need MTM and reach out to their local pharmacists, and pharmacists in turn reach out to the local care coordinators. "It is bidirectional," Kumbera said of this communication process.


Catherine Cooke

Catherine Cooke, PharmD, is a pharmacist working with OutcomesMTM to triage CareFirst patients to local pharmacists for medication reviews. Cooke is president of PosiHealth Inc., Ellicott City, Md., and clinical associate professor at University of Maryland School of Pharmacy in Baltimore. Although MTM is required for Medicare patients, CareFirst has made MTM available to all its members, Cooke said. "Over a million members in Maryland are eligible to get this review," she said.

Cooke trains local care coordinators in how to determine which patients should be referred for MTM services, such as those patients with uncontrolled disease. "The top three factors are: Do the patients have a basic understanding of their medications, are we getting the results we want, and are there any patient concerns," she said.

Provider status

One of the important issues connected with MTM is to ensure that pharmacists be paid for their time in counseling patients, Cooke said. "I am billing through the OutcomesMTM system, which serves as an intermediate here." Being able to bill for these services allows MTM to become a revenue generator for pharmacies, she said, adding that patients appreciate the service, which builds customer loyalty to a pharmacy.

Pharmacists in the OutcomesMTM network are trained in how to document and bill for their services using what the company calls the Connect (TM) Platform, Kumbera said. "It connects our pharmacists with our payers to manage the whole process." For example, if the pharmacist finds that a patient should not be receiving a medication, he or she will call the prescriber and be paid for that interaction, she said.

"For the pharmacist, there can be a challenge in how the employer compensates the pharmacist," Cooke said. "Some pharmacy chains encourage MTM or allow it, but there is no direct benefit to the pharmacist." Other chains, she said, give the pharmacist either a financial incentive or a change in practice that allows the pharmacist time for MTM and integrates it into the normal work function. DT

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

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- Other glucocorticoid effects: Caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2%) are headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, and constipation.

DRUG INTERACTIONS

Avoid Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice). May cause increased systemic corticosteroid effects.

USE IN SPECIFIC POPULATIONS

Hepatic impairment: Monitor patients for signs and/or symptoms of hypercorticism.

The Important Safety Information does not include all the information needed to use UCERIS safely and effectively. Please see Brief Summary of Prescribing Information on the following pages and Full Prescribing Information at www.UCERIS.com.

CORE study designs: Two randomized, double-blind, placebo-controlled studies were conducted in a total of 899 adult patients with active, mild to moderate UC (Ulcerative Colitis Disease Activity Index [UCDAI]: ≥4 and ≤10 at entry). The primary endpoint was induction of combined clinical remission and mucosal healing (defined as a UCDAI score of ≤1, with scores of 0 for both rectal bleeding and stool frequency, normal mucosa with no friability on endoscopy, and a ≥1-point reduction in the endoscopic index [EI] score) after 8 weeks of treatment.[1]

*In a pooled analysis of 2 Phase III clinical trials.[1,3]

References: 1. UCERIS Prescribing Information. Santarus, Inc. January 2013. **2.** Brunner M, Ziegler S, Di Stefano AF, et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. *Br J Clin Pharmacol.* 2005;61:31-38. **3.** Data on file. Santarus, Inc. **4.** US Food and Drug Administration. Drugs at FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed January 15, 2013.

SANTARUS, INC.®

www.UCERIS.com/Pharmacy

NEW UCERIS™ (budesonide) extended release tablets

BRIEF SUMMARY
Please see package insert for Full Prescribing Information available at www.uceris.com
UCERIS (budesonide) extended release tablets, for oral use
Rx Only

INDICATIONS AND USAGE UCERIS (budesonide) extended release tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.

CONTRAINDICATIONS UCERIS is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of UCERIS. Anaphylactic reactions have occurred with other budesonide formulations.

WARNINGS AND PRECAUTIONS

Hypercorticism and Adrenal Axis Suppression When glucocorticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Glucocorticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic glucocorticosteroid is recommended. Since UCERIS is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed. **Transferring Patients from Systemic Glucocorticosteroid Therapy** Care is needed in patients who are transferred from glucocorticosteroid treatment with higher systemic effects to glucocorticosteroids with lower systemic effects, such as UCERIS, since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal suppression or benign intracranial hypertension, may develop. Adrenocortical function monitoring may be required in these patients and the dose of glucocorticosteroid treatment with high systemic effects should be reduced cautiously. **Immunosuppression** Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of glucocorticosteroids. In patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of glucocorticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior glucocorticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See prescribing information for VZIG and IG.) If chicken pox develops, treatment with antiviral agents may be considered. Glucocorticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections. Replacement of systemic glucocorticosteroids with UCERIS tablets may unmask allergies (e.g., rhinitis and eczema), which were previously controlled by the systemic drug. **Increased Systemic Glucocorticoid Susceptibility** Reduced liver function affects the elimination of glucocorticosteroids, and increased systemic availability of oral budesonide has been demonstrated in patients with liver cirrhosis. **Other Glucocorticosteroid Effects** Caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

ADVERSE REACTIONS

Systemic glucocorticosteroid use may result in the following:

- Hypercorticism and Adrenal Suppression
- Symptoms of steroid withdrawal in those patients transferring from Systemic Glucocorticosteroid Therapy
- Immunosuppression
- Increased Systemic Glucocorticosteroid Susceptibility
- Other Glucocorticosteroid Effects

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of UCERIS has been evaluated in controlled and open-label clinical trials which enrolled a combined total of 1105 patients with ulcerative colitis. In two 8-week, placebo-controlled studies in patients with active disease (Study 1 and Study 2), a total of 255 patients received UCERIS 9 mg, 254 patients received UCERIS 6 mg, and 258 patients received placebo. They ranged in age from 18-77 years (mean 43), 56% were male, and 75% were Caucasian. The most common adverse reactions were headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, and constipation. The adverse reactions occurring in 2% or more of patients on therapy with UCERIS 9 mg are summarized in Table 1.

Table 1. Summary of Adverse Reactions in Two Placebo Controlled Trials Experienced by at Least 2% of the UCERIS 9 mg Group (Studies 1 and 2)

	UCERIS 9 mg (N = 255) n (%)	UCERIS 6 mg (N = 254) n (%)	Placebo (N = 258) n (%)
Headache	29 (11.4)	37 (14.6)	27 (10.5)
Nausea	13 (5.1)	12 (4.7)	11 (4.3)
Decreased Blood Cortisol	11 (4.3)	6 (2.4)	1 (0.4)
Upper Abdominal Pain	10 (3.9)	8 (3.1)	5 (1.9)
Fatigue	8 (3.1)	5 (2.0)	5 (1.9)
Flatulence	6 (2.4)	8 (3.1)	5 (1.9)
Abdominal Distension	6 (2.4)	4 (1.6)	2 (0.8)
Acne	6 (2.4)	2 (0.8)	5 (1.9)
Urinary Tract Infection	5 (2.0)	1 (0.4)	1 (0.4)
Arthralgia	5 (2.0)	5 (2.0)	4 (1.6)
Constipation	5 (2.0)	1 (0.4)	2 (0.8)

Of UCERIS 9 mg patients, a total of 15% discontinued treatment due to any adverse event (including adverse reactions) compared with 17% in the placebo group. Table 2 summarizes the percentages of patients reporting glucocorticoid related effects in the 2 placebo-controlled studies.

Table 2. Summary of Glucocorticoid Related Effects in Two Placebo-Controlled Trials (Studies 1 and 2)

	UCERIS 9 mg (N = 255) n (%)	UCERIS 6 mg (N = 254) n (%)	Placebo (N = 258) n (%)
Overall	26 (10.2)	19 (7.5)	27 (10.5)
Mood changes	9 (3.5)	10 (3.9)	11 (4.3)
Sleep changes	7 (2.7)	10 (3.9)	12 (4.7)
Insomnia	6 (2.4)	6 (2.4)	8 (3.1)
Acne	6 (2.4)	2 (0.8)	5 (1.9)
Moon face	3 (1.2)	3 (1.2)	4 (1.6)
Fluid retention	2 (0.8)	3 (1.2)	3 (1.2)
Hirsutism	1 (0.4)	0	0
Striae rubrae	0	0	2 (0.8)
Flushing	0	1 (0.4)	3 (1.2)

No clinically significant differences were observed with respect to the overall percentages of patients with any glucocorticoid related effects between UCERIS and placebo after 8 weeks of induction therapy. Study 3 was an open-label study evaluating UCERIS 9 mg once daily for 8 weeks in 60 patients who had previously completed an 8-week induction study (Study 1), but had not achieved remission. Among patients who took UCERIS 9 mg up to 16 weeks cumulatively across Study 1 and Study 3 combined, similar rates of adverse reactions and glucocorticoid-related effects were seen compared to those who took UCERIS 9 mg for 8 weeks in Study 1. In Study 4, the safety of long-term treatment with UCERIS 6 mg was evaluated in a placebo-controlled 12-month maintenance study of 123 patients. Patients who had previously completed 8 weeks of therapy in any induction study (Study 1, 2, or 3) and were in remission were randomized to UCERIS 6 mg or placebo once daily for 12 months. In patients who took UCERIS 6 mg for up to 12 months, similar rates of adverse reactions were seen between placebo and UCERIS 6 mg. After up to 12 months of study treatment, 77% (27/35) of the patients in the UCERIS 6 mg and 74% (29/39) of the patients in the placebo treatment groups had normal bone density scans. In Study 4, the glucocorticoid related effects were similar in patients with up to 12 months of therapy with UCERIS 6 mg and placebo. (Table 3)

Table 3. Summary of Glucocorticoid Related Effects Over 12-month Treatment (Study 4)

	UCERIS 6 mg (N = 62) n (%)	Placebo (N = 61) n (%)
Overall	9 (14.5)	7 (11.5)
Insomnia	4 (6.5)	4 (6.6)
Mood changes	4 (6.5)	2 (3.3)
Moon face	3 (4.8)	3 (4.9)
Sleep changes	3 (4.8)	3 (4.9)
Acne	3 (4.8)	0
Hirsutism	3 (4.8)	0
Flushing	1 (1.6)	1 (1.6)
Fluid retention	1 (1.6)	1 (1.6)

Postmarketing Experience The following adverse reactions have been identified during postapproval use of oral budesonide. 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. *Immune System Disorders:* anaphylactic reactions *Nervous System Disorders:* benign intracranial hypertension *Psychiatric Disorders:* mood swings

DRUG INTERACTIONS

Interaction with CYP3A4 inhibitors Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4 activity in the liver and in the intestinal mucosa) caused an eight-fold increase of the systemic exposure to oral budesonide. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin) is indicated, discontinuation of UCERIS should be considered. After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. Ingestion of grapefruit or grapefruit juice should be avoided in connection with UCERIS administration. **Inhibitors of Gastric Acid Secretion** Since the dissolution of the coating of UCERIS is pH dependent, the release properties and uptake of the compound may be altered when UCERIS is used after treatment with gastric acid reducing agents (e.g., PPIs, H2 blockers and antacids).

USE IN SPECIFIC POPULATIONS

Pregnancy *Teratogenic Effects: Pregnancy Category C* Budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (approximately 0.05 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis). There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Nonteratogenic Effects:* Hypoadrenalism may occur in infants born of mothers receiving glucocorticosteroids during pregnancy. Such infants should be carefully observed. **Nursing Mothers** The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum budesonide concentration for the 400 and 800 mcg total daily doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after inhalation. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide plasma concentrations obtained from five infants at about 90 minutes after breast feeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant). The recommended daily dose of UCERIS extended release tablets is higher (9 mg daily) compared with inhaled budesonide (up to 800 µg daily) given to mothers in the above study. The maximum budesonide plasma concentration following a 9 mg daily dose (in both single- and repeated-dose pharmacokinetic studies) of oral budesonide is approximately 5-10 nmol/L which is up to 10 times higher than the 1-2 nmol/L for an 800 mcg daily dose of inhaled budesonide at steady state in the above inhalation study. Since there are no data from controlled trials on the use of UCERIS by nursing mothers or their infants, and because of the potential for serious adverse reactions in nursing infants from UCERIS, a decision should be made whether to discontinue nursing or to discontinue UCERIS, taking into account the clinical importance of UCERIS to the mother. Budesonide, is secreted in human milk. Data from budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother. Assuming the coefficient of extrapolation between the inhaled and oral doses is constant across all dose levels, at therapeutic doses of UCERIS, budesonide exposure to the nursing child may be up to 10 times higher than that by budesonide inhalation. **Pediatric Use** Safety and effectiveness of UCERIS in pediatric patients have not been established. Glucocorticosteroids, such as UCERIS may cause a reduction of growth velocity in pediatric patients. **Geriatric Use** Clinical studies of UCERIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, UCERIS should be used cautiously in elderly patients due to the potential for decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Hepatic Impairment** Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism. Discontinuing the use of UCERIS tablets should be considered in these patients.

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticosteroids are rare. Treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy. If glucocorticosteroids are used at excessive doses for prolonged periods, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may occur. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage may be reduced temporarily. Single oral budesonide doses of 200 and 400 mg/kg were lethal in female and male mice, respectively. The signs of acute toxicity were decreased motor activity, piloerection and generalized edema.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility *Carcinogenicity* Carcinogenicity studies with budesonide were conducted in rats and mice. In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 mcg/kg (approximately 0.023 times the maximum recommended human dose on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In an additional two-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). The concurrent reference glucocorticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 0.1 times the maximum recommended human dose on a body surface area basis). *Mutagenesis* Budesonide was not genotoxic in the Ames test, the mouse lymphoma cell forward gene mutation ($TK^{+/-}$) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethality test, the rat hepatocycte UDS test and the mouse micronucleus test. *Impairment of Fertility* In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately 0.07 times the maximum recommended human dose on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg (approximately 0.02 times the maximum recommended human dose on a body surface area basis) and above. No such effects were noted at 5 mcg/kg (approximately 0.005 times the maximum recommended human dose on a body surface area basis).

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U.S. Patent Nos: 7,410,651; 7,431,943; RE43799; 8,293,273.

1-UCE13033 V1

Up front » In Depth

Mari Edlin

Pharmacist-driven MTM could save ACOs a bundle

A typical accountable care organization (ACO) with 10,000 Medicare beneficiaries might save up to $1.1 million annually in emergency room and hospitalization costs by improving medication adherence for patients with diabetes, according to Health Affairs. The shift toward accountable care is opening the door to greater reference to pharmacist expertise.

More than 250 organizations have contracted with the Centers for Medicare and Medicaid Services (CMS) under an ACO model for Medicare beneficiaries, and the private market is keeping up a similar pace in accountable care contracts.

With their unique roles, pharmacists are moving away from being only drug dispensers to becoming consultants and medication managers in the coordinated care environment of ACOs. The role is already accepted in the Medicare space under the Medication Therapy Management (MTM) program.

Emerging role

Edith Rosato, RPh, CEO of the Academy of Managed Care Pharmacy, said that pharmacists can document improvements in care and costs information, which benefits ACOs by contributing to measures that earn shared savings. Their emerging role encompasses:

- Fine-tuning risk stratification criteria
- Prioritizing pharmacy services to identify and manage high-risk patients
- Making sure that electronic health records include pharmacist interventions, such as MTM
- Broadening current performance metrics and cost data

AMCP is actively defining quality metrics to be used by MTM programs.

"Managed care pharmacists and insurers will need to reassess their programs and make sure their workforces can be nimble in addressing the planning and coordination that are needed to help ACOs reach their targets," Rosato said.

Although pharmacists by themselves are not designated as eligible ACO participants, the Department of Health and Human Services allows the contracted ACO organizations to use their discretion in including pharmacists as participants in the big picture.

Specifically, only providers billing under Medicare Part A and Part B can participate directly in shared savings; however, the ACOs themselves can choose to award pharmacists a portion of the additional payments received from Medicare.

Integrated models

Transition to an ACO is proving to be less complicated than might be expected for organizations that previously embraced an integrated care model.

Joseph Manganelli, PharmD, MPA, director of pharmacy, Montefiore Care Management Organization in Yonkers, N.Y., the only Pioneer ACO in the state, said that his organization is "fully in the door" of involvement with pharmacists in coordinated care.

Member stratification, Manganelli said, makes it possible for care managers to turn to pharmacists for drug utilization review and for recommendations on optimizing drug therapy. Pharmacy partners have access to data from Montefiore programs that identify high-risk patients and enroll them in intensive care management programs.

In the general risk population for Montefiore's ACO, pharmacists work closely with nurses and other healthcare providers to enroll patients in case- and disease-management programs, conduct drug use evaluation to identify duplications in pharmacotherapy, make recommendations about treatments, and counsel members about proper medication use. The result is fewer admissions and readmissions, Manganelli said.

The organization relies on pharmacists' expertise in the hospital and the discharge environments, Manganelli continued, especially for medication reconciliation, and depends as well as on their ability to promote discussion with patients.

More than 250 organizations have contracted with CMS under an ACO model for Medicare beneficiaries.

Manganelli's primary concern has to do with patient use of outside providers. Medicare beneficiaries assigned to an ACO — assignment is made retrospectively — can choose their providers without regard to either a network or differential cost. Outside physicians probably will not have access to an ACO's electronic health records and can miss historical patient data.

The hope is that in time patients will seek out their ACO providers exclusively and that providers within extended communities will have far-reaching access to patient data.

Business as usual

Coordinated care is nothing new to HealthCare Partners, a mixed-model medical group employing 13 full-time

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Pharmacist-driven MTM could save ACOs a bundle

Continued from pg. 29

pharmacists and serving 740,000 patients in Southern California. Although it is a Pioneer ACO, the integrated group has always leveraged the expertise of pharmacists, said Mark Shinmoto, PharmD, director, pharmacy services; for this organization, pharmacist participation is "business as usual."

One of the biggest challenges is that under the ACO infrastructure, it is difficult for clinicians to completely perform care coordination when Medicare patients choose outside providers, agreed Shinmoto. "That makes it hard to manage patients during admissions and readmissions, two of the largest cost-drivers."

Two pilots

HealthCare Partners is currently conducting two pilots designed to introduce some control over the process.

The first, a telephonic reconciliation program after discharge for high-risk patients, is designed to minimize readmissions attributed to inappropriate use of medications. Of medications reviewed post-discharge, 30% required intervention for a variety of reasons, including duplicate drugs, changes in dose or frequency, termination of therapy, missed refills, drug additions, and patient education.

According to Shinmoto, the study indicates the potential role of the pharmacist to bridge the gap in medication reconciliation between the hospital and home, and thus to provide physicians with an accurate medication list for each of their discharged patients.

The other program identifies patients who are not achieving therapy goals, such as appropriate HbA1c levels, and then initiates and titrates medical therapy based on physician protocols.

NCQA recognition

Kelsey-Seybold in Texas has the distinction of becoming the first healthcare provider to be accredited as an ACO by the National Committee for Quality Assurance (NCQA).

The system operated as a team model before becoming an accredited ACO. It is a multi-specialty group practice with 370 physicians in 20 locations, 12 of which house pharmacies.

Pharmacists are responsible for typical MTM services for Medicare patients, and the clinics are expanding services to a commercial population, offering medication reconciliation post-discharge.

"Pharmacists see patients much more often than physicians do. We are the last connection in the chain to touch patients."
— Cathy C. Salinas, RPh
Director of Pharmacy
Kelsey-Seybold

Cathy C.Salinas, RPh, director of pharmacy, said that Kelsey-Seybold pharmacists might eventually offer their services to persons who are not patients of its medical staff.

In addition, pharmacists in the clinics can conduct therapeutic interchange for drug categories outlined in advance by physicians, without having to obtain approval.

Kelsey-Seybold also includes a managed care department for which pharmacists assist physicians with medication adherence issues.

"Pharmacists see patients much more often than physicians do," Salinas said. "We are the last connection in the chain to touch patients."

Shared accountability

SelectHealth, based in Salt Lake City, operates on what Eric Cannon, PharmD, FAMCP, chief of pharmacy and director of health and wellness, considers a shared accountability model rather than an ACO. The insurance arm of Intermountain Healthcare, SelectHealth is integrated with 22 hospitals and a medical group comprising more than 185 clinics that employ pharmacists to manage drug utilization and polypharmacy issues.

Cannon said that the organization's pharmacists conduct MTM services and practice collaboratively with physicians and care managers. Some of the clinics specialize in specific conditions, such as diabetes and hypertension, as well as polypharmacy and management of certain blood thinners.

Clinics rely on pharmacists to follow-up with patients who have problems with their medications; pharmacists can change doses and make medication changes if necessary — often freeing physicians from those duties.

Positive results, Cannon said, include increased dispensing of generics, improved hypertension, reduction in the number of bleeds by patients on blood thinners, and decreases in side effects.

A natural extension

While Salina Wong, director of clinical pharmacy programs for Blue Shield of California, acknowledged that the role of pharmacists is changing, their capabilities have always been in place, she said, encouraging them to practice at the top of their licenses. The health plan has 10 ACO arrangements.

"While is it uncommon for pharmacists to practice in a primary care physician office, they serve as a natural extension in an ACO," she said.

The ACO model forges new relationships with retail pharmacists, who are moving from dispensing to consulting roles. Wong foresees more participation of pharmacists on the administrative side, such as in technology promotion, including e-prescribing, and performance of data analyses.

Continued on pg. 37

Mallinckrodt

Some People Talk About The Future.
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Investing In Options For ADHD Treatment

Methylphenidate HCl ER Tablets, USP CII

- First AB-rated generic to CONCERTA®
- Now available in **27 mg**, **36 mg**, and **54 mg** tablet strengths

INDICATION

Methylphenidate hydrochloride extended-release tablets, USP are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65.

IMPORTANT RISK INFORMATION

DRUG DEPENDENCE

Methylphenidate hydrochloride extended-release tablets should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

CONTRAINDICATIONS

- Methylphenidate HCl ER Tablets are contraindicated in patients
  - With a known hypersensitivity to the product or its components
  - With marked anxiety, tension, or agitation
  - With glaucoma
  - With tics or a family history or diagnosis of Tourette's syndrome
  - Using or within 2 weeks of using a monoamine oxidase inhibitor

Serious adverse events, including sudden death, stroke and myocardial infarction, have been reported in patients taking usual doses. The most common adverse reaction (>5%) reported in children and adolescents was upper abdominal pain. The most common adverse reactions (>10%) reported in adults were dry mouth, nausea, decreased appetite, headache and insomnia.

Please see Brief Summary of Full Prescribing Information on following page.

For more information scan the QR code with a web-enabled device and visit us at **www.mallinckrodt.com**

Customer Service: 800-325-8888
For Medical Information call Product Monitoring: 800-778-7898
www.mallinckrodt.com

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BRIEF SUMMARY - Consult full prescribing information before use.

Methylphenidate Hydrochloride Extended-Release Tablets USP
Initial U.S. Approval: 2000

WARNING: DRUG DEPENDENCE

Methylphenidate hydrochloride extended-release tablets should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

CONTRAINDICATIONS

Hypersensitivity to Methylphenidate

Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been observed in patients treated with methylphenidate hydrochloride extended-release tablets. Therefore, methylphenidate hydrochloride extended-release tablets are contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product *[see Adverse Reactions (6.6)]*.

Agitation

Methylphenidate hydrochloride extended-release tablets are contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Glaucoma

Methylphenidate hydrochloride extended-release tablets are contraindicated in patients with glaucoma.

Tics

Methylphenidate hydrochloride extended-release tablets are contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome *[see Adverse Reactions (6.4)]*.

Monoamine Oxidase Inhibitors

Methylphenidate hydrochloride extended-release tablets are contraindicated during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO-inhibitor (hypertensive crises may result) *[see Drug Interactions (7.1)]*.

WARNINGS AND PRECAUTIONS

Serious Cardiovascular Events

Sudden Death and Pre-Existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2 to 4 mmHg) and average heart rate (about 3 to 6 bpm) *[see Adverse Reactions (6.5)]*, and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications, should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events

Pre-Existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid 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.

Emergence of New Psychotic or Manic Symptoms

Treatment-emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in patients without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in patients with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Potential for Gastrointestinal Obstruction

Because the methylphenidate hydrochloride extended-release tablets are nondeformable and do not appreciably change in shape in the GI tract, methylphenidate hydrochloride extended-release tablets should not ordinarily be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, methylphenidate hydrochloride extended-release tablets should only be used in patients who are able to swallow the tablet whole *[see Patient Counseling Information (17)]*.

Hematologic Monitoring

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

ADVERSE REACTIONS

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

- Drug Dependence *[see Box Warning]*
- Hypersensitivity to Methylphenidate *[see Contraindications (4.1)]*
- Agitation *[see Contraindications (4.2)]*
- Glaucoma *[see Contraindications (4.3)]*
- Tics *[see Contraindications (4.4)]*
- Monoamine Oxidase Inhibitors *[see Contraindications (4.5) and Drug Interactions (7.1)]*
- Serious Cardiovascular Events *[see Warnings and Precautions (5.1)]*
- Psychiatric Adverse Events *[see Warnings and Precautions (5.2)]*
- Seizures *[see Warnings and Precautions (5.3)]*
- Long-Term Suppression of Growth *[see Warnings and Precautions (5.4)]*
- Visual Disturbance *[see Warnings and Precautions (5.5)]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions (5.6)]*
- Hematologic Monitoring *[see Warnings and Precautions (5.7)]*

The most common adverse reaction in double-blind clinical trials (>5%) in pediatric patients (children and adolescents) was abdominal pain upper. The most common adverse reactions in double-blind clinical trials (>5%) in adult patients were decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis *[see Adverse Reactions (6.1)]*.

The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased *[see Adverse Reactions (6.3)]*.

The development program for methylphenidate hydrochloride extended-release tablets included exposures in a total of 3906 participants in clinical trials. Children, adolescents, and adults with ADHD were evaluated in 6 controlled clinical studies and 11 open-label clinical studies (see Table 3). Safety was assessed by collecting adverse events, vital signs, weights, ECGs, and by performing physical examinations and laboratory analyses.

Other Adverse Reactions Observed in Methylphenidate Hydrochloride Extended-Release Tablets Clinical Trials

This section includes adverse reactions reported by methylphenidate hydrochloride extended-release tablets-treated subjects in double-blind trials that do not meet the criteria specified for Table 4 or Table 5 and all adverse reactions reported by methylphenidate hydrochloride extended-release tablets-treated subjects who participated in open-label and postmarketing clinical trials.

Blood and Lymphatic System Disorders: Leukopenia

Eye Disorders: Accommodation disorder, Dry eye

Vascular Disorders: Hot flush

Gastrointestinal Disorders: Abdominal discomfort, Abdominal pain, Diarrhea

General Disorders and Administrative Site Conditions: Asthenia, Fatigue, Feeling jittery, Thirst

Infections and Infestations: Sinusitis

Investigations: Alanine aminotransferase increased, Blood pressure increased, Cardiac murmur, Heart rate increased

Musculoskeletal and Connective Tissue Disorders: Muscle spasms

Nervous System Disorders: Lethargy, Psychomotor hyperactivity, Somnolence

Psychiatric Disorders: Anger, Hypervigilance, Mood altered, Mood swings, Panic attack, Sleep disorder, Tearfulness, Tic

Reproductive System and Breast Disorders: Erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Rash, Rash macular

Vascular Disorders: Hypertension

Discontinuation Due to Adverse Reactions

Adverse reactions in the 4 placebo-controlled studies of children and adolescents leading to discontinuation occurred in 2 methylphenidate hydrochloride extended-release tablets patients (0.6%) including depressed mood (1, 0.3%) and headache and insomnia (1, 0.3%) and 6 placebo patients (1.9%) including headache and insomnia (1, 0.3%), irritability (2, 0.6%), headache (1, 0.3%) psychomotor hyperactivity (1, 0.3%), and tic (1, 0.3%).

In the 2 placebo-controlled studies of adults, 25 methylphenidate hydrochloride extended-release tablets patients (6.0%) and 6 placebo patients (2.8%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% in the methylphenidate hydrochloride extended-release tablets patients included anxiety (1.7%), irritability (1.4%), blood pressure increased (1.0%), and nervousness (0.7%). In placebo patients, blood pressure increased and depressed mood had an incidence of >0.5% (0.9%).

In the 11 open-label studies of children, adolescents and adults, 266 methylphenidate hydrochloride extended-release tablets patients (7.0%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% included insomnia (1.2%), irritability (0.8%), anxiety (0.7%), decreased appetite (0.7%), and tic (0.6%).

Tics

In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with methylphenidate hydrochloride extended-release tablets.

In a second uncontrolled study (n=682 children) the cumulative incidence of new onset tics was 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

Blood Pressure and Heart Rate Increases

In the laboratory classroom clinical trials in children (Studies 1 and 2), both methylphenidate hydrochloride extended-release tablets once daily and methylphenidate three times daily increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1 to 4 mm Hg during the day, relative to placebo. In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with methylphenidate hydrochloride extended-release tablets and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for methylphenidate hydrochloride extended-release tablets and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively. In one placebo-controlled study in adults (Study 6), dose-dependent mean increases of 3.9 to 9.8 bpm from baseline in standing pulse rate were observed with methylphenidate hydrochloride extended-release tablets at the end of the double-blind treatment vs. an increase of 2.7 beats/minute with placebo. Mean changes from baseline in standing blood pressure at the end of double-blind treatment ranged from 0.1 to 2.2 mm Hg (systolic) and -0.7 to 2.2 mm Hg (diastolic) for methylphenidate hydrochloride extended-release tablets and was 1.1 mm Hg (systolic) and -1.8 mm Hg (diastolic) for placebo. In a second placebo-controlled study in adults (Study 5), mean changes from baseline in resting pulse rate were observed for methylphenidate hydrochloride extended-release tablets and placebo at the end of the double-blind treatment (3.6 and -1.6 beats/minute, respectively). Mean changes from baseline in blood pressure at the end of the double–blind treatment for methylphenidate hydrochloride extended-release tablets and placebo-treated patients were -1.2 and -0.5 mm Hg (systolic) and 1.1 and 0.4 mm Hg (diastolic), respectively *[see Warnings and Precautions (5.1)]*.

DRUG INTERACTIONS

MAO Inhibitors

Methylphenidate hydrochloride extended-release tablets should not be used in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitors *[see Contraindications (4.5)]*.

Vasopressor Agents

Because of possible increases in blood pressure, methylphenidate hydrochloride extended-release tablets should be used cautiously with vasopressor agents *[see Warnings and Precautions (5.1)]*.

Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of methylphenidate hydrochloride extended-release tablets on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPAA in pregnant rats was 1 to 2 times that seen in trials in volunteers and patients with the maximum recommended dose of methylphenidate hydrochloride extended-release tablets based on the AUC.

The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. Methylphenidate hydrochloride extended-release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of methylphenidate hydrochloride extended-release tablets on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if methylphenidate hydrochloride extended-release tablets are administered to a nursing woman.

In lactating female rats treated with a single oral dose of 5 mg/kg radiolabeled methylphenidate, radioactivity (representing methylphenidate and/or its metabolites) was observed in milk and levels were generally similar to those in plasma.

Pediatric Use

Methylphenidate hydrochloride extended-release tablets should not be used in children under six years, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established.

Geriatric Use

Methylphenidate hydrochloride extended-release tablets have not been studied in patients greater than 65 years of age.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Methylphenidate is a Schedule II controlled substance under the Controlled Substances Act.

Abuse

As noted in the *Box Warning*, methylphenidate hydrochloride extended-release tablets should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse.

In two placebo-controlled human abuse potential studies, single oral doses of methylphenidate hydrochloride extended-release tablets were compared to single oral doses of immediate-release methylphenidate (IR MPH) and placebo in subjects with a history of recreational stimulant use to assess relative abuse potential. For the purpose of this assessment, the response for each of the subjective measures was defined as the maximum effect within the first 8 hours after dose administration.

In one study (n=40), both methylphenidate hydrochloride extended-release tablets (108 mg) and 60 mg IR MPH compared to placebo produced statistically significantly greater responses on the five subjective measures suggestive of abuse potential. In comparisons between the two active treatments, however, methylphenidate hydrochloride extended-release tablets (108 mg) produced variable responses on positive subjective measures that were either statistically indistinguishable from (Abuse Potential, Drug Liking, Amphetamine, and Morphine Benzedrine Group [Euphoria]) or statistically less than (Stimulation – Euphoria) responses produced by 60 mg IR MPH.

In another study (n=49), both doses of methylphenidate hydrochloride extended-release tablets (54 mg and 108 mg) and both doses of IR MPH (50 mg and 90 mg) produced statistically significantly greater responses compared to placebo on the two primary scales used in the study (Drug Liking, Euphoria). When doses of methylphenidate hydrochloride extended-release tablets (54 mg and 108 mg) were compared to IR MPH (50 mg and 90 mg), respectively, methylphenidate hydrochloride extended-release tablets produced statistically significantly lower subjective responses on these two scales than IR MPH. Methylphenidate hydrochloride extended-release tablets (108 mg) produced responses that were statistically indistinguishable from the responses on these two scales produced by IR MPH (50 mg). Differences in subjective responses to the respective doses should be considered in the context that only 22% of the total amount of methylphenidate in methylphenidate hydrochloride extended-release tablets is available for immediate release from the drug overcoat *[see System Components and Performance (11.1)]*.

Although these findings reveal a relatively lower response to methylphenidate hydrochloride extended-release tablets on subjective measures suggestive of abuse potential compared to IR MPH at roughly equivalent total MPH doses, the relevance of these findings to the abuse potential of methylphenidate hydrochloride extended-release tablets in the community is unknown.

Dependence

As noted in the *Box Warning*, careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow up.

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of methylphenidate hydrochloride extended-release tablets overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, muscle twitching, convulsion, grand mal convulsion, confusional state, hallucinations (auditory and/or visual), hyperhidrosis, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus arrhythmia, hypertension, mydriasis, and dry mouth.

Recommended Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for methylphenidate hydrochloride extended-release tablets overdosage has not been established.

The prolonged release of methylphenidate from methylphenidate hydrochloride extended-release tablets should be considered when treating patients with overdose.

Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

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Up front
In Depth

Julia Talsma, Content Channel Director

Managed Medicaid captures almost half of fee-for-service prescriptions, shifts patient care: IMS Institute report

The shift of Medicaid patients from fee-for-service to Managed Medicaid during 2011 resulted in a massive shift of prescriptions nationally, with nearly half of all Medicaid prescriptions now filled by Managed Medicaid, according to a recent study released by the IMS Institute for Healthcare Informatics.

Study findings were presented April 4 during the Academy of Managed Care Pharmacy Annual Meeting in San Diego.

The study

"Medicaid accounts for 16 cents of every U.S. healthcare dollar, and is expected to grow to 20% by 2021 largely driven by the upcoming expansion of Medicaid as part of the Affordable Care Act," stated the IMS Institute study, "Impact on Patient Care of Shift From Fee-For-Service to Managed Medicaid."

"The shared cost model between states and the federal government, combined with the continuing weak economic climate and the impending expansion, has prompted many states to shift from historically common fee-for-service payment models to managed care models, and several states with large Medicaid populations made such changes during 2011," the report noted.

Other considerations for making the shift include expected savings in drug-cost rebates, lower dispensing fees and ingredient costs to pharmacies, and potential for lowering both usage rates and cost escalation trends.

With states playing a bigger role in the healthcare system overall next year as a result of the Medicaid expansion, the IMS Institute decided to share recent data on prescription drug utilization in four states that have moved a substantial number of Medicaid beneficiaries to Managed Medicaid.

FIGURE 1

ANTIPSYCHOTIC GENERIC UTILIZATION RATES BY STATE AND COHORT

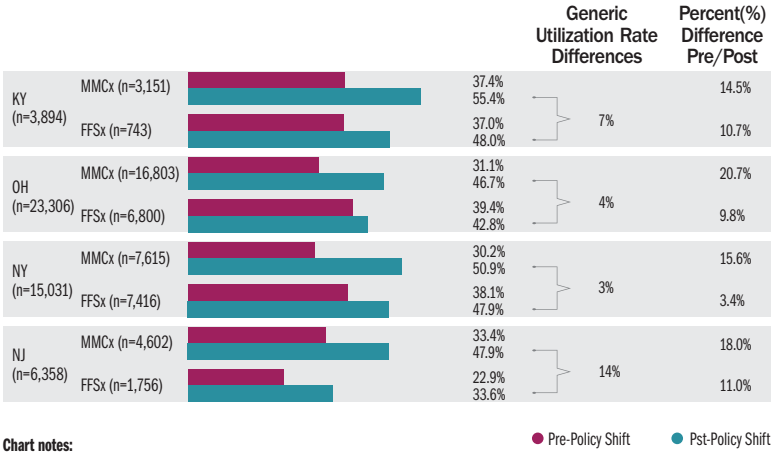

Chart notes:
MMCx - Managed Medicaid Prescriptions
FFSx - Fee-for-service Medicaid Prescriptions
Generic forms of two products (Zyprexa®, November 2011 and Seroquel®, March 2012) were introduced during the post-policy change period.
Generic utilization rate represents generic share of prescriptions.

Source: IMS Institute for Healthcare Informatics

"Prescription drug usage is typically an indicator of effective overall disease management, particularly in chronic diseases such as these," noted the report's introduction.

The number of monthly prescriptions dispensed through Managed Medicaid increased from 4.9 million in September 2011 to 12.5 million in June 2012, according to study data.

The study analyzed the impact of care on Managed Medicaid beneficiaries in Kentucky, New Jersey, New York, and Ohio since 2011, focusing on three therapeutic areas: antipsychotic drugs, diabetes agents, and respiratory medications. According to the report, the initial impact, in the first nine months following the change, showed widely varying impacts on patient care. Some therapy areas in some states showed essentially no change from Fee-for-service programs, while others showed significant changes.

"We compared prescription drug use for the cohort of patients for 9 to 12 months before moving into a Managed Medicare plan and then 9 to 12 months after the change to Managed Medicare.

"We also took a look at a cohort of patients who were in a fee-for-service model and remained there," said Murray Aitken, executive director, IMS Institute for Healthcare Informatics, adding, "While it is still early days, our research reveals some important signs of impact."

Continued on pg. 34

Managed Medicaid shifts patient care

Continued from pg. 33

Antipsychotic use

All four states analyzed in the study demonstrated a greater use of antipsychotic generic drugs when they were available for Managed Medicaid beneficiaries compared with fee-for-service Medicaid patients, Aitken said.

"The generic utilization rates for Managed Medicare patients taking antipsychotics were between 3% and 14% higher than for fee-for-service patients in each state after the policy shifts," he said. "Patients in Managed Medicaid plans in Kentucky and New Jersey were more likely to be using generic antipsychotic medicines compared to those in fee-for-service plans."

During the study period, both Zyprexa and Seroquel lost patent exclusivity and generics became available. During the post-policy shift period, more than 55% of Managed Medicaid beneficiaries in Kentucky were using antipsychotic generics. In Ohio, the percentage was about 47%, in New Jersey, it was about 48%, and in New York, it was 51%.

"There is still variation in terms of the extent to which generics are used. In addition, there is also a variation in terms of Managed Medicaid plans versus fee-for-service plans," Aitken noted.

Diabetes care

The IMS study also showed the impact upon care of diabetes patients moved to Managed Medicaid plans.

In New York, more diabetes patients received diabetes drugs, with an increase in the average number of prescriptions in the post-policy shift period of 5% (and an increase of 13% in prescriptions for the most commonly used diabetes treatment) and a change from an annualized average of 11.2 scripts per patient to 11.8 scripts per patient.

In the fee-for-service cohort, the average number of diabetes medications remained stable at about 12 scripts before and after policy changes.

FIGURE 2

NY DIABETES MEDICAID PRESCRIPTIONS PER PATIENT BY COHORT

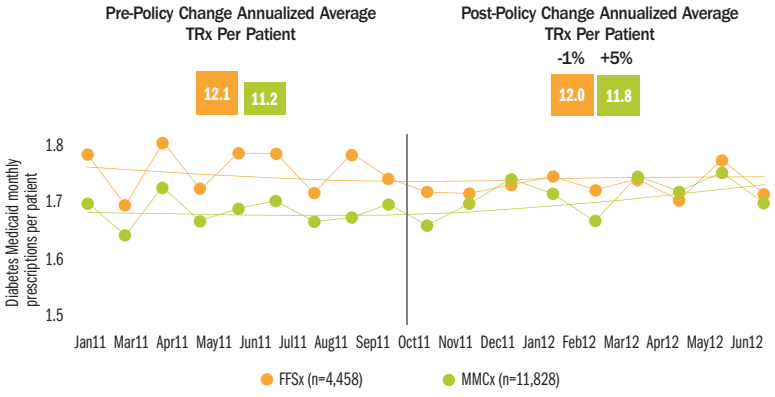

Chart notes:
Annualized prescriptions indicates an average number of diabetes prescriptions per patient per year in the Medicaid program in New York.

Source: IMS Institute for Healthcare Informatics

FIGURE 3

AVERAGE RESPIRATORY PRESCRIPTION UTILIZATION PER PATIENT BY STUDY COHORT & STATE

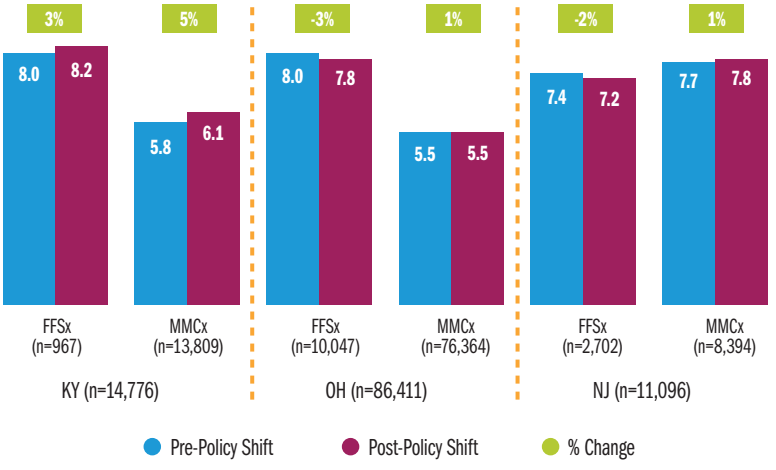

Chart notes:
Prescriptions are annualized so that they can be compared across States, because each State had different pre- and post-periods based on timing of policy changes.

Source: IMS Institute for Healthcare Informatics

"Aggressive management of diabetes is understood by the Managed Medicaid plans to be an important way to manage the overall costs. With the prescription drug benefits being carved in now, there is a greater incentive for the plans to be optimizing the treatment overall for the patient," Aitken told *Drug Topics*.

He added, "We also saw a greater use of metformin and the lower-cost drugs for the treatment of diabetes."

Respiratory medications

Patients in Kentucky with respiratory disorders who were switched to Managed Medicaid had an increased utilization rate of 5% compared to only a 3% increase for the patients who remained in fee-for-service Medicaid during the study. In New Jersey and Ohio, Managed Medicare patients used 1% more prescriptions per patient in each state. All Managed Medicaid programs showed an increase in scripts per patient per month in all three states.

"It would be interesting to talk to state Medicaid directors in these different states to compare notes on what is going on," Aitken noted. "We also see absolute levels of some of these drugs. When you see significant variations, it would be difficult to conclude that everyone is optimized."

Fee-for-service patients in Kentucky, Ohio, and New Jersey used approximately 26% to 27% more respiratory prescriptions per patient than managed care patients did, both before and after the policy shift.

"This was consistent with the policy that more severely ill patients remain on fee-for-service payment models," Aitken said.

Conclusion

Significant variation across states and therapeutic areas continue to exist after the shift to Managed Medicaid, the study noted, reflecting longstanding differences in clinical practice, Medicaid program design, and patient profiles.

Further analyses are warranted to determine the impact on health outcomes and the overall costs associated with Medicaid programs, the report concluded.

"We urge states to put systems in place to measure and monitor prescription drug use and ultimately outcomes. Each year states will need to assess the impact of these programs on the health of the Medicaid population," Aitken said.

Edith A. Rosato, RPh, IOM, CEO of the Academy of Managed Care Pharmacy, said in a press statement that the Academy was encouraged by the positive results of the study on patients who received care through Managed Medicaid programs.

"Given the variability in state programs, Managed Medicaid plans will need to be continually evaluated," Rosato said.

She added, "Initial findings suggest that patients could be better managed in these programs, particularly when the drug benefit is carved into a state's managed care plan rather than maintained in a fee-for-service program." DT

Julia Talsma, Content Channel Director

Community pharmacists can bend medication adherence curve

Medication adherence continues to be a challenge for patients, particularly for those who are new to therapy with diseases that are asymptomatic and who may not feel as if they need medication.

In a recent study published in the *Journal of Managed Care Pharmacy (http://www.amcp.org/jmcp/)*, patients who were new to therapy and were being treated for one of six chronic conditions refilled their medications only approximately 18% to 54% of the time over a 12-month period.

The cost of nonadherence to the U.S. healthcare system has been estimated at $290 billion, according to research published in 2009 by the New England Health Institute.

Predict and intervene

Community pharmacy programs can help to bend the medication adherence curve using predictive modeling and risk stratification, as well as product-specific interventions, said Walgreens experts at the World Congress Summit in Philadelphia.


Kristi Rudkin

Kristi Rudkin, PharmD, senior director of product development for Walgreens, and Michael S. Taitel, PhD, Walgreens senior director of clinical outcomes and analytic services, shared the findings of their research into what will help patients better manage their conditions and stay adherent to their medications.

"Medication adherence is a challenge. The same patient can have multiple barriers to the same medication over time, so it is difficult to pinpoint one solution," said Rudkin in an interview with *Drug Topics*.

The WAG approach

Walgreens is developing a predictive model for medication adherence and using risk stratification to identify patients who may need extra help with medication adherence. It is also using these tools to target those new to therapy based on their risk profiles, said Taitel.


Michael Taitel

Patients fall into two categories: those who are new to Walgreens and new to therapy and existing patients who are new to therapy. Examination of existing patients' previous adherence to other therapies makes it easier to predict which ones need intervention to support medication adherence.

"For those who are new to Walgreens, we can rely on the characteristic of the drug and the characteristics of the prescriber, but probably more importantly we look at census tract data — the neighborhood and the patient's health insurance copayment amounts," Taitel said. "So cost is a predictor and can be a barrier for many people, but it is not the No. 1 barrier. The No. 1 barrier is forgetfulness."

Other factors that contribute to adherence rates among new-to-therapy patients who refill late include side effects, doubts about the need for medication, regimen complexity, and miscellaneous barriers, Taitel said.

Face-to-face: Statins

In a retrospective cohort study that included 76 community pharmacies in the Midwest, pharmacist-led face-to-face counseling helped improve medication adherence for patients who were new to statin therapy and were followed for 12 months, Taitel said.

Patients considered to be adherent had a medication possession ratio (MPR) of at least 80%. There were 586 patients who participated in two face-to-face counseling sessions with a pharmacist and 516 who received usual care. At 12 months, there was a 7.2% difference in individuals in the intervention group who were adherent (40.9% with an MPR ≥80%) compared to those in the control group (33.7% with an MPR ≥80%).

"This represents a 21% improvement," Taitel said. "This is a piece of the answer, making sure those patients who are new to therapy get a good start. They know they can rely on another healthcare professional, their pharmacist."

Face-to-face: Injections

Face-to-face counseling also made a difference for patients who were new to therapy injections. By coaching patients about where and when to inject; setting expectations about possible side effects, such as nausea; and ensuring patients have needles at the outset of therapy, pharmacists can have an impact on medication adherence.

In a research study supported by a pharmaceutical manufacturer, patients were coached at the first refill to determine how comfortable they were with self-injections, and side effects were assessed. More than 40,000 patients were randomized to the face-to-face counseling and coaching, and approximately 4,600 were in the control group.

"Part of the issue with side effects is the unexpected," Taitel said. "If patients know that a particular side effect is common and expect it, then they will be able to get through it. Setting up expectations is important."

The persistency curve showed a positive result 270 days after the first refill, with 40% of patients who had been coached still on treatment compared with only 37% who had not been coached about injection training.

'Test patients had 8.4% more days of therapy," Taitel said. "From the beginning, we are keeping patients more adherent, and they are staying more adherent and not returning to the baseline."

"Based on the last sold prescription, Walgreens will estimate when [patients] are due for a refill, and three days before that, the pharmacy will make an automated refill call. Patients can automatically refill without having to enter the script number."

—Kristi Rudkin, Pharm D, *Senior Director, Product Development, Walgreens*

Refill reminders

The automated telephone reminders, also known as automated refill reminders (ARR), also helped move the adherence rate for patients who were on maintenance medications for chronic conditions.

"The goal of ARR was to help patients remember to refill their prescriptions," said Rudkin. "Based on the last sold prescription, Walgreens will estimate when they are due for a refill, and three days before that, the pharmacy will make an automated refill call. Patients can automatically refill without having to enter the script number, and it also serves as a reminder that they are due for a refill."

The persistence for the intervention group was 7.8 days longer than for the control group, which was followed for almost 1 year. The intervention group included 151,418 scripts; the control group had 327,975 scripts. The MPR was 67.3% in the intervention group and 64.9% in the control group.

"From our research and others, the refill reminders are an important piece to the adherence challenge," Taitel said. "It is one of the many interventions that need to occur to help patients be adherent. It is a reminder for those who need it the most." DT

Pharmacist-driven MTM could save ACOs a bundle

Continued from pg. 30

National organizations

The National Community Pharmacists Association (NCPA) highlights expertise of pharmacists as ACO partners, outlining natural pharmacist contributions such as optimization of appropriate medication use, reduction of medication-related problems, medication reconciliation after hospitalization, diabetes management, and improvement of health outcomes.

Kurt Proctor, BS Pharm, PhD, senior vice president, strategic initiatives, NCPA, emphasized pharmacists' close relationships with providers and patients. "In some cases, they can be utilized as physician extenders," Proctor said.

Although some ACOs are not at a point to integrate pharmacists yet, Proctor is confident that with time, ACOs will recognize what pharmacists can bring to the patient-care experience. Medication management, Proctor said, remains a critical issue for providers.

Although the ACO is an evolving model, Anne Burns, RPh, vice president of professional affairs for the American Pharmacists Association, is optimistic about the integration of pharmacists into ACOs.

"The ACO is responsible for the overall health of its members — a population-based management strategy — which encompasses measures for evaluating medication utilization," she said. "The whole focus now is on team-based care."

Burns, however, recognizes some of the challenges connected with that process of integration.

"Pharmacists have to get their foot in the door, highlight their efficiencies, and break down barriers by establishing agreements that clearly outline a pharmacist's role," Burns said. "The ACO provides that opportunity."

She noted that more opportunities exist in rural areas and in smaller communities with fewer providers, circumstances in which pharmacists can assume more responsibility based on the scope of their practice. DT

Mari Edlin *is a freelance writer based in Sonoma, Calif.*

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The new reality

Pharmacists report good-to-excellent compensation, yet stress levels high

Julia Talsma, Content Channel Director

Most pharmacists working in all pharmacy settings describe themselves as "satisfied" to "extremely satisfied" with their current positions, an attitude that can be attributed to low unemployment, good salaries and benefits, and annual raises.

This was some of the good news from data collected in *Drug Topics*' 2013 salary survey, which tabulated responses from more than 1,400 pharmacists, including 661 community pharmacists, 454 hospital pharmacists, and 323 pharmacists working in other settings. The survey was deployed the last week of March and results were tallied in mid-April.

Job satisfaction was highest among pharmacists who worked in hospitals (83%), independent retail pharmacies (84%), and other settings (85%) such as academia, ambulatory care clinics, community health centers, long-term-care settings, and government pharmacies. However, only 64% of pharmacists who worked for chain drugstores reported being "satisfied" to "extremely satisfied" with their current positions.

Similar to last year's findings, this year's results show the ever-increasing workloads for pharmacists leading to more on-the-job stress levels.

The good financial picture

In 2013, most pharmacists are working full-time (85.8%), a rate slightly higher than the 85% reported last year. Only 1.2% are temporary workers or unemployed, compared to 2% in 2012.

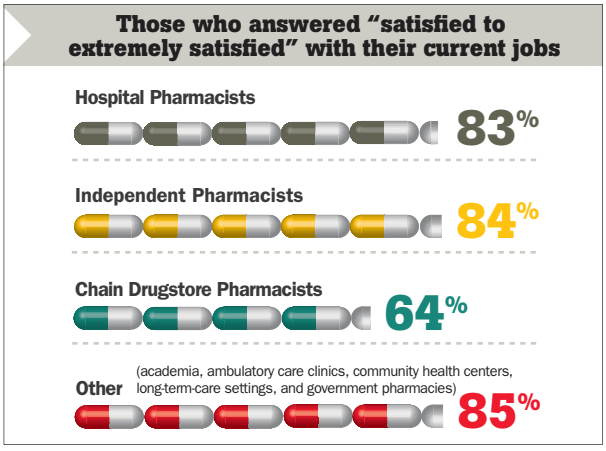
Approximately 90% of hospital pharmacists who responded to the survey reported they were working full-time, compared to 88% of pharmacists working in other settings, 85% working for chain drugstores, and 74% working for independent pharmacies.

About half of the pharmacists in all settings are paid hourly, and more than half of these healthcare professionals make between $51 and $60 per hour. Approximately one-third are compensated at an hourly rate of $61 or more.

In the hospital setting, about one-third reported their hourly rates at between $51 and $60 per hour, compared with one-third of chain pharmacists, one-quarter of independent pharmacists, and 19% of those in other settings.

Among those receiving $61 per hour and above were 20% of hospital pharmacists, 25% of chain pharmacists, 11% of independent pharmacists, and 6% of pharmacists in other settings.

For pharmacists who receive salaries, 23% reported annual base salaries at $101,000 to $115,000; 44% were earning $116,000 to $140,000; and 12% made $141,000 and above.



Source: 2013 Drug Topics *Annual Salary Survey*

The salaries reported in our survey were high among the hospital and chain pharmacists, with 24% and 20% reporting annual base salaries from $101,000 to $115,000, respectively.

In the $116,000 to $140,000 salary range, 44% of hospital pharmacists and 54% of chain pharmacists reported earnings, and in the $141,000 and above range, 15% of hospital pharmacists and 4% of chain pharmacists were receiving compensation at that level. Pharmacists in other settings also reported good salary ranges for these levels (25% at $101,000 to $115,000, 39% at $116,000 to $140,000, and 13% at $141,000 and above). Of the independents who reported annual base salaries, 21% earned $101,000 to $115,000, 32% earned $116,000 to $140,000, and 8% were at $141,000 and above.

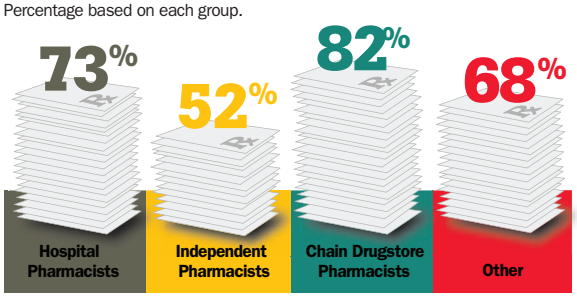
Other income and benefits

In regard to additional income earned in the retail pharmacy sector, last year was a good year for pharmacists. Approximately 72% of chain pharmacists and 43% of independent pharmacists reported receiving additional income in the form of commission, bonuses, and profit-sharing. Only 34% in other pharmacy settings and 29% in the hospital setting reported additional income received in 2012.

The benefits that employers offered pharmacists in 2012 were good, with the majority of pharmacists reporting packages that included paid holidays, paid vacation, and health insurance. The majority of pharmacists working in the hospital, chain drugstore, or other settings also were offered paid sick days, dental insurance, life insurance, and 401K plans. Independents also were offered good benefits, but at a lower

Increased workload – respondents who answered yes

Percentage based on each group.



Workloads have increased in all settings, but **73%** of **hospital** and **82%** of **chain pharmacists** report increased workloads, compared with **half** of **independents** and **68%** in **other** settings.

Source: 2013 Drug Topics *Annual Salary Survey*

rate, with only 37% offered dental insurance, 32% offered life insurance, and 47% offered 401K plans.

For those who responded to the *Drug Topics*' survey, in 2012 raises were given to 72% of chain pharmacists, 68% of hospital pharmacists, 60% of pharmacists in other settings, and 29% of independents. Most of last year's raises were between 1% and 3%. Chain pharmacists (70%), hospital pharmacists (65%), and pharmacists in other settings (55%) expect raises in 2013, compared to only 30% of independents.

The right fit

Pharmacists working in the hospital, independent pharmacy, and other settings reported high satisfaction with their current positions. However, a higher percentage of hospital and chain drugstore pharmacists reported increased stress levels resulting from increased work volume, inadequate staff support, increased paperwork, and a negative workplace environment.

Almost 90% of hospital pharmacists reported increased stress levels compared with 75% of chain drugstore pharmacists. According to John Benson, PharmD, pharmacy director of Promise Hospital of Salt Lake City, Utah, workloads and stress levels have increased because drug therapy and medical care in general have become more complex.

John Benson

"We continue to get more sophisticated in our understanding of disease and therapy of disease. There are an ever-increasing number of options to choose from to treat disease," said Benson, who works for a small acute-care facility that specializes in prolonged hospitalizations. "So the complexity of healthcare has added to the workload with much more to know, monitor, and follow up on. In addition, the number of patients that we care for continues to grow."

Because Medicare and Medicaid will continue to drive reimbursements for hospitals, Benson said, healthcare systems will have to continue to be able to function and perform with an ever-shrinking reimbursement.

Benson noted that he was extremely satisfied with his career choice. As a pharmacy student, Benson already knew that he wanted to pursue a career in hospital pharmacy, attracted by the level of engagement with patients, the ability to become more involved in drug-therapy decision-making, and the ability to collaborate with other healthcare professionals.

A personal connection

William MacDonald, BS Pharm, has been practicing pharmacy since 1970 and is a staff pharmacist for Rite Aid Pharmacy in Canton, Mich., a western suburb of Detroit. He too is extremely satisfied with his position; he has been working for the chain drugstore for seven years and says he knows about 80% of his customers by name.

MacDonald noted that pharmacists' salaries have dramatically increased during his career. "There was a time when I thought if I could be making $20,000 a year, that would be great," he said.

There are some challenges the chain pharmacists must contend with, such as a reduction in staff support due to declining prescriptions. "We used to do a high volume of scripts per week, but mail-order pharmacy has cut into that," he said.

MacDonald and his pharmacist partner now work with two pharmacy technicians who split 36 hours between them. "We don't have help after 4 o'clock, so the afternoon rush hour is the worst time," he said. "But I just don't let stress bother me a lot."

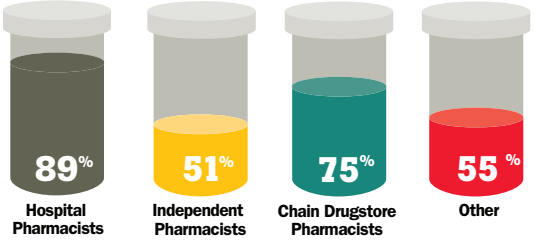
Successful multitasking

Peggy Knight, BS Pharm, a staff pharmacist for Fruth Pharmacy in Gallipolis, Ohio, said that work volume is increasing as pharmacists take on additional responsibilities, such as immunizations, monthly inventory control, and medication therapy management (MTM).

MTM does consume a lot of time, she said, because of the need to identify opportunities for intervention, engage with patients, and contact physicians.

Increased stress level – respondents who answered yes

Percentage based on each group.



Stress levels increased in all settings, but **89%** of **hospital** and **75%** of **chain pharmacists** report this, compared with about half of **independents** and **55%** in **other** settings.

Source: 2013 Drug Topics *Annual Salary Survey*


Peggy Knight

Vaccinations also have to be incorporated into the workflow. Sometimes if she is in the middle of an immunization procedure for a patient, she will continue to check a few prescriptions while the patient is filling out the paperwork. At times, she may have to ask patients to wait 15 minutes for a script to be filled because she is busy with an immunization.

In addition, inventory control has become an important task that now includes the participation of the pharmacist. After the occurrence of some pharmacy thefts, this yearly task has evolved into a monthly monitoring process in which she has to count the controlled substances as a step toward discouraging further thefts.

"It is difficult getting all the tasks done in a day while still taking care of patients the way you like to," said Knight, who has worked approximately eight years for Fruth Pharmacy, a regional chain with 26 stores. "I feel more supported than some of my friends who work for other places."

Because Fruth Pharmacy is locally run, Knight said, she can easily get in touch by phone with management if there is a problem. The organization's management is very responsive to what is happening at its drug stores.

Knight is the only pharmacist at her store and works a 12-hour shift with three pharmacy technicians.

Before coming to this position, she spent 15 years as a hospital pharmacist and sometimes had to cover the hospital in the middle of the night.

"If the hospital was not staffed 24/7 [with a pharmacist], you might have to get up at 2 a.m. to mix an IV or to make a calculation over the phone," she said. "I got tired of that."

Passion for pharmacy

Despite the challenges of community pharmacy, including some level of increased paperwork, the majority of independent pharmacists who responded to the salary survey reported steady work volumes, adequate staff support, and a positive workplace environment — all translating into a passion for pharmacy.

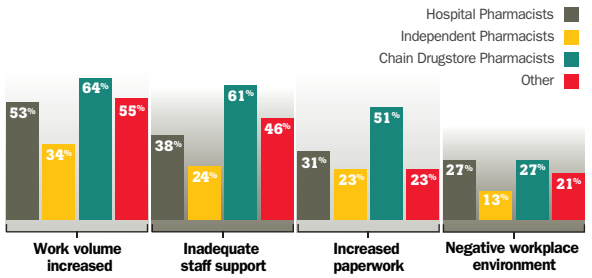
Clinical pharmacist David Pope, PharmD, is very optimistic about working for an independent pharmacy where, he said, he has the freedom to develop, create, and implement new clinical programs. With access to the CEO and owner of Barney's Pharmacy in Augusta, Ga., Pope doesn't have to cut through several layers of management to develop an idea and see it through.


David Pope

Another advantage to practice in an independent pharmacy, he said, is the ability to get to know his patients and their families. "You are a part of their lives. You don't just dispense their medicines," said Pope, who is also editor-in-chief of CreativePharmacist.com. "You are partnering with patients to improve their health."

Reasons for increased stress level

Percentage based on each group; respondents could select multiple responses



Greater work volume, inadequate staff support, and increased paperwork have affected more than half of the chain pharmacists. However, the negative workplace environment was reported by **27% of hospital** and **chain pharmacists,** compared with only **21% in other settings** and **13% of independents.**

Source: 2013 Drug Topics *Annual Salary Survey*

Specialties and visibility

Although work volumes at his independent pharmacy have continued to be steady over the last 10 years, independent pharmacies are able to compete with other drugstores because they have developed specific niches, whether compounding, clinical programs, diabetes management, or other specific patient services.

"Patients are willing to partner with me to improve their health through such things as classes, compounding, etc., even if they have to driver farther," Pope said.

Community pharmacies, whether they are with chains or independents, want their pharmacists to be more visible — not behind the counter, but out front.

"The more pharmacists are able to talk to patients out in front, the more they will see patient change," Pope said. "If you see patients come in with a high AIC or high blood pressure, and you are able to counsel them about their medicines and see clinical improvement, there is great job satisfaction and personal satisfaction that comes along with that."

A window of opportunity

Faced with changes in healthcare, such as restrictive pharmacy networks, shrinking margins, and pharmacy benefits management audits, independent pharmacists might be expected to have the highest level of stress in the industry. "In every shadow of concern, there is a window of opportunity. Independent pharmacists are so resilient," Pope said.

Pharmacy associations, such as the Georgia Pharmacy Association, the National Community Pharmacists Association, and the American Pharmacists Association, have been championing the power of community pharmacists. As the Affordable Care Act opens the door next year to more patients through health insurance exchanges and the expansion of Medicaid, community pharmacists will be there as patients come through the door.

"I think community pharmacy has room to grow in terms of volume," Pope said. "There are no reasons for prescriptions to be diverted elsewhere. They can be handled by the local pharmacy." DT

NEW DRUG REVIEW Diana M. Sobieraj, PharmD

First JAK inhibitor approved as second-line RA treatment

In November 2012, FDA approved tofacitinib (Xeljanz, Pfizer) 5-mg tablets for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have not shown an adequate response to methotrexate or who are intolerant to methotrexate. Tofacitinib, an oral nonbiologic disease-modifying antirheumatic drug (DMARD), can be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs. It is contraindicated for use with biologic DMARDs or with immunosuppressive agents, such as azathioprine and cyclosporine.

Tofacitinib is the first treatment for RA with a new class of drugs, Janus kinase (JAK) inhibitors. JAKs are enzymes that transmit signaling from cytokines and growth-factor receptors involved in hematopoiesis and immune function. Tofacitinib inhibits JAKs; this in turn blocks the signaling of several cytokines and interleukins involved in lymphocyte function.

Tofacitinib was approved with a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide for patients, a communication plan for healthcare providers and pharmacists, and periodic submissions of assessments of the REMS. The manufacturer will also be conducting postmarketing clinical trials to evaluate long-term safety of tofacitinib and to determine its efficacy and safety in children with polyarticular juvenile idiopathic arthritis.

Efficacy

FDA approved tofacitinib on the basis of two six-month dose-ranging studies and five confirmatory studies, which evaluated approximately 5,000 patients with RA. Based on two dose-finding studies, tofacitinib 5 mg and 10 mg twice daily were evaluated in five confirmatory trials.

Trials evaluated patients with moderate-to-severe RA in addition to one of the following characteristics: inadequate DMARD response, inadequate nonbiologic DMARD response, inadequate methotrexate response, or inadequate tumor necrosis factor inhibitor response. Tofacitinib was used either alone or in addition to a nonbiologic DMARD, often methotrexate. In the trial that evaluated patients with inadequate response to methotrexate, adalimumab was also used as a comparator.

Primary end points of the trials included the American College of Rheumatology 20 (ACR20), change in Health Assessment Questionnaire–Disability Index (HAQ-DI), and rates of Disease Activity Score DAS28–4 (ESR) less than 2.6.

In all the studies, patients treated with tofacitinib at either 5 mg or 10 mg twice daily had a higher ACR20 response rate than that of the placebo group, regardless of background DMARD therapy. In patients with inadequate response to methotrexate, addition of tofacitinib 5 mg or 10 mg twice daily increases achievement of a Disease Activity Score of DAS28–4 (ESR) less than 2.6 (1% in methotrexate plus placebo, 6% in methotrexate plus tofacitinib 5 mg, and 13% in methotrexate plus tofacitinib 10 mg groups).

Tofacitinib has a boxed warning of risk for serious infections, lymphoma, and other malignancies.

Physical function as measured by the HAQ-DI improved from baseline to 3 months in patients who inadequately responded to methotrexate when tofacitinib 5 mg or 10 mg twice daily was added to methotrexate. The mean differences in both tofacitinib groups were significant [-0.22 (-0.35 to -0.10) in patients taking tofacitinib 5 mg and -0.32 (-0.44 to -0.19) in tofacitinib 10-mg groups]. The manufacturer reports that similar findings were noted in the other trials as well.

Safety

Tofacitinib carries a boxed warning of risk for serious infections, lymphoma, and other malignancies. The most common adverse event observed in the clinical trial program was serious infection, although the difference in risk was not significant when tofacitinib was compared to placebo, using data at 3 months [risk difference 1.1 (-0.4 to 2.5) events per 100 patient years]. Longer-term data compared to placebo is not yet available.

The most common serious infections were pneumonia, cellulitis, herpes zoster, and urinary tract infections. Although no cases of tuberculosis (TB) were reported at three months, by 12 months six patients in the tofacitinib 10-mg group had TB. Patients must be tested for latent TB before initiation of treatment with tofacitinib, and if the test results are positive,

Continued on pg. 63

CPE CREDIT: 2.0

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EDUCATIONAL OBJECTIVES

Goal: To assist pharmacists in their understanding of the principles of pain management and the pharmacology of pain medications so that they can optimize pain control and best advise patients on the appropriate use of analgesics.

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

- **Discuss the general principles of analgesic therapy**
- **Discuss the role of non-opioid analgesics in the management of pain**
- **Discuss the strategies for anticipating and managing common adverse effects and drug-drug interactions of non-opioid analgesics**

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

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

ACPE #0009-9999-13-007-H01-P

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

Activity Fee: There is no fee for this activity.

Initial release date: 5/10/2013
Expiration date: 5/10/2015

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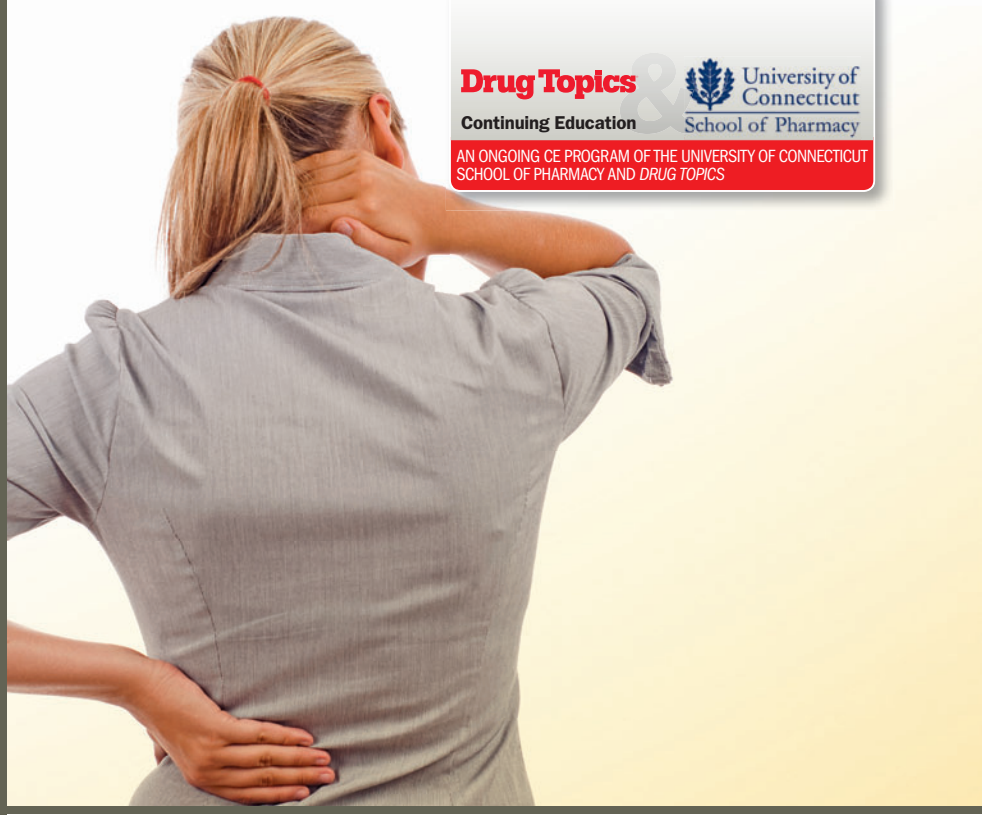

Drug Topics & University of Connecticut School of Pharmacy
Continuing Education
AN ONGOING CE PROGRAM OF THE UNIVERSITY OF CONNECTICUT SCHOOL OF PHARMACY AND *DRUG TOPICS*

Pharmacology and therapeutics of pain medications: Part 1

Trinh Pham, PharmD, BCOP
ASSOCIATE CLINICAL PROFESSOR, UNIVERSITY OF CONNECTICUT SCHOOL OF PHARMACY, STORRS, CONN.

Abstract

Pharmacologic treatment options for pain management can be broadly categorized as non-opioid and opioid analgesics. This second article in our pain management series focuses on non-opioid analgesics, which include acetaminophen, selective and non-selective nonsteroidal anti-inflammatory analgesics, and adjuvant analgesics. These agents are very effective in the management of a variety of acute and chronic pain conditions but are associated with a myriad of side effects. A comprehensive review of the mechanism action of these agents, side-effects profile, and recommendations for the prevention and management of these effects will be presented. The general principles of analgesic therapy will also be reviewed to guide pharmacists in the process of evaluating the appropriateness of a pain medication regimen and determining alternative analgesic options that will provide optimal pain relief for patients.

Faculty: Trinh Pham, PharmD, BCOP
Dr. Pham is associate clinical professor, University of Connecticut School of Pharmacy, Storrs, Conn.

Faculty Disclosure: Dr. Pham has no actual or potential conflict of interest associated with this article.

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IMAGE: THINKSTOCK / ISTOCKPHOTO

Pain Management Considerations in Medication Therapy Management CPE Series

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

This month, the professional development activity will cover pharmacology and therapeutics of pain medications, focusing on non-opioid analgesics. Next month, the activity will focus on opioid analgesics in the management of pain. In July, regulatory and ethical issues in pain management will be covered. The knowledge-based activities will conclude in August with management of common pain conditions by pharmacists, including osteoarthritis, low back pain, fibromyalgia, sprains, strains, contusions, and generalized headaches.

The Pain Management series will also be offering application-based activities for an additional 2 CPE credits. Online interactive case-based studies will be available with 1 hour of CPE credit, starting September and continuing in October 2013.

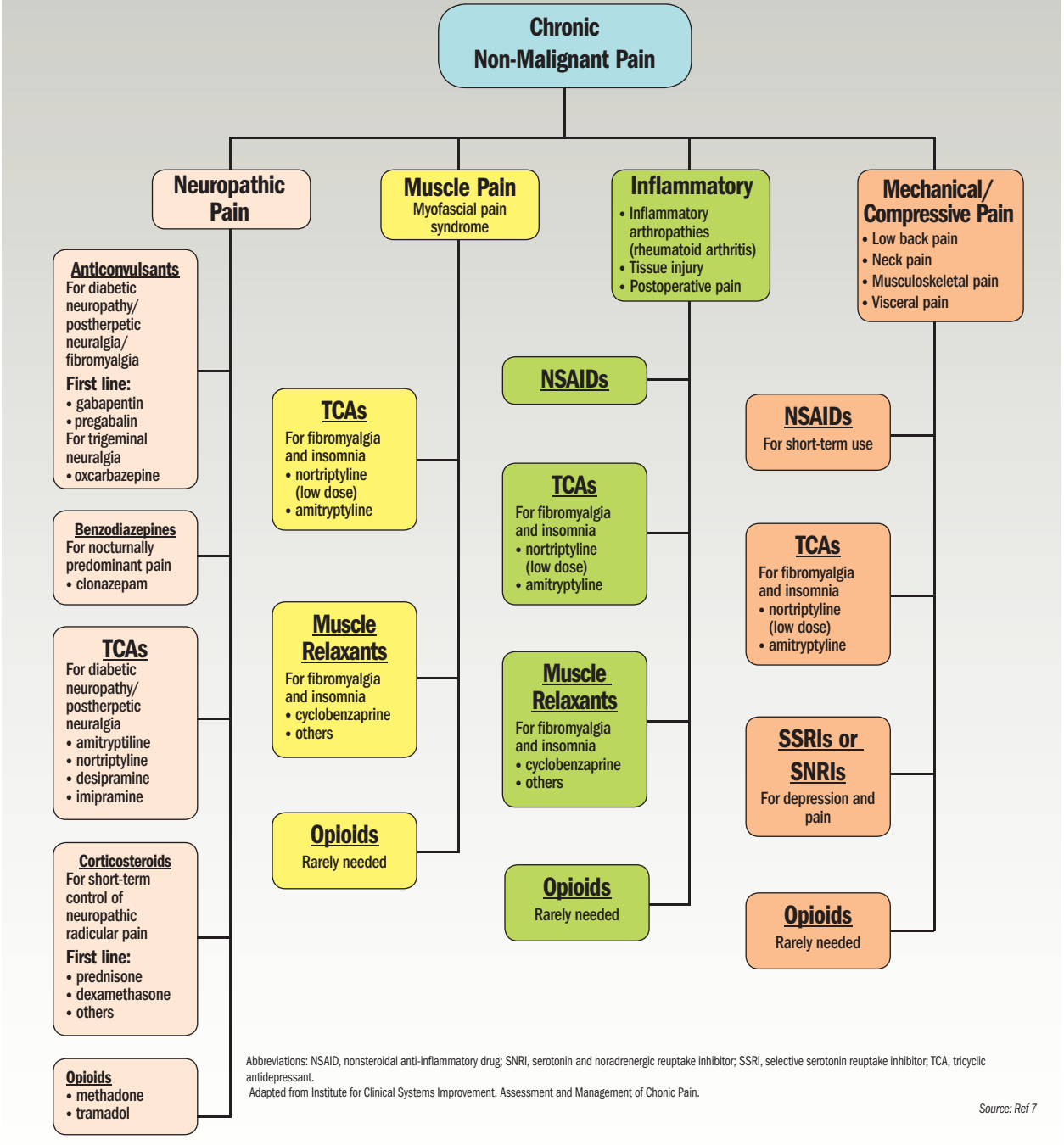
Pain is ubiquitous. It affects everyone at some point in their lifetime and all populations are at risk, regardless of age, gender, ethnicity, income, or geographic location. In the U.S., approximately 100 million Americans suffer from chronic pain conditions, more than the number affected with diabetes, coronary heart disease, and cancer combined.[1,2] Worldwide, the prevalence rate of chronic pain is 20% and for those age 65 years and older, the prevalence increases to 50%.[3] The four most common types of acute pain people experience, as indicated by The National Institutes of Health Statistics survey, are low back pain (29%), severe headache or migraine pain (17%), neck pain (15%), and facial ache or pain (5%).[2] Some other examples of common acute pain in which patients require analgesia include perioperative pain, posttraumatic pain, obstetric pain, and procedural pain. Among many types of chronic pain, those with a high prevalence rate include arthritis (rheumatoid and osteoarthritis), low back pain, headaches, and neuropathic pain.[4] As discussed in the first article of this continuing education series in the April issue of *Drug Topics*, "Pain management for pharmacists: Concepts and definitions," pain significantly decreases quality of life, increases healthcare costs, and results in lost productivity in the workforce.[5] On the other hand, when pain is treated appropriately and effectively, patients experience positive outcomes such as improvement in fatigue, sleep, and depression. Furthermore, patients are able to work effectively, have improved quality of life, and may possibly have a reduction in mortality risk.[3] Successful management of pain relies on the accurate diagnosis of the pain pathophysiology and the underlying mechanisms of pain because this influences the choice of analgesic. Once the correct assessment and diagnosis of pain has been made, pharmacists have the opportunity to be an integral member of the healthcare team in its management through their knowledge of analgesic drug pharmacology and making recommendations for analgesic therapeutic options based on the pain diagnosis and a patient's comorbid conditions. Furthermore, pharmacists have the capability to assess the risks and benefits of specific analgesic agents based on their side-effects profile, potential drug-drug interactions, and drug-disease interactions. In addition, pharmacists can provide services such as monitoring patients for response to therapy and/or side effects.

Principles of pain management

Pain is considered to be the "fifth vital sign." All individuals should be routinely asked about pain at each outpatient visit, during every shift for hospitalized patients, and more frequently for patients with active and unrelieved pain. The purpose of asking about or screening for pain is to address pain as part of "routine care" for all patients. Once it is recognized that a person is experiencing pain from the screening process, the next step is to assess the pain based on a patient interview, a comprehensive evaluation of the pain that includes performing a medical history, physical exam, and diagnostic studies, as indicated, to arrive at a diagnosis for the patient. Pharmacists are involved in this process when a patient presents to the pharmacy and the pharmacist is the first healthcare provider that the patient approaches. The pharmacist should know how to perform a pain assessment interview to determine if the patient should be referred to the emergency department (ED), their primary care provider, or if the patient may be treated with over-the-counter (OTC) medications (see the pain management CE article in the April *Drug Topics* issue).[5]

Once the pain has been diagnosed, the next step is to treat its underlying source. It is important to note that there is no reason to withhold pain management until the pain work-up is complete and the source of pain is identified. Unmanaged or undertreated acute pain can result in physiologic consequences (e.g., insulin resistance, excessive stress response, impaired immune function, delay in normal gastrointestinal (GI) function, venous thromboembolism), lead to prolonged chronic pain states, result in possible decreased responsiveness to pain treatment, and may cause negative psychologic effects and emotional distress for the patient and family members.[6] It should also be noted that patients may present with more than one type of pain and that pain types are not mutually exclusive. This has significant implications in the management of pain because multimodal analgesic therapy may be necessary. This approach involves examples such as using

FIGURE 1 **RECOMMENDATIONS FOR PAIN MANAGEMENT**



Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin and noradrenergic reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
Adapted from Institute for Clinical Systems Improvement. Assessment and Management of Chonic Pain.

Source: Ref 7

drugs from two different classes with different mechanisms of action, combining pharmacologic with non-pharmacologic therapy, or administration of a local anesthetic and epidural opioid with systemic analgesics.[4]

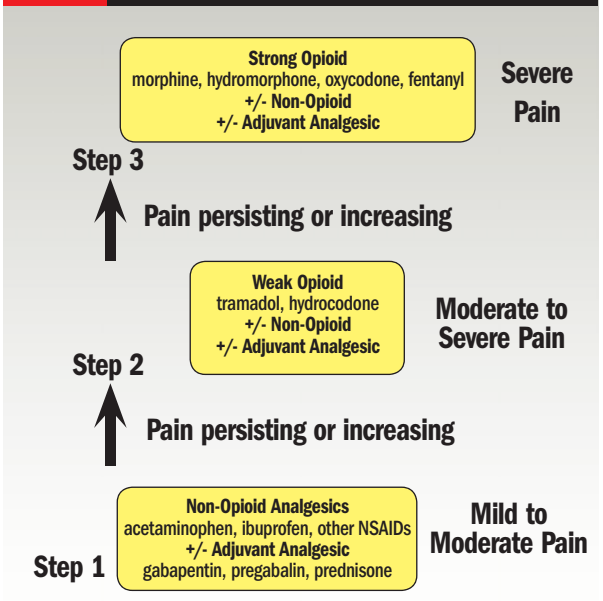
In general, treatment options for pain broadly include non-pharmacologic therapy (i.e., exercise, massage, physical rehabilitation, behavioral management, interventional pain management), pharmacologic therapy (i.e.,non-opioids, opioids, adjuvant analgesics), or a combination of these treatment choices. The treatment plan for pain management should be based on the specific pain diagnosis and the classification of the pain (**Figure 1**).[7] An ideal, optimal analgesic regimen is supported by evidence-based guidelines, takes into account the patient's comorbid conditions, is simple to administer, has minimal side effects, favors patient compliance, is not costly, and most importantly, provides maximal pain relief.

The goal of pain management is for patients to take the analgesics for the short-

est duration of time at the lowest effective dose that provides effective pain relief and minimal side effects. Acute pain is usually treated for a brief period of time with short-acting analgesics and the frequency of administration may be prescribed on an as-needed basis. In contrast, superior pain relief is achieved with around-the-clock (ATC) dosing for chronic, continuous pain. The ATC analgesic agent should be long-acting, if available, to minimize the frequency of administration. Additionally, for chronic pain, a short-acting, rapid-onset analgesic should be available on an as-needed basis to manage breakthrough or intermittent pain. At the start of the analgesic initiation and with each dose adjustment, patients should be monitored for a response to the analgesic therapy and any manifestations of adverse effects. The analgesic agent should be initiated at the lower dosing range and the dose may be titrated up until pain relief is achieved or side effects occur. If intolerable side effects occur, these may be managed by changing the dose or route of administration, trying a different drug within the same class, and/or adding a drug that counteracts the side effects (e.g., proton pump inhibitor (PPI) for gastric mucosa irritation, or a bowel regimen for constipation). It should be noted that there is a ceiling effect with non-opioid analgesics in which there is no additional pain relief beyond a specific maximum dose; however, there is an increase in the likelihood of side effects. The use of combination analgesics from different classes minimizes side effects by allowing the use of lower doses of each individual analgesic in addition to facilitating pain relief in the patient who is not responding to single-agent therapy.

The preferred route of administration of an analgesic depends on convenience, patient preference, GI function, and the desired time interval for drug onset of effect. For outpatient pain management, the oral route is preferred because it is the most convenient, flexible, and associated with stable drug concentrations if taken on a regular basis. Alternatives for the patient who is experiencing nausea, vomiting, or difficulty swallowing include rectal, subcutaneous, and sublingual routes of administration. Some topical analgesics provide local pain relief and have the advantage of minimizing systemic exposure when side effects are a concern. These agents can be offered for patients who have pain in a discrete, localized area. Transdermal administration provides continuous drug delivery and is a good option for patients who have difficulty swallowing or being compliant with their oral ATC regimen. In the inpatient setting, intravenous bolus administration offers rapid onset of effect for the patient who has severe, excruciating pain. Continuous intravenous administration allows achievement of stable drug concentrations along with the capability for rapid dose titration to accomplish pain relief in a short time.

FIGURE 2 **WHO ANALGESIC LADDER**



Source: Ref 8

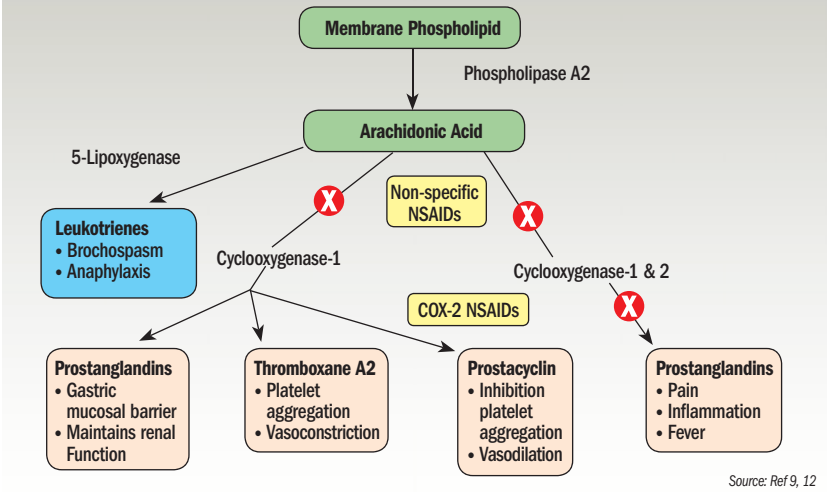
The World Health Organization (WHO) has introduced the analgesic ladder as a treatment guide for pain management. Although developed for cancer pain, the recommendations are valid in treating patients with acute or chronic pain requiring analgesics. The WHO analgesic ladder is depicted in **Figure 2**.[8] In summary, the WHO organization recommends that an analgesic should be provided only after a thorough clinical examination and pain assessment has been performed. The first step in the WHO analgesic ladder involves the use of a non-opioid analgesic if the pain is mild to moderate. Start with the lowest possible effective analgesic dose against the patient's pain and gradually increase the dose until the patient is comfortable. The "right" dose is one that will allow adequate pain relief with minimal side effects. Since every patient responds differently to pain medications, there are no standard doses. If pain relief is not achieved at the maximum recommended dose of a non-opioid, then an opioid may be added or substituted. When performing patient counseling, the pharmacist should emphasize the need to take the medication as scheduled to achieve effective pain relief. To help the patient and his or her caretaker, the patient's regimen should be written in full and include names of drugs, reason for use, the dose (e.g., number of tablets or mL), and the scheduled time interval in which to take the medications throughout the day.[8]

Pharmacologic management of pain

Analgesic medications are divided into the two categories of opioids and non-opioids. This article in our pain management series discusses non-opioid analgesics, and next month's article will address the opioid analgesics. The non-opioid analgesics are a diverse group of drugs that are further classified as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and adjuvant agents, which includes medications that have other primary indications but are also useful as analgesics or adjunct analgesics. The non-opioids are effective in controlling pain for a variety of conditions including osteoarthritis, rheumatoid arthritis, tension-type headaches, neuropathic pain, and mild-to-moderate nociceptive acute pain.

Acetaminophen. Acetaminophen is a derivative of p-aminophenol that is believed to inhibit prostaglandin synthesis within the

FIGURE 3 **PHOSPHOLIPID PATHWAY**



Source: Ref 9, 12

central nervous system and has little effect on peripheral prostaglandin synthesis; thus, it is considered to be a central-acting agent that does not provide peripheral anti-inflammatory activity.[9] It is among the most commonly used analgesics in the world because of its favorable safety and drug-interaction profile. Acetaminophen is available in oral solid and liquid formulations, as well as rectal and intravenous dosage formulations. Unlike NSAIDs, acetaminophen does not cause GI mucosa erosion, impair platelet aggregation, or impair uric acid excretion.[9] It is well tolerated with minimal side effects and has a low incidence of cross-reactivity in patients who experience hypersensitivity to aspirin or other nonselective NSAIDs. Hepatotoxicity may occur if the daily dose of acetaminophen exceeds 4 g for more than a few consecutive days. For patients who are poorly nourished, suspected of chronic alcoholism, being treated with other hepatotoxic medications, or have existing hepatic dysfunction, the maximum daily dose is less and may be as low as 2 g daily.[4] To reduce the risk of hepatotoxicity, liver failure, and death related to acetaminophen overdose, FDA asked drug manufacturers to limit the strength of acetaminophen in prescription drug products, which are predominantly combinations of acetaminophen and opioids, to 325 mg per tablet, capsule, or other dosage unit.[10]

Nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are important analgesic and anti-inflammatory options for millions of patients and are amongst the most widely used class of medications through OTC purchases and written prescriptions. In an average week, approximately 43 million adults take acetaminophen, 41 million take aspirin, 39 million take ibuprofen, and 11 million take naproxen in the United States.[11] NSAIDs are effective in relieving mild-to-moderate pain, inflammation, and fever, and are commonly used for the short- and long-term management of conditions such as musculoskeletal pain, osteoarthritis, and rheumatoid arthritis. The primary mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX), resulting in blockade of synthesis of prostaglandins implicated in pain, fever, and inflammation (**Figure 3**).[9,12] There are at least two isoforms of COX, COX-1 and COX-2; COX-1 is constitutively expressed in most normal tissues and COX-2 is not normally present but is largely induced by noxious stimuli that cause pain and inflammation.[12] In addition to prostaglandins involved with pain and inflammation, COX-1 also produces prostaglandins with beneficial effects in the GI tract (i.e., stimulate secretion of mucous and bicarbonate, increase mucosal blood flow, promote epithelial proliferation), kidneys (i.e., increase renal blood flow, glomerular filtration rate, vasodilation), and platelets (aggregation). Nonselective NSAIDs inhibit COX-1 and COX-2; conversely, selective NSAIDs preferentially inhibit COX-2. Although there are many classes of NSAIDs, they all have similar anti-inflammatory and nociceptive pathways with varying pharmacokinetic and pharmacodynamic properties (**Table 1**).[4,13]

NSAIDs offer significant benefits in pain management, but unfortunately they are also associated with considerable adverse events including GI, cardiovascular, renal, hematologic, and less commonly, hepatic and immunologic dysfunction. **Table 2** lists the risks associated with NSAID therapy and strategies to minimize complications in patients taking these agents for analgesia.[4,9,14-17] It is important to note that not all users of NSAIDs have equal risk of developing adverse events and individual NSAIDs have different toxicity profiles. Thus, being able to identify patients who are at risk for developing toxicities and knowledgeable in the differences in toxicity profile of individual NSAIDs allows clinicians flexibility when formulating optimal analgesic regimens for their patients.

Adverse events with NSAIDs can occur at any time while taking the medication. Generally, the incidence increases with increased duration and dosage. Of all the reported adverse events, GI toxicity is the most common. Both upper and lower GI adverse effects can occur in patients receiving NSAIDs, although the majority of the complications are in the upper GI. The manifestations of upper GI effects include dyspepsia (upset stomach), nausea, abdominal pain, GI bleeding, gastric and duodenal mucosal erosions and ulcers. The mechanism of injury is due to inhibition of prostaglandins that stimulate the production and secretion of mucous and bicarbonate, increase mucosal blood flow, and promote epithelial proliferation that protects the stomach and small intestine.[12] The factors that place a patient at increased risk for developing NSAID-induced GI complications are listed in **Table 3**.[17] The risk of developing GI complications is greatest within the first 3 months of NSAID therapy.[18] It should be noted, however, that GI adverse effects can occur anytime throughout the course of therapy and patients should be monitored closely for these effects. Dyspepsia has been estimated to occur in 15% to 60% of patients but has little relationship to the development of erosions or ulcerations. The addition of a PPI, histamine-2 receptor

TABLE 1

ACETAMINOPHEN AND EXAMPLES OF NSAIDS

	Onset of Effect (hrs)	Duration of Effect (hrs) and Dosing Interval	Comments
Paraaminophenols			
Acetaminophen (Tylenol)		q 4-6 h	Safe alternative for patients at risk for GI complications, bleeding disorders, aspirin insensitive, or pregnant patients. Available in IV formulation
Salicylates			
Aspirin (acetylated) (Bayer, Ecotrin)	0.5	4-6; QID	
Choline magnesium tris-alicylate (non-acetylated) (Trilisate)	2	4-6; BID – TID	Minimal inhibition of platelet aggregation, option for patients at increased risk of bleeding
Salsalate (Amigesic, Argesic-SA, Marthritic)	NA	NA; BID	
Diflunisal (Dolobid[a])	Analgesic: 1	Analgesic: 8-12; Anti-inflammatory: <12; BID	Less GI irritation and platelet effects than aspirin
Propionic acid derivatives			
Ibuprofen (Advil, Motrin)	Analgesic: 0.5-1 Anti-inflammatory: <7 days	4-6; QID to q 4 h	Fewer side effects than other nonselective NSAIDs
Naproxen (Aleve, Anaprox, Naprosyn)	Analgesic: 1 Anti-inflammatory: 2 weeks	Analgesic: <7 Anti-inflammatory: <12 BID to QID	Available as delayed-release[b] Preferred nonselective NSAID for patients with cardiovascular risks
Ketoprofen (Actron, Orudis, Oruvail)	0.5	6; TID to QID	Extended-release available[b]
Flurbiprofen (Ansaid)	1-2	Variable; BID, TID, or QID	
Fenoprofen (Nalfon)	72	4-6; QID	
Oxaprozin (Daypro)	0.5-4	Variable; QD	55 hours half-life
Indoleacetic acids			
Indomethacin (Indocin)	0.5	4-6; BID, TID, QID	Limited use due to side effects[c]
Benzothiazine derivatives (oxicams)			
Piroxicam (Feldene)	1	Variable; q 24 h	
Meloxicam (Mobic)	NA	q 24 h	
Pyrrole-acetic acid derivatives			
Diclofenac (Voltaren, Cataflam, Cambia)	1-4.5	12-24; BID, TID, QID	Lower risk of GI side effects[d] Greater potential for hepatic dysfunction. Available for topical application as patch, gel, and solution
Ketorolac (Toradol)	NA	QID to q 4 h	Therapy should not exceed 5 days
COX-2 selective			
Celecoxib (Celebrex)	0.75 to several months	4-8; BID or QD	Does not inhibit platelet aggregation, alternative for patients with aspirin sensitivity
Arylalkanoic acid			
Tolmetin (Tolectin)	Analgesic: 1-2 Anti-inflammatory: several days to 1 week	Variable; TID	
Sulindac (Clinoril)	1	12-24; BID	Greater potential for hepatic dysfunction
Others			
Meclofenamate (Meclomen)	Less than 1	4-6; QID to q 4 h	Also indicated for treatment of primary dysmenorrhea and idiopathic heavy menstrual blood loss
Mefenamic acid (Ponstel)	2-4	Less than 6; QID	For treatment of primary dysmenorrhea
Nabumetone (Relafen)	72	Variable; BID	

Abbreviations: BID, twice daily; COX, cyclooxygenase; GI, gastrointestinal; IV, intravenous; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; q, every; QD, every day; QID, 4 times daily; TID, 3 times daily.
[a]no long available in the U.S.; [b]not recommended for initial treatment of acute pain; [c]exacerbation of Parkinson's, seizures, psychiatric disorders; corneal deposits, retinal disturbances; [d]acute hemolytic anemia, rash, avoid use in patients with porphyria

Source: Ref 4,13

antagonist (H2-antagonist), or misoprostol may ameliorate GI complications. The H2-antagonists are effective in preventing ulcers in patients taking NSAIDs but are less effective in healing gastroduodenal ulcers compared to a PPI, when continuing or discontinuing an NSAID.[13] Thus, a PPI is recommended over an H2-antagonist to promote treatment and healing of a gastroduodenal ulcer. Furthermore, after initial ulcer healing, a PPI is recommended over an H2-antagonist in NSAID therapy continuation to prevent ulcer recurrence in patients now considered to be at high risk for NSAID-induced GI complications.[13] The addition of a PPI may also be beneficial for patients with a history of NSAID-induced GI bleeding who are receiving a selective NSAID such as celecoxib.[13] Table 3 provides guidelines for appropriate use of GI protectants based on the patient's level of risk for developing GI complications.[13,19]

There are three fixed-dose combinations of a NSAID and GI protectant available by prescription and they include: ibuprofen 800 mg with famotidine 26.6 mg, enteric-coated naproxen 375 mg or 500 mg with immediate-release esomeprazole 20 mg, and diclofenac sodium 50 or 75 mg with misoprostol 200 mcg. The FDA-approved indications for these agents are for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis, in addition to ankylosing spondylitis for the naproxen combination, in patients at risk of developing NSAID-induced GI ulcers and their complications.[20-22] The naproxen combination product is not recommended for the initial treatment of acute pain where rapid onset is desired because the absorption of the naproxen is delayed compared to absorption from other naproxen-containing products.[21] The combination product may be useful in decreasing the pill burden and improving compliance for patients, however, they may be more expensive than prescriptions of individual NSAIDs and GI protectants.

Adverse events with NSAIDs can occur at any time while taking the medication.

Prostaglandins have an important role in renal perfusion and diminished levels of these prostanoids result in sodium retention, peripheral edema, hypertension, and renal dysfunction. This effect occurs with both nonselective NSAIDs and selective COX-2 inhibitors. On the other hand, selective COX-2 inhibitors are more prothrombotic compared to nonselective NSAIDs and increase the risk of cardiovascular (CV) events such as acute myocardial infarction (MI). This is based on the hypothesis that selective COX-2 inhibitors reduces prostacyclin production without changes in thromboxane and the alteration imbalance between these prostanoids has been proposed to lead to a more thrombogenic state (Figure 3).[9,12,23] Numerous clinical trials showed increased CV risks with selective COX-2 inhibitors. The VIGOR (Vioxx Gastrointestinal Outcomes Research) trial showed a 5-fold increased risk of MI with rofecoxib compared to naproxen, the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial showed a 2-fold increase in MI in patients treated with rofecoxib compared to placebo, and the APC (Adenoma Prevention with Celecoxib) trial showed an increased CV risk compared to placebo.[24-26] It is controversial if nonselective analgesics have less potential for increasing CV risk factors. The ADAPT trial (Alzheimer's Disease Anti-Inflammatory Prevention Trial) comparing celecoxib versus naproxen and the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) trial comparing etoricoxib versus diclofenac showed worrisome trends toward increased CV events with naproxen and the rate of CV risk was similar with diclofenac.[27,28] The decision to treat patients with a nonselective NSAID or a selective COX-2 inhibitor should be individually evaluated regarding their risk-benefit profile together with individual patient risk factors. The information provided in **Table 4** may help in deciding which agent has the least GI toxic effects and which agent has the least COX-2 inhibitory effect if CV risk is a factor for consideration.[12,29] **Table 5** is an algorithm that aids in decision making when both CV and GI toxicity have to be considered in a patient.[30]

Topical NSAIDs. Diclofenac is the only FDA-approved topical NSAID in the United States. It is available in three different formulations: patch, gel, and solution. Topical formulations provide localized delivery of medications with the advantage of reduced systemic exposure of the drugs, thus leading to decreased systemic side effects. The FDA-approved indications for diclofenac include osteoarthritis of the knee for the topical solution and osteoarthritis of the knee and hand for the gel formulation. Published clinical trials indicate that topical diclofenac is efficacious in reducing pain symptoms for arthritis in superficial joints such as the knee or hand.[31-34] Clinicians have used this agent on the feet, shoulders, or elbows although there is no supporting evidence for this practice. Deeper joints such as the hip and larger areas such as the spine are not suitable for topical diclofenac.[35] The diclofenac patch is FDA-approved for patients with sprains, strains, and contusions, and has been used for osteoarthritis of the knee in clinical practice.[36,37] The most common adverse effects associated with topical diclofenac are mild local skin reactions, and dry skin at the applications site (18%) is the most commonly reported side effect.[38]

Common Drug–Drug Interactions

Acetaminophen/NSAIDs and ethanol. Chronic alcohol abuse is a risk factor for drug interaction with acetaminophen because alcoholism leads to reduced amounts of a protein transporter that carries glutathione to the mitochondria of hepatocytes. Glutathione is responsible for inactivating N-acetyl-para-benzoquino-

Pause&Ponder

OTC NSAIDs are readily available to the public and have significant side effects. Will you change the screening questions you will use when advising patients about the use of these agents? If so, what types of questions will you ask, and why?

TABLE **2**

ADVERSE EFFECTS OF NSAIDS

Adverse effect	Preventive measure	Comments
Gastrointestinal		
Dyspepsia, abdominal pain or discomfort	Enteric-coated or buffered NSAIDs may decrease GI upset but does not decrease the risk for mucosal damage. Take with food. Co-administer with H_2RA.	More than 50% of patients improve without treatment.
GI ulcers or bleeding	The decision of whether or not to use an NSAID is dependent on level of risk and risk factors for developing GI complications. See Table 3. If possible, avoid use of NSAIDs in persons with history of NSAID-induced GI complications. If NSAIDs are necessary: • Combine with PPI, H_2RA, or misoprostol OR • Use COX-2 selective NSAID	Misoprostol prevents ulcer-related bleeding complications but is not well tolerated because of GI side effects and poor compliance due to frequency of administration. Category X in pregnancy. Use NSAIDs with less GI problems (ibuprofen, diflunisal, diclofenac, selective COX-2 inhibitors).
Cardiovascular		
Myocardial infarction (MI), stroke, hypertension (HTN)	Avoid COX-2 inhibitors for patients with MI or stroke risks. Use lowest effective dosage.	Mean BP increase is 5 mmHg. Avoid in patients with CHF, use with caution in patients with HTN. Naproxen is preferred alternative for patients with history of MI.
Renal		
Renal insufficiency or renal failure	Use lowest dose possible. Avoid indomethacin. Monitor renal function.	Usually resolves with discontinuation. Patients at highest risk: elderly, volume depleted, preexisiting renal disease, comorbidities[a], diuretics, ACE inhibitors, renal toxic drugs.
Hematologic		
Bleeding	Avoid NSAIDs if possible in persons with platelet defects, thrombocytopenia, coagulopathy, on anticoagulation.	Use NSAIDs with minimal or no bleeding risk in high-risk patients or acetaminophen if possible. Stop aspirin 1 week prior to surgery, most other NSAIDs 2-3 days prior.
Hypersensitivity		
Respiratory Urticaria-angioedema	Patients who are sensitive to aspirin may be cross-sensitive to other NSAIDs.	Use NSAIDs with caution in persons with asthma, rhinitis, nasal polyps, or wheals, urticaria, hypotension.
Hepatic		
Liver dysfunction Rare hepatic necrosis	Patients at increased risk: Alcoholism, history of liver disease	Monitor liver function enzymes at baseline and periodically.
Central nervous system (CNS)		
Attention or memory deficits Headache, tinnitus	Elderly patients and concomitant use of medications affecting CNS function increases risk.	If side effects occur: lower dose, switch to another NSAID or drug class, discontinue if side effects persist.
Prolonged pregnancy or labor, fetal effects from antiplatelet activity	Avoid towards end of pregnancy (6-8 weeks before term). Use acetaminophen.	

Abbreviations: ACE, angiotensin converting-enzyme inhibitors; BP, blood pressure; CHF, congestive heart failure; COX, cyclooxygenase; H_2RA, histamine-2 receptor antagonist; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors.

[a]congestive heart failure, diabetes, cirrhosis, multiple myeloma

Source: Ref 4, 9, 14-17

TABLE 3

RISK FACTORS ASSOCIATED WITH RISK OF DEVELOPING GI COMPLICATIONS FROM NSAIDS

Advanced age
Threshold is not exact, but patients >60 years of age are considered at moderate to high risk

History of peptic ulcer disease
Helicobacter pylori infection is additive risk factor in patients with history of peptic ulcer disease

History of previous NSAID-related GI complications

Concomitant use of NSAID with:
Other NSAIDs (both OTC and prescription NSAID use)
Low-dose aspirin (75-325 mg daily)
Corticosteroid
Anticoagulants

Risk Level for GI Complications from NSAIDs and Protective Strategies Based on Risk Level	
Low	**None of the above risk factors present.** Nonselective NSAID monotherapy with the least ulcerogenic potential agent (ibuprofen, diclofenac) or COX-2 selective agent (celecoxib) at lowest effective dose for the shortest duration.
Moderate	**Advanced age or 1 to 2 of the above risk factors present, excluding previous history of NSAID-related GI complications** Nonselective NSAID monotherapy **with** PPI, H_2RA, or misoprostol, **OR** COX-2 selective agent (celecoxib) at lowest effective dose for shortest duration. Treat **known** *H. pylori* infection.
High	**Previous history of NSAID-related GI complications or >2 of above risk factors present** COX-2 selective agent (celecoxib) at lowest effective dose for shortest duration, **OR** nonselective NSAID monotherapy with PPI or misoprostol, (H_2RA inadequate in high-risk patients) and *H. pylori* eradication.

Abbreviations: COX, cyclooxygenase; GI, gastrointestinal; H_2RA, histamine-2 receptor antagonist; NSAID, nonsteroidal anti-inflammatory drugs; OTC, over-the-counter; PPI, proton pump inhibitor.

Source: Ref 13, 17, 19

TABLE 4

GI TOXICITY AND IN VITRO SELECTIVITY FOR CYCLOOXYGENASE (COX) ENZYMES OF VARIOUS NSAIDS

	5- to 50-fold COX-2 selectivity[a]	
↑ **Increasing COX-2 selectivity**	Etodolac[a] Meloxicam[a] Celecoxib Diclofenac[a] Sulindac[a]	
	Less than 5-fold COX-2 selectivity	**Risk of GI toxicity of NSAIDs**
↑ **Increasing COX-1 selectivity**	Ketoralac Flurbiprofen Ketoprofen Indomethacin Aspirin Naproxen Tolmetin Ibuprofen Fenoprofen	Ketorolac (highest) Piroxicam Ketoprofen Indomethacin Naproxen Meloxicam Diclofenac Ibuprofen Celecoxib (lowest)

Abbreviations: GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a]Note: although considered to be nonselective NSAIDs, these agents possess significant COX-2 activity, similar to the selective NSAID, celecoxib, *in vitro*.

Source: Ref 12, 29

neimine (NAPQI), the highly reactive hepatotoxic metabolite of acetaminophen. Thus, a deficiency of glutathione is associated with increased risk for hepatotoxicity.[39] The labels on acetaminophen-containing products warn of an increased risk of hepatotoxicity with consumption of more than three alcoholic drinks per day. Patients are counseled to abstain from heavy alcohol consumption if acetaminophen is a necessary component of their drug therapy or to not exceed 2 g/day of acetaminophen if they cannot abstain from drinking. Alcohol and NSAIDs each increases a patient's risk for developing gastric and duodenal ulcers and when both are consumed concomitantly, there is an additive increase in the risk of significant bleeding, ulceration, and GI perforation.[39] In 2008, the FDA issued a warning that the product label for OTC NSAIDs contains a new "stomach bleeding warning," which highlights the potential for stomach bleeding when taken with moderate amounts of alcohol in addition to other risk factors.[40] Patients who consume more than three alcoholic drinks per day and are on chronic NSAID therapy should be advised against drinking or alternative non-NSAID analgesics should be considered since the risk of GI bleeding and ulcer is high.

NSAIDs and antihypertensive drugs. NSAIDs may attenuate the blood-pressure-lowering effect of antihypertensive medications such as beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics. The effect usually occurs after more than five days of NSAID therapy, thus it is a concern for patients who are receiving chronic NSAIDs.[39] Patients who are taking concurrent antihypertensives and NSAIDs must have vigilant monitoring of their blood pressure and appropriate actions taken as needed to maintain goal blood pressure.

Acetaminophen/NSAIDs and anticoagulants. NSAIDs have direct antiplatelet effects and when combined with an anticoagulant such as warfarin there is a significant increase in the international normalized ratio (INR) and the risk of GI bleeding.[16,39] Acetaminophen may also increase the INR in warfarin-treated patients. This effect occurs when patients were taking 4 g/day of acetaminophen and has also been reported for doses as low as 2 g/day. If it is necessary for a patient to use either an acetaminophen or

NSAID concurrently with warfarin, INR monitoring should be performed as indicated and the anticoagulant dose should be adjusted to the appropriate therapeutic dose. Furthermore, a GI protectant should be initiated to prevent the risk of bleeding complications.[16] If it is not possible to maintain the INR within therapeutic range, alternative analgesics, such as opioids, that do not have drug-drug interactions with warfarin should be considered.

NSAIDs and cardioprotective doses of aspirin (81-325 mg a day). Because of its antiplatelet activity, low-dose aspirin is indicated for the prevention of second MI, unstable angina pectoris, thrombotic events after coronary artery bypass procedures, and CV events in high-risk individuals. A concern of concomitant use of an NSAID with a cardioprotective dose of aspirin is reduced antiplatelet activity of aspirin resulting in diminished cardioprotective effect. The data are conflicting for different NSAIDs and more data are needed to answer this question.[39] However, if a patient is taking ibuprofen, it is recommended that ibuprofen should be taken more than 4 hours before or more than 2 hours after aspirin to maintain the cardioprotective effect of aspirin.[13] There is increased risk of GI bleeding when low-dose aspirin is used in conjunction with NSAIDs, therefore, the addition of a GI protectant is warranted in these patients.[13]

Adjuvant analgesics (co-analgesics). Adjuvant analgesics (AA) are drugs that are not identified as analgesics based on their pharmacologic properties but have been shown in clinical practice to have an analgesic effect for certain painful conditions when used as monotherapy or in combination with other analgesics. AAs have become increasingly important in the treatment of pain in combination with opioids or other analgesics and are an integral component of the WHO analgesic ladder. Some common pain conditions for which AAs have been shown to be effective include neuropathic pain (e.g., peripheral diabetic neuropathy, postherpetic neuralgia, HIV-related neuropathy), cancer pain (e.g., bone metastasis, neuropathic pain), and chronic non-cancer pain (e.g., headache, chronic lower back pain, fibromyalgia, migraine and other headaches, osteoarthritis).[4,41] **Table 6** lists the most commonly used AAs, their indications, side effects, and recommendations for monitoring.[4,41,42] A therapeutic effect of AAs is that they have a dose-sparing effect on opioids, which reduces opioid side effects, and add a different mechanism of action in opioid-resistant pain. AAs have a narrow therapeutic window where small changes in dosing can lead to a significant increase in the likelihood of side effects. There is a ceiling effect with AAs in which there is no further pain relief above a specific dose. The use of AAs in the treatment of pain is an example of a multimodal analgesic application that tailors a pain regimen to a specific patient's pain diagnosis. As with any medication regimen that involves polypharmacy, the risks and benefits of increasing adverse events and a patient's pill burden should be weighed carefully. Drug-drug interactions are also a concern for the many available AAs. It is beyond the scope of this article to comprehensively review all the potential drug-drug interactions with AAs. As part of their routine in monitoring drug therapy, pharmacists should take the time to check the patient's medication list to ensure that there are no significant drug-drug interactions.

GI Risk with NSAID[a]

Low

Moderate

High

TABLE 5

RECOMMENDATIONS FOR NSAIDS BASED ON GI AND CV RISK FACTORS

Low CV Risk (not on antiplatelet drugs)	High CV Risk (on antiplatelet drugs)
Non-selective NSAID	Naproxen or nonselective NSAID with lowest COX-2 inhibition activity Consider adding PPI or misoprostol
COX-2 Inhibitor **OR** Non Selective NSAID + PPI or misoprostol	Naproxen or nonselective NSAID with lowest COX-2 inhibition activity Add a PPI or misoprostol
COX-2 selective inhibitor + PPI or misoprostol **OR** Nonselective NSAID **with** PPI or misoprostol	Avoid NSAIDs if possible (consider opioids) **If NSAIDs are necessary:** Consider naproxen if CV risk outweighs GI risk **OR** COX-2 Inhibitor if GI risk outweighs CV risk All patients should receive PPI or misoprostol

Abbreviations: COX, cyclooxygenase; CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.
[a]See Table 3 for GI risk factors

Source: Ref 30

Pause&Ponder

Many of the adjuvant analgesics are used for neuropathic pain. How would a patient describe their pain if it was neuropathic in nature? Are there adjectives they might use that would lead you in the direction of recommending an adjuvant analgesic for their pain?

Conclusion

As the first healthcare provider from whom patients seek advice for pain relief or who sees patients after they have obtained an analgesic prescription from a prescriber, pharmacists are in a unique position to ensure that patients are achieving appropriate and effective pain treatment. Pharmacists are medication experts who have

TABLE 6

MAJOR CLASSES OF SELECTED COMMONLY USED ADJUVANT ANALGESICS

Antidepressants	Common indications/side effects	Comments
Tricyclic antidepressants Amitriptyline Nortriptyline Desipramine	PHN, DPN, cancer pain Common: anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention), hypotension, sedation.	Start at lowest dose possible and titrate up to effect to minimize side effects, especially in elderly. Nortriptyline better tolerated than amitriptyline because of less sedation and anticholinergic effect. Allow at least 6-8 weeks therapy with at least 2 weeks at maximum tolerated dose to determine efficacy with pain relief.
Serotonin norepinephrine reuptake inhibitors Duloxetine Venlafaxine	DPN, fibromyalgia Duloxetine: nausea is most common side effect and minimized by starting at 30 mg QD for 1 week before increasing to 60 mg QD Venlafaxine: Blood pressure increase, cardiac conduction abnormality	Allow at least 4-6 weeks of adequate trial therapy. Venlafaxine should be tapered when discontinued because of withdrawal syndrome.
Anticonvulsants		
Gabapentinoids Gabapentin Pregabalin	DPN, PHN, HIV-related neuropathy. Dose-dependent dizziness and sedation, which may be minimized by starting at the lower dose and titrate up slowly.	Gabapentin: allow 3-8 weeks for titration of dose plus 2 weeks at maximum dose to assess efficacy. Pregabalin: allow 4 weeks adequate trial period. Require dose adjustment in renal insufficiency.
Divalproex sodium	FDA approved for migraine headache prophylaxis. Sedation, nausea, vomiting. Hepatotoxicity, pancreatitis, thrombocytopenia, androgenization with hirsutism, abnormal thyroid function test.	Side effects limit wider use in chronic pain.
Topical Agents		
Lidocaine patch 5%	NP, PHN, allodynia	Allow 3 weeks adequate trial period. Does not have systemic effect. Should be applied directly to site of pain or allodynia for localized pain control. Apply 12 hours on and 12 hours off.
Corticosteroids		
Dexamethasone	Cancer bone pain from metastasis, NP. Gastritis, hyperglycemia, hypertension, fluid retention, immunosuppression, mania, delirium, psychosis.	Must be tapered off when discontinued.
Bisphosphonates		
Pamidronate Zoledronic acid	Cancer bone pain from metastasis. Constipation, nausea, diarrhea, hypocalcemia, nephrotoxicity, osteonecrosis of the jaw.	Pamidronate should be administered intravenously over at least 2 hours every 4 weeks. Zoledronic acid may be administered intravenously over 15 minutes every 3-4 weeks.

Abbreviations: DPN, diabetic peripheral neuropathy; NP, neuropathic pain; PHN, post-herpetic neuralgia; QD, every day.

Source: Ref 4, 41-42

a pivotal role in assessing the appropriateness of medication orders and should be an integral member of the healthcare team in the management of patients with pain. Pharmacists may establish their role in the successful treatment of patients with pain by being educated on the treatment options available for pain management, knowing how to utilize these treatment options, and being prepared to make recommendations for managing side effects and choosing alternatives when a patient is not tolerating or responding to the therapy. Pharmacists also have the responsibility of providing education to patients about dosing, administration, and adverse effects of their medication therapy. Subsequent articles in this series on pain management will apply the pharmacist's foundation knowledge of pain management to representative patient cases. •

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

TEST QUESTIONS

1. **All of the following statements are correct regarding nonsteroidal anti-inflammatory drugs except:**
   - **a.** Gastric mucosa erosion is due to decreased production of mucous, bicarbonate, and gastrointestinal (GI) blood flow
   - **b.** Increase in platelet aggregation activity may occur with these agents
   - **c.** Renal side effect is due to inhibition of prostaglandin synthesis
   - **d.** Asthma may be exacerbated in patients with recurrent nasal polyps

2. **In applying the World Health Organization Ladder to pain management, which of the following statements is correct:**
   - **a.** Every patient has to start at step 1 of the ladder with a non-opioid analgesic and work up the ladder.
   - **b.** Patients may not receive opioids as the first analgesic no matter what the pain level.
   - **c.** Adjuvant analgesics is a treatment option for all steps within the ladder.
   - **d.** Non-opioid analgesics should only be used for step 1 within the ladder.

3. **The maximum daily dose for acetaminophen is:**
   - **a.** 4 g for normal, healthy patients
   - **b.** 2 g for patients with underlying liver dysfunction
   - **c.** 2 g for patients with a heavy alcohol ingestion history
   - **d.** All of the above

4. **Which of the following factors increases the risk of GI side effects with NSAIDs?**
   - **a.** Advanced age
   - **b.** Renal dysfunction
   - **c.** Liver dysfunction
   - **d.** All of the above

5. **Which of the following medications is a selective COX-2 inhibitor?**
   - **a.** Piroxicam
   - **b.** Diflunisal
   - **c.** Celecoxib
   - **d.** Meloxicam

6. **Which of the following is not an advantage of acetaminophen?**
   - **a.** It has anti-inflammatory activity.
   - **b.** Minimal risk of GI ulcers.
   - **c.** No inhibition of platelet aggregation
   - **d.** Does not have cross reactivity with aspirin-sensitive patients

7. **Which of the following NSAIDs has the most potential for causing GI ulcerations?**
   - **a.** Diclofenac
   - **b.** Piroxicam
   - **c.** Ketorolac
   - **d.** Meloxicam

8. **Which of the following adverse effects from nonselective NSAIDs may be minimized by using a selective COX-2 inhibitor?**
   - **a.** Cardiovascular dysfunction
   - **b.** Renal insufficiency
   - **c.** GI mucosa erosion
   - **d.** All of the above

9. **For which of the following type of pain are tricyclic antidepressants effective?**
   - **a.** Nociceptive pain
   - **b.** Neuropathic pain
   - **c.** Cancer pain
   - **d.** Lower back pain

10. **Which of the following is a physiologic consequence of under treatment of pain?**
    - **a.** Impaired immune function
    - **b.** Increased rate of GI emptying
    - **c.** Increased production of insulin
    - **d.** Decreased coagulation

11. **Which of the following agents are indicated to decrease the risk of GI ulcerations with NSAIDs?**
    - **a.** Omeprazole **b.** Misoprostol
    - **c.** Famotidine **d.** All of the above

12. **Which of the following NSAID treatment options is appropriate for a 70-year-old patient with a previous history of duodenal ulcer and no cardiovascular risk factors?**
    - **a.** Naproxen plus famotidine
    - **b.** Celecoxib
    - **c.** Ibuprofen and omeprazole
    - **d.** b and c

13. **Which of the following side effects is associated with tricyclic antidepressants?**
    - **a.** Ataxia
    - **b.** Anticholinergic effects
    - **c.** Extrapyramidal side effects
    - **d.** Hematologic side effects

14. **Which of the following is true regarding initiating analgesic therapy?**
    - **a.** Around-the-clock pain medications should be started for acute pain
    - **b.** Initiate analgesics when the source of pain is identified
    - **c.** Short-acting, fast-onset analgesics should be available as needed in the pain regimen for patients with chronic pain
    - **d.** All of the above

15. **Which of the following agents is indicated for the treatment of neuropathic pain?**
    - **a.** Pregabalin
    - **b.** Piroxicam
    - **c.** Celecoxib
    - **d.** All of the above

16. **Which of the following is an FDA-approved indication for topical diclofenac patch?**
    - **a.** Osteoarthritis of the knee
    - **b.** Rheumatoid arthritis
    - **c.** Osteoarthritis of the hip
    - **d.** Sprained ankle

17. **Which of the following is the best treatment option for a patient with acute pain requiring an anti-inflammatory agent? The patient has no GI risk factors but does have a history of myocardial infarction and is on low-dose aspirin.**
    - **a.** Celecoxib
    - **b.** Ibuprofen and misoprostol
    - **c.** Naproxen and omeprazole
    - **d.** Celecoxib and omeprazole

18. **Which of the following is true regarding misoprostol as a GI protectant?**
    - **a.** It is not well tolerated due to GI side effects
    - **b.** It is category X in pregnant women
    - **c.** It is associated with poor compliance
    - **d.** All of the above

19. **Which of the following adjuvant analgesics is indicated for the treatment of cancer bone pain due to metastasis?**
    - **a.** Divalproex
    - **b.** Pamidronate
    - **c.** Gabapentin
    - **d.** Amitriptyline

20. **What is the indication for topical lidocaine patch?**
    - **a.** Osteoarthritis
    - **b.** Ankle sprain
    - **c.** Post-herpetic neuralgia
    - **d.** Bone pain

LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

Controlled substance disposal: DEA issues Proposed Rule

Industry awaits final rule on implementation

The Drug Enforcement Administration (DEA) published its notice of proposed rulemaking (the Proposed Rule) late last year in connection with disposal of controlled substances. The Proposed Rule is a coordinated effort to implement the Secure and Responsible Drug Disposal Act of 2010. Stakeholders continue to wait for final regulations.

The Proposed Rule is intended to provide a pathway for the secure disposal of controlled substances by DEA registrants and "ultimate users" of the medications. By expanding the options to collect controlled substances, DEA hopes to further curtail any potential diversion of controlled substances. Some methods to be used under the Proposed Rule include take-back events, mail-back programs, and collection-box locations.

Collectors defined

The Proposed Rule seeks to provide a definition of "collector" that would include those types of entities permitted to collect and dispose of controlled substances.

Currently, this function is limited to law enforcement and entities connected with reverse distribution. Under the Proposed Rule, law enforcement and reverse distributors would continue to be allowed to undertake collection activities.

However, manufacturers, distributors, and retail pharmacies would also be allowed to administer mail-back programs as well as to maintain collection boxes.

LTC facilities

Of interest, the Proposed Rule also allows retail pharmacies to place collection boxes in long-term-care facilities for the purpose of disposing of controlled substances on behalf of both current and former residents of that facility. This would alleviate a recurring problem in facilities with respect to controlled substances that are not currently returnable, except through limited channels.

Requirements

Despite the inclusion of more types of entities eligible to participate in the disposal of controlled substances, there are still requirements for record-keeping and accounting under the Proposed Rule.

For example, the Proposed Rule describes requirements for the packaging of medications sent through the mails, contains provisions for security at the collection site, and specifies timing requirements related to the disposal of controlled substances.

The Proposed Rule also requires that participants in any controlled-substance disposal program provide for a mechanism by which liners and packages containing the controlled substances can be tracked and audited.

In addition to describing the types of entities will be allowed to oversee the disposal of controlled substances, the Proposed Rule also places restrictions on which individuals will be allowed oversight privileges.

The DEA has expressed concern in the Proposed Rule over the participation of certain individuals. Specifically, the Proposed Rule does not permit participation in the disposal process by an individual who has been convicted of any felony offense related to controlled substances or any individual who has had an application for DEA registration revoked or suspended. Furthermore, if an individual has ever surrendered a DEA registration for cause, that person would be excluded from participation in the disposal program.

Destruction

Finally, DEA has set forth requirements in the Proposed Rule relating to how a controlled substance may be destroyed.

Specifically, the manner of destruction must be such that the controlled substance will be placed in a "nonretrievable" state. The intended result is to render the controlled substance into a condition ensuring that it is no longer at risk for diversion.

Although DEA is not requiring any particular form of destruction, examples provided in the Proposed Rule include chemical digestion or incineration. Neither the flushing nor the mixing of controlled substances with coffee grounds or kitty litter meets the "nonretrievable" standard, according to DEA. DT

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

Ned Milenkovich *is a member at McDonald Hopkins, LLC, and chairs its drug and pharmacy practice group. He is also Vice-Chairman of the Illinois State Board of Pharmacy. Contact Ned at 312-642-1480 or at nmilenkovich@mcdonaldhopkins.com.*

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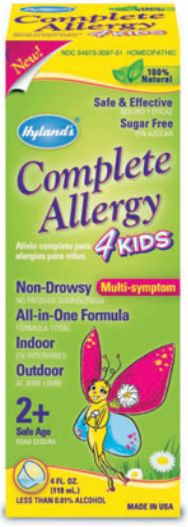

Hyland's Complete Allergy 4 Kids offers safe allergy relief for children two years of age and up.

The SinuCleanse Neti Pot can be used daily to stave off or relieve uncomfortable sinus symptoms and congestion.

PHOTOS COURTESY OF VITACOST / HYLAND'S / MED-SYSTEMS INC.

OTC

Spring is here, and showers of allergens fill the air

MIRANDA HESTER, CONTENT COORDINATOR

Spring is in the air, and so is pollen, and that means the return of seasonal allergies, while sinuses struggle to keep up with rapid weather changes. With more than 10% of Americans suffering from seasonal allergies, you're likely to see your share of patients seeking symptomatic relief.

Schering-Plough has introduced **Claritin RediTabs,** a new formulation of its popular Claritin remedy, designed to treat allergy symptoms such as itchy and runny noses, sneezing, itchy and watery eyes, and itchy nose and throat. While the regular formulation can take up to 60 minutes to provide allergy relief, the quick-dissolving tablets cut down on that wait time by up to half an hour. The product comes in two formulations, one that provides non-drowsy allergy relief for 12 hours and one that works for 24 hours. Claritin RediTabs are safe for children over the age of six. Possible side effects include headache and dry mouth. Patients with kidney and liver disease as well as children under the age of six should consult a doctor before using the product.

Chattem's **Allegra** line, containing fexofenadine, offers several options designed to provide relief from allergy symptoms for the entire family.

- **Allegra Allergy** comes in 12-hour and 24-hour relief formulations that start working within an hour to provide fast, non-drowsy, 24-hour relief for common allergy symptoms such as sneezing, runny nose, itchy, watery eyes, and itchy nose or throat.
- **Allegra-D** also comes in 12-hour and 24-hour formulations. Containing pseudoephedrine in addition to fexofenadine, the product gives fast, non-drowsy relief to allergy symptoms such as sneezing, runny nose, itchy, watery eyes, and itchy nose or throat, and helps clear nasal congestion and sinus pressure.

Both Allegra Allergy and Allegra-D are safe for adults and children over the age of 12, although patients over the age of 65 or those who have kidney disease should consult with their doctor before using them.

- Children ages 2 and older can find long-lasting non-drowsy relief with **Children's Allegra Allergy Oral Suspension**. The raspberry-flavored liquid provides 12 hours of non-drowsy relief from common allergy symptoms such as sneezing, runny nose, watery eyes, and itchy nose or throat. Only two doses should be taken within a 24-hour period. A dose cup is included.
- Older children, from ages six to 12, can also use **Children's Allegra Allergy Meltable Tablets**. Each orange-cream-flavored disintegrating tablet provides non-drowsy relief from sneezing, runny nose, itchy or watery eyes, and itchy nose or throat for up to 12 hours. Two tablets may be taken by adults and children over the age of 12 every 12 hours; no more than four

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Spring is here

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tablets should be taken in a 24-hour period. For children between the ages of six and 12, one tablet may be taken every 12 hours; no more than two tablets should be taken in a 24-hour period. This product should not be used by children under the age of six.

For patients looking for an herbal allergy remedy, **Vitacost** is offering **Butterbur Extract** capsules, synthesized for relief of nasal allergy symptoms.

Butterbur, a shrublike plant with large, broad leaves and purplish-pink flowers, is native to Europe and northern Asia. Extracts of the plant's roots, leaves, and flowers have been used as far back as the Middle Ages to keep the immune system healthy, alleviate common aches and pain, and support healthy respiratory function.

Each capsule has 75 mg of butterbur extract, which contains the active ingredient petasin. The capsules are free of milk, eggs, peanuts, tree nuts, shellfish, fish, soy, gluten, and titanium dioxide, and meet CGMP standards. Diabetics, expectant mothers, women who are breastfeeding, and hypoglycemic patients should consult their doctors before using the product. *(These statements have not been evaluated by FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.)*

New from **Bell Lifestyle Products** is **Master Herbalist Allergy Relief.** The nutraceutical provides year-round relief from environmental and seasonal nasal congestion, sneezing, inflammation of the eyes, seasonal pollen and plant allergies, perennial allergies, house dust, pet allergies, food allergies, and asthma. Featuring all-natural ingredients, including basil, sage, mint, perilla, lobelia, quercetin, and rosemary, the product also contains rosmarinic acid, which helps stop sneezing and nasal congestion at their source. According to the manufacturer, it is the only nutraceutical shown to be effective in treating seasonal rhinitis in humans. *(FDA has not evaluated these statements. These products are not intended to diagnose, treat, cure, or prevent any disease.)*

Parents in search of safe allergy relief for their children can turn to **Hyland's Complete Allergy 4 Kids.** Specially designed for children two years of age and up, the sugarless homeopathic formula has a mild and pleasant taste. A combination of non-drowsy all-natural ingredients provides safe and gentle relief for common indoor and outdoor allergy symptoms, including runny nose, itchy, watery eyes, itchy nose and throat, stuffy nose, and facial pain. The product contains no pseudoephedrine. The quick-dissolving tablets are easy to administer, relieve symptoms quickly, and have no side effects. Each bottle contains 125 tablets. *(These statements are based upon traditional homeopathic practice. FDA has not reviewed them.)*

For a nonpharmaceutical means to relieve nasal congestion, **SinuCleanse** offers the **Neti Pot, Neti Cap,** and **Squeeze.** All three products use a saline solution to help irrigate sinuses and lessen congestion. Studies have found that saline irrigation improves sinus symptoms and congestion in allergy sufferers. Although doctors aren't sure exactly how it works, one study concluded that it's possible that the solution clears out the inflammatory chemicals, such as histamines, that create nagging symptoms. The solution can even be used as a preventive measure when patients feel symptoms coming on.

- The **Neti Pot** is a nasal cup shaped like a genie's lantern. To use it, the patient stands over the sink, head turned slightly to the side, and pours the saline solution into the upper nostril using the long spout of the pot. The solution then drains out the lower (opposite) nostril. The patient applies the solution to each nostril in turn. The Neti Pot can be used daily to stave off congestion and sinus headaches, and may even be used as a preventive measure before the appearance of symptoms.
- Away from home, the **Neti Cap** offers a convenient alternative. Each package contains two Neti Caps, designed by an ear, nose, and throat physician to fit over the tops of most 26-mm to 28-mm plastic water bottles, and 30 packets of all-natural, pharmaceutical-grade saline. Each packet should be used with 8 oz. of water. Adults and children four years of age and over may use 1-2 packets up to every 2 hours as needed. Each packet contains 700 mg of sodium bicarbonate USP and 2300 mg of sodium chloride. The Neti Cap should be washed with soap and water after each use.
- The **SinuCleanse Squeeze** bottle is designed for users who prefer a positive pressure device. Its anti-backflow technology prevents contamination of the saline solution during and after use, while its wide-mouth design makes it easy for users to fill and dry the Squeeze bottle and keep it clean. The SinuCleanse "umbrella valve," which sits on the underside of the cap, allows air to flow only one way into the bottle and

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RX & OTC

New products

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New drugs

Alcon, a division of Novartis, has announced FDA approval of **Simbrinza Suspension,** indicated for the reduction of elevated intraocular pressure (IOP) in patients with primary open-angle glaucoma or ocular hypertension. Elevated IOP is the only modifiable risk factor for glaucoma. Glaucoma is a group of eye diseases that lead to progressive damage of the optic nerve and can result in gradual, irreversible loss of vision, and eventually blindness, if left untreated. Simbrinza is a fixed-dose combination of a carbonic anhydrase inhibitor (brinzolamide 1.0%) and an alpha 2 adrenergic receptor agonist (brimonidine tartrate 0.2%). It can decrease elevated IOP by 21%-35%. In addition, it is the only fixed-dose combination therapy for glaucoma without a beta-blocker available in the United States. Patients should administer one drop of Simbrinza into the affected eye(s), three times per day. **(www.alcon.com)**

FDA has approved Janssen's **Invokana** (canagliflozin) tablets, used with diet and exercise to improve glycemic control in adults with type 2 diabetes. Invokana is the first diabetes treatment approved in a new class of drugs known as sodium-glucose co-transporter 2 (SGLT2) inhibitors. Invokana works by blocking the reabsorption of glucose by the kidney, increasing glucose excretion, and lowering blood glucose levels in diabetes patients who have elevated blood glucose levels. Type 2 diabetes is the most common form of the disease, affecting about 24 million people and accounting for more than 90% of diabetes cases diagnosed in the United States. Over time, high blood sugar levels can increase the risk for serious complications, including heart disease, blindness, and nerve and kidney damage. **(www.invokana.com)**

FDA has approved Biogen Idec's **Tecfidera** (dimethyl fumarate) delayed-release capsules for the treatment of adults with relapsing forms of multiple sclerosis (MS), including the most common form, relapsing-remitting multiple sclerosis. Joining two other approved oral disease-modifying medications for MS — Gilenya (fingolimod) and Augabio (teriflunomide) — Tecfidera has been shown to significantly reduce relapses and development of brain lesions and to slow disability progression over time. Tecfidera should be started at a dose of 120 mg BID. It can be increased to 240 mg BID after 1 week at the starting dose. **(www.tecfidera.com)**

Tris Pharma has announced FDA approval of **Karbinal ER** (carbinoxamine maleate) in extended-release oral suspension in the 4 mg/5 mL strength. The company said the drug was the first liquid sustained-release histamine-H1 receptor blocker for seasonal and perennial allergic rhinitis in children 2 and older. The product is dosed once every 12 hours. **(www.trispharma.com)**

FDA has approved the 200-mg strength of Warner Chilcott's **Doryx** (doxycycline hyclate) antibiotic delayed-release tablets, which the company plans to release in July. Doryx delayed-release tablets are already available in the 75-mg, 100-mg, and 150-mg strengths. **(www.wcrx.com)**

FDA has approved Taro Pharmaceutical Industries' **Topicort** (desoximetasone) topical spray, 0.25%, a corticosteroid indicated for the treatment of plaque psoriasis in patients 18 years of age or older. According to the manufacturer, the U.S. market for corticosteroid spray is approximately $100 million in annual sales. **(www.taro.com)**

New generics

BD Rx Inc. announced in late April that FDA had approved its **metoclopramide injection, USP, [1]** an antiemetic currently on the drug shortage list. The injectable may be used for treatment of symptoms associated with acute and recurrent diabetic gastric stasis; for prophylaxis of vomiting associated with emetogenic cancer chemotherapy; and for prophylaxis of postoperative nausea and vomiting in circumstances where nasogastric suction is undesirable.

Metoclopramide injection is the second drug in the company's recently launched line of BD Simplist generic prefilled injectable products. The first product, BD Simplist **diphenhydramine hydrochloride Injection, USP, [2]** an injectable antihistamine, launched at the end of March. According to the company, the injectable treatments are designed to improve patient care and safety by decreasing the number of steps in the traditional vial and syringe injection sequence and thus reduce the potential risk of medication errors. While traditional injections require up to 20 steps on the part of the physician, the Simplist requires about 12, in addition to featuring easy-to-read labels, barcoding for easy identification, and individually packaged, prefilled syringes. **(www.bdrxinc.com)**

In April, Lupin Pharmaceuticals received final FDA approval for the **Daysee**

PHOTOS COURTESY OF BD RX INC.

pill (levonorgestrel and ethinyl estradiol tablets, USP, 0.15 mg / 0.03 mg, and ethinyl estradiol tablets, USP, 0.01 mg), a generic version of Teva's Seasonique tablets, indicated for contraception in women. The Daysee tablets are packaged in extended-cycle wallets containing 13 weeks' worth of tablets: 84 tablets containing 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol, and seven tablets containing 0.01 mg ethinyl estradiol. Lupin has already begun shipping the product. **(www.lupinpharmaceuticals.com)**

FDA has approved **Diclegis** (doxylamine succinate and pyroxidine hydrochloride), from Duchesnay Inc., for the treatment of morning sickness. Diclegis is a generic version of Bendectin, a drug initially approved in 1956 and withdrawn from the market in 1983. Diclegis comes in the form of a single pill and will be available only with a prescription. Morning sickness affects a large proportion of pregnant women. In most cases it can be managed through dietary measures such as snacking throughout the day and drinking ginger ale. But in rare cases, it is so severe that the woman requires hospitalization and treatment with intravenous fluids. **(www.diclegis.com)**

New indication

Sucampo Pharmaceuticals and Takeda Pharmaceuticals U.S.A. have announced FDA approval of **Amitiza** (lubiprostone), making it the first oral treatment for opioid-induced constipation (OIC) in adults with chronic non-cancer pain. OIC is a common adverse effect of chronic opioid use. This is the third indication for Amitiza, which is also approved in the U.S. for the treatment of chronic idiopathic constipation (CIC) in adults and irritable bowel syndrome with constipation in adult women. Amitiza is a specific activator of ClC-2 chloride channels in the intestinal epithelium. Through activation of apical ClC-2 channels in the intestinal epithelium, Amitiza bypasses the antisecretory action of opiates. For OIC, 24 µg should be taken twice daily. **(www.amitizahcp.com)**

OTC

Douglas Laboratories has launched **Metabolic Lean**, a dietary supplement for weight management. According to a company statement, the product combines ingredients that help to promote lipolysis, thermogenic activity, and insulin function, and have also been shown to increase adiponectin levels, which facilitate proper fat metabolism and glucose regulation. Key ingredients include two plants, *Sphaeranthus indicus* and *Garcinia mangostana,* capsicum extract, and a chromium complex. **(www.douglaslabs.com)**.

Recently launched, **UrgentRX Fast Acting Powders** are portable packets of such products as generic Benadryl, aspirin, and Pepto-Bismol that dissolve sublingually without the need for water, enabling them to go to work three times faster than pills do. Each credit-card-sized, single-dose packet targets an everyday ailment, such as aches and pains, allergies, and heartburn. There are also fast-acting powders for more serious conditions, including allergies and heart attacks.

According to the manufacturer, after being on the market for only two days, UrgentRX Critical Care saved the life of a skier having a heart attack. It produced the same dramatic result for a worker in the UrgentRX factory; in the throes of a heart attack, he grabbed a packet off the line and saved his own life.

UrgentRX products, the manufacturer states, are now carried on all American Airlines flights, by state ski patrols across the country, and in ambulances in 42 states. The UrgentRX powders can be ordered online from Walgreens, Amazon.com, and Drugstore.com, and can be purchased through various national retailers. **(www.urgentrx.com)**. DT

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Spring is here

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closes when there is pressure inside. It will not pull air and contaminants in through the tip.

• **SinuCleanse Saline Refills** for all three products contain all-natural, preservative-free ingredients and are available in 60- and 100-count boxes.

Children and infants suffering from nasal congestion can find relief with natural, nonmedicated **Ocean for Kids Saline Nasal Spray** from **Valeant Consumer Products**. Fitted with a smaller spray tip especially for kids, the spray, containing saline and glycerin, instantly helps to clear nasal congestion and soothe nasal dryness, and is safe for frequent daily use. The manufacturer states that the nasal spray can help relieve congestion by thinning mucus; it can soothe dry, irritated nasal passages caused by allergies, cold, and flu; it helps to reduce nosebleeds resulting from nasal dryness; it restores moisture lost to drug-induced dryness; and it moisturizes and irrigates membranes after nasal surgery.

Ocean for Kids Saline Nasal Spray contains glycerin to soothe little noses, as well as saline solution to clear them.

PHOTO COURTESY OF VALEANT CONSUMER PRODUCTS

When held upright, the bottle can be used as a mister; held horizontally, it produces a stream; and held upside down, it produces drops when squeezed. Drops should be used in treating infants.

For patients whose symptoms include itchy, watery eyes, **McNeill**'s **Visine-A** can provide relief. Its active ingredients of pheniramine, an antihistamine, and naphazoline, a decongestant, diminish eye itchiness and wateriness by reducing the histamines produced by the eye and constrict irritated blood vessels to reduce redness. Visine-A is safe for use by adults and children over the age of 6, but should not be used by either children or adults for more than 3 days, as a rebound effect may bring renewed inflammation to the eye. If the symptoms last for more than 3 days or pressure develops, a doctor should be consulted. DT

First JAK inhibitor approved

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should be treated for TB before initiation of tofacitinib therapy. All patients should be monitored for active TB as well as for other infections during treatment, since infections that have led to hospitalization or death have been observed during tofacitinib therapy. Because of the unavailability of data, live vaccines should not be administered to patients taking tofacitinib, and immunizations should be updated before initiation of therapy.

Patients who have had a malignancy previous to tofacitinib treatment or develop a malignancy during tofacitinib treatment need to consider the risk and benefits of tofacitinib. Of the 3,328 patients in the clinical trial program who received tofacitinib with or without a DMARD, there have been 11 solid tumors and one lymphoma case at 12 months. No malignancies have been reported in the 809 patients treated with placebo.

In a small trial of renal transplant patients, five of 218 patients treated with tofacitinib developed post-transplant lymphoproliferative disorder associated with Epstein-Barr virus, compared with no patients among the 11 treated with cyclosporine.

Other side effect/safety findings included gastrointestinal perforations, lymphocytosis, neutropenia, decreased hemoglobin, liver enzyme elevations, and lipid elevations. The most commonly reported side effects were upper respiratory tract infections, headache, diarrhea, hypertension, and nasopharyngitis.

Dosage

The recommended dose of tofacitinib is 5 mg twice daily. Tofacitinib should not be initiated in patients with: severe hepatic impairment, a lymphocyte count less than 500 cells/mm^3, an absolute neutrophil count less than 1000 cells/mm^3, or hemoglobin levels less than 9 g/dL. Tofacitinib should be interrupted for the management of lymphopenia, neutropenia, and anemia, either by reducing the dose to 5 mg daily or holding the dose until lab values have normalized.

There are also recommendations that the dose should be reduced to 5 mg daily in patients who have moderate-to-severe renal insufficiency or moderate hepatic impairment, as well as in patients who are receiving potent inhibitors of cytochrome P450 3A4, such as ketoconazole, and receiving one or more concomitant medications that can result in moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Patients taking potent CYP3A4 inducers may have a reduced response to tofacitinib. DT

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JP AT LARGE Jim Plagakis, RPh

Apply sparingly to right ear until nurse stops shouting

Why can't you tell me what happened to the refills?" The person interrogating me was a registered nurse. The volume of her voice had risen and her tone had become close to a shriek because I wasn't playing monkey to her kid rattling the cage at the zoo.

She continued. "This was a February 15 e-prescription for clonidine 0.2 mg."

"I know it is for clonidine, with instructions of *i qd*."

"How do you know that?"

"Because I am looking at Mrs. Smith's record as we speak." My voice was very calm, as soothing as I could make it. This woman was not going to get the idea that she could get Jim Plagakis jangled. I was the picture of a well-mannered pharmacist — not my usual style, I admit.

"Well, then you can see that the prescription has five refills."

"No, I can't."

"What? What do you mean, you can't?"

"Our technicians are professionals. They know what a hassle it is when the refills run out and the patient needs the medicine. Recording the refills electronically is just as important to them as getting the instructions recorded accurately."

I thought of the instructions I had seen on an e-prescription that morning. Apply one tablet sparingly to the right ear three times every hour for nausea and vomiting.

"Well, Mister, I am holding the chart. It says e-prescription with five refills on February 15th, sent to your pharmacy."

I sighed. My Dalai Lama persona was fading. "Just authorize the refills right now, over the phone, and I will add them to the prescription."

"We don't do things that way."

"How do you do it?"

"We have to get it authorized by the doctor."

"We are getting to the danger zone, ma'am. I am going to give the patient six tablets as an emergency supply so you can get this straightened out."

"You can't just give her tablets willy nilly. You have to wait for the doctor."

"I'm confident that the doctor knows that discontinuing clonidine abruptly can put her life in danger. How do you spell your last name?"

"Why do you need that?"

"So the patient's family can pass the correct name on to their attorney when the patient dies."

The top of the pyramid

Nurses are at the top of the pyramid of patient care. They were the heroes of the 1918 influenza pandemic. Many died.

My bed was in the hallway when I was admitted to Cleveland General Hospital with polio in 1950. I was usually awake when they removed a dead child from an iron lung in the middle of the night. After orderlies did their job with alcohol, it took less than an hour for the nurses to bring in the next kid for that iron lung

Nurses were all over us, all day long. The ward was overcrowded. Two beds to a cubicle meant for one. The iron lungs down the middle. Parents were allowed to visit for one hour once a week.

The nurses watched our bowels, stretched our atrophying muscles with love, and wrapped us in Sister Kenny's steaming hot woolen towels.

When the doctors came in, the nurses were keenly attentive. Arms at their sides, nodding: Yes, Doctor, yes. I noticed that the doctors did absolutely nothing except boss the nurses around.

My respect for nurses will never diminish, but I will not tolerate a nurse questioning me as if I were some kind of nurse's aide.

When the doc's out, watch out

Recently, *The New York Times* ran an article titled, "When the doctor is not needed." In the near future, nurses (and pharmacists) will be shouldering much of the load for primary care. The reasons? Too many patients. Doctors who are too expensive.

The authors of the Affordable Care Act have keen eyes. They know how well pharmacists are educated. You will be ordering tests and prescribing drugs.

By and large, nurses still are not experts on drug therapy. They're in the minor leagues in some small town where the Class A team is named the Fleas. Many of them need to stop pretending before they hurt someone.

On the phone years ago, I asked a registered nurse to slow down. "Was that Seldane [terfenadine, an antihistamine]?," I asked her, "Or Feldene [piroxicam]?"

Her answer? "Yes." DT

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