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VOL. 88 NO. 4

ADVANSTAR HEALTHCARE

For the management of fibromyalgia

Savella relieves symptoms of fibromyalgia

- **Delivers simultaneous improvements on 3 measures of fibromyalgia[1]**
  - Pain reduction
  - Improvement in patient global fibromyalgia assessment
  - Improvement in physical function
- **Decrease in pain as early as week 1 of treatment with a stable dose in patients who reported global improvement[1]**
- **Low potential for pharmacokinetic drug-drug interactions[1]**
  - Clinically important interactions may occur with MAOIs, serotonergic drugs (including other SSRIs, SNRIs, lithium, tryptophan, antipsychotics, and dopamine antagonists), triptans, catecholamines (epinephrine and norepinephrine), CNS-active drugs (including clomipramine), and select cardiovascular agents (digoxin and clonidine)
- **A dual reuptake inhibitor that blocks the uptake of norepinephrine over serotonin with approximately 3 times greater potency in vitro[1]**
  - The clinical significance of in vitro data is unknown
- **Widely available on managed care formularies[2]**

Savella®
milnacipran HCl
12.5 mg, 25 mg, 50 mg, 100 mg tablets
For the management of fibromyalgia

Savella is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of such drugs in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on Savella should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of drug therapy or at times of dose changes, either increases or decreases. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Savella is not approved for use in the treatment of major depressive disorder. Savella is not approved for use in pediatric patients.

References: 1. Savella (milnacipran HCl) prescribing information. Forest Pharmaceuticals, Inc. St Louis, MO. **2.** MediMedia Database as of 6/2/10 for Savella.

Contraindications

- Savella is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) concomitantly or within 14 days of discontinuing treatment with an MAOI. There have been reports of serious, sometimes fatal, reactions in patients started on an MAOI who were receiving or had recently discontinued a serotonin reuptake inhibitor. At least 5 days should be allowed after stopping Savella before starting an MAOI.
- Savella is contraindicated in patients with uncontrolled narrow-angle glaucoma and should be used with caution in patients with controlled narrow-angle glaucoma. In clinical trials, Savella was associated with an increased risk of mydriasis.

Warnings and Precautions

- Prescriptions for Savella should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.
- Development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs and SNRIs alone, including Savella, but particularly with concomitant use of serotonergic drugs (including triptans), drugs that impair metabolism of serotonin (including MAOIs), or antipsychotics or other dopamine antagonists. The management of these reactions should include immediate discontinuation of Savella and the concomitant agent and supportive symptomatic treatment. The concomitant use of Savella with serotonin precursors is not recommended.
- SNRIs, including Savella, have been associated with cardiovascular effects, including cases of elevated blood pressure, requiring immediate treatment. In clinical trials, sustained increases in systolic and diastolic blood pressure occurred more frequently in Savella-treated patients compared to placebo. Among patients who were non-hypertensive at baseline, approximately twice as many patients receiving Savella, vs placebo, became hypertensive at the end of the study. Clinically significant increases in pulse (≥20 bpm) occurred more frequently in Savella-treated than placebo-treated patients. Blood pressure and heart rate should be monitored prior to initiating treatment with Savella and periodically throughout treatment. Pre-existing hypertension, tachyarrhythmias, and other cardiac diseases should be treated before starting therapy with Savella. Savella should be used with caution in patients with significant hypertension or cardiac disease. Concomitant use of Savella with drugs that increase blood pressure and pulse has not been evaluated, and such combinations should be used with caution. For patients who experience a sustained increase in blood pressure or heart rate while receiving Savella, either dose reduction or discontinuation should be considered.
- Savella should be prescribed with caution in patients with a history of seizure disorder or mania.
- Savella has been associated with mild elevations of ALT and AST (1 to 3 times the upper limit of normal). Rarely, reports of serious liver injury, including fulminant hepatitis, have been reported in patients treated with milnacipran. Savella should be discontinued in patients who develop jaundice or other evidence of liver dysfunction and should not be resumed unless another cause can be established.
- As with other SNRIs and SSRIs, withdrawal symptoms have been observed following discontinuation of milnacipran. A gradual dose reduction is recommended.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Savella. Elderly patients may be at greater risk. Discontinuation should be considered for patients with symptomatic hyponatremia.
- SSRIs and SNRIs, including Savella, may increase the risk of bleeding events. Patients should be cautioned regarding the risk of bleeding associated with concomitant use of Savella and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.
- Savella can affect urethral resistance and micturition. Caution is advised in the use of Savella in patients with a history of dysuria, notably in male patients with a history of obstructive uropathies as these patients may experience higher rates of genitourinary adverse events.
- Savella should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Use in Specific Populations

- There are no adequate and well-controlled studies in pregnant women. Savella should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adverse Reactions

- In clinical trials, the most frequently occurring adverse reaction was nausea (37% vs 20% for placebo). The most commonly occurring adverse reactions (≥5% and greater than placebo) were headache (18% vs 14%), constipation (16% vs 4%), dizziness (10% vs 6%), insomnia (12% vs 10%), hot flush (12% vs 2%), hyperhidrosis (9% vs 2%), vomiting (7% vs 2%), palpitations (7% vs 2%), heart rate increased (6% vs 1%), dry mouth (5% vs 2%), and hypertension (5% vs 2%).

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

For Full Prescribing Information, visit www.Savella.com.

Savella®
milnacipran HCl
12.5 mg, 25 mg, 50 mg, 100 mg tablets
For the management of fibromyalgia

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Pharmaceuticals • Therapeutics • Healthcare • Ethicare • Managed Care • Specialty Sales

Cypress Bioscience, Inc.

Savella® (milnacipran HCl) Tablets **Rx Only**
Brief Summary of Full Prescribing Information
Initial U.S. Approval: 2009

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS Savella is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of such drugs in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on Savella should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Savella is not approved for use in the treatment of major depressive disorder. Savella is not approved for use in pediatric patients [*see Warnings and Precautions, Use in Specific Populations*].

INDICATIONS AND USAGE: Savella is indicated for the management of fibromyalgia. Savella is not approved for use in pediatric patients [*see Use in Specific Populations*].

CONTRAINDICATIONS: Monoamine Oxidase Inhibitors-Concomitant use of Savella in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. In patients receiving a serotonin reuptake inhibitor in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Savella and MAOIs have not been evaluated in humans. Therefore, it is recommended that Savella should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 5 days should be allowed after stopping Savella before starting an MAOI [see *Dosage and Administration, Warnings and Precautions*]. **Uncontrolled Narrow-Angle Glaucoma-**In clinical trials, Savella was associated with an increased risk of mydriasis. Mydriasis has been reported with other dual reuptake inhibitors of norepinephrine and serotonin; therefore, do not use Savella in patients with uncontrolled narrow-angle glaucoma.

WARNINGS AND PRECAUTIONS: Suicide Risk-Savella is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. Patients, both adult and pediatric, with depression or other psychiatric disorders may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking these medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants, including drugs that inhibit the reuptake of norepinephrine and/or serotonin, may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. In the placebo-controlled clinical trials of adults with fibromyalgia, among the patients who had a history of depression at treatment initiation, the incidence of suicidal ideation was 0.5% in patients treated with placebo, 0% in patients treated with Savella 100 mg/day, and 1.3% in patients treated with Savella 200 mg/day. No suicides occurred in the short-term or longer-term (up to 1 year) fibromyalgia trials. Pooled analyses of short-term placebo-controlled trials of drugs used to treat depression (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with these drugs compared to placebo in adults beyond age 24; there was a reduction in suicidality risk with antidepressants compared to placebo in adults age 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 drugs used to treat depression in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug versus placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1 of the full prescribing information. There were 14 additional cases reported in patients under the age of 18, while 5 additional cases were reported in patients between 18 and 24 years of age. Patients between 25 and 64 years of age reported 1 fewer case of suicidality, while patients over the age of 65 reported 6 fewer cases. No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, have been reported in adult and pediatric patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who may experience worsening depressive symptoms, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment due to worsening depressive symptoms or emergent suicidality, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can produce withdrawal symptoms *[see Dosage and Administration—Recommended Dosing, Dosage—Discontinuing Savella,* and *Warnings and Precautions—Discontinuation of Treatment with Savella]*. **Families and caregivers of patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Savella should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions-**The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Savella, but particularly with concomitant use of serotonergic drugs (including triptans), with drugs which impair metabolism of serotonin (including MAOIs) or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) *[see Drug Interactions]*. Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. The concomitant use of Savella with MAOIs is contraindicated *[see Contraindications]*. If concomitant treatment of Savella with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions]*. The concomitant use of Savella with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions]*. Treatment with Savella and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated. **Effects on Blood Pressure-**Inhibition of the reuptake of norepinephrine (NE) and serotonin (5-HT) can lead to cardiovascular effects. SNRIs, including Savella, have been associated with reports of increase in blood pressure. In a double-blind, placebo-controlled clinical pharmacology study in healthy subjects designed to evaluate the effects of milnacipran on various parameters, including blood pressure at supratherapeutic doses, there was evidence of mean increases in supine blood pressure at doses up to 300 mg twice daily (600 mg/day). At the highest 300 mg twice daily dose, the mean increase in systolic blood pressure was up to 8.1 mm Hg for the placebo group and up to 10.0 mm Hg for the Savella treated group over the 12 hour steady state dosing interval. The corresponding mean increase in diastolic blood pressure over this interval was up to 4.6 mm Hg for placebo and up to 11.5 mm Hg for the Savella treated group. In the 3-month placebo-controlled fibromyalgia clinical trials, Savella treatment was associated with mean increases of up to 3.1 mm Hg in systolic blood pressure (SBP) and diastolic blood pressure (DBP) [*see Adverse Reactions*]. In the placebo-controlled trials, among fibromyalgia patients who were non-hypertensive at baseline, approximately twice as many patients in the Savella-treatment arms became hypertensive at the end of the study (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) compared with the placebo patients: 7.2% of patients in the placebo arm versus 19.5% of patients treated with Savella 100 mg/day and 16.6% of patients treated with Savella 200 mg/day. Among patients who met systolic criteria for pre-hypertension at baseline (SBP 120-139 mmHg), more patients became hypertensive at the end of the study in the Savella treatment arms than placebo: 9% of patients in the placebo arm versus 14% in both the Savella 100 mg/day and the Savella 200 mg/day treatment arms. Among fibromyalgia patients who were hypertensive at baseline, more patients in the Savella treatment arms had a >15 mmHg increase in SBP than placebo at the end of the study: 1% of patients in the placebo arm versus 7% in the Savella 100 mg/day and 2% in the Savella 200 mg/day treatment arms. Similarly, more patients who were hypertensive at baseline and were treated with Savella had DBP increases > 10 mmHg than placebo at the end of study: 3% of patients in the placebo arm versus 8% in the Savella 100 mg/day and 6% in the Savella 200 mg/day treatment arms. Sustained increases in SBP (increase of ≥ 15 mmHg on three consecutive post-baseline visits) occurred in 2% of placebo patients versus 9% of patients receiving Savella 100 mg/day and 6% of patients receiving Savella 200 mg/day. Sustained increases in DBP (increase of ≥ 10 mmHg on 3 consecutive post-baseline visits) occurred in 4% of patients receiving placebo versus 13% of patients receiving Savella 100 mg/day and 10% of patients receiving Savella 200 mg/day. Sustained increases in blood pressure could have adverse consequences. Cases of elevated blood pressure requiring immediate treatment have been reported. Concomitant use of Savella with drugs that increase blood pressure and pulse has not been evaluated and such combinations should be used with caution *[see Drug Interactions]*. Effects of Savella on blood pressure in patients with significant hypertension or cardiac disease have not been systematically evaluated. Savella should be used with caution in these patients. Blood pressure should be measured prior to initiating treatment and periodically measured throughout Savella treatment. Pre-existing hypertension and other cardiovascular disease should be treated before starting therapy with Savella. For patients who experience a sustained increase in blood pressure while receiving Savella, either dose reduction or discontinuation should be considered. **Effects on Heart Rate-**SNRIs have been associated with reports of increase in heart rate. In clinical trials, relative to placebo, Savella treatment was associated with mean increases in pulse rate of approximately 7 to 8 beats per minute [*see Adverse Reactions*]. Increases in pulse ≥ 20 bpm occurred more frequently in Savella-treated patients when compared to placebo: 0.3% in the placebo arm versus 8% in the Savella 100 mg/day and 8% in the 200 mg/day treatment arms. The effect of Savella on heart rate did not appear to increase with increasing dose. Savella has not been systematically evaluated in patients with a cardiac rhythm disorder. Heart rate should be measured prior to initiating treatment and periodically measured throughout Savella treatment. Pre-existing tachyarrhythmias and other cardiac disease should be treated before starting therapy with Savella. For patients who experience a sustained increase in heart rate while receiving Savella, either dose reduction or discontinuation should be considered. **Seizures-**Savella has not been systematically evaluated in patients with a seizure disorder. In clinical trials evaluating Savella in patients with fibromyalgia, seizures/convulsions have not been reported. However, seizures have been reported infrequently in patients treated with Savella for disorders other than fibromyalgia. Savella should be prescribed with care in patients with a history of a seizure disorder. **Hepatotoxicity-**In the placebo-controlled fibromyalgia trials, increases in the number of patients treated with Savella with mild elevations of ALT or AST (1-3 times the upper limit of normal, ULN) were observed. Increases in ALT were more frequently observed in the patients treated with Savella 100 mg/day (6%) and Savella 200 mg/day (7%), compared to the patients treated with placebo (3%). One patient receiving Savella 100 mg/day (0.2%) had an increase in ALT greater than 5 times the upper limit of normal but did not exceed 10 times the upper limit of normal. Increases in AST were more frequently observed in the patients treated with Savella 100 mg/day (3%) and Savella 200 mg/day (5%) compared to the patients treated with placebo (2%). The increases of bilirubin observed in the fibromyalgia clinical trials were not clinically significant. No case met the criteria of elevated ALT > 3x ULN and associated with an increase in bilirubin ≥ 2x ULN. There have been cases of increased liver enzymes and reports of severe liver injury, including fulminant hepatitis with milnacipran from foreign postmarketing experience. In the cases of severe liver injury there were significant underlying clinical conditions and/or the use of multiple concomitant medications. Because of underreporting, it is impossible to provide an accurate estimate of the true incidence of these reactions. Savella should be discontinued in patients who develop jaundice or other evidence of liver dysfunction. Treatment with Savella should not be resumed unless another cause can be established. Savella should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease. **Discontinuation of Treatment with Savella-**Withdrawal symptoms have been observed in clinical trials following discontinuation of milnacipran, as with other SNRIs and SSRIs. During marketing of milnacipran, and other SNRIs and SSRIs, there have been spontaneous reports of adverse events indicative of withdrawal and physical dependence occurring upon discontinuation of these drugs, particularly when discontinuation is abrupt. The adverse events include the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe. Patients should be monitored for these symptoms when discontinuing treatment with Savella. Savella should be tapered and not abruptly discontinued after extended use. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate *[see Dosage and Administration]*. **Hyponatremia-**Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Savella. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower

than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SNRIs, SSRIs, or Savella. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk [*see Geriatric Use*]. Discontinuation of Savella should be considered in patients with symptomatic hyponatremia. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. **Abnormal Bleeding-**SSRIs and SNRIs, including Savella, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Savella and NSAIDs, aspirin, or other drugs that affect coagulation. **Activation of Mania-**No activation of mania or hypomania was reported in the clinical trials evaluating effects of Savella in patients with fibromyalgia. However those clinical trials excluded patients with current major depressive episode. Activation of mania and hypomania have been reported in patients with mood disorders who were treated with other similar drugs for major depressive disorder. As with these other agents, Savella should be used cautiously in patients with a history of mania. **Patients with a History of Dysuria-**Because of their noradrenergic effect, SNRIs including Savella, can affect urethral resistance and micturition. In the controlled fibromyalgia trials, dysuria occurred more frequently in patients treated with Savella (1%) than in placebo-treated patients (0.5%). Caution is advised in use of Savella in patients with a history of dysuria, notably in male patients with prostatic hypertrophy, prostatitis, and other lower urinary tract obstructive disorders. Male patients are more prone to genitourinary adverse effects, such as dysuria or urinary retention, and may experience testicular pain or ejaculation disorders. **Controlled Narrow-Angle Glaucoma-**Mydriasis has been reported in association with SNRIs and Savella; therefore, Savella should be used cautiously in patients with controlled narrow-angle glaucoma. Do not use Savella in patients with Uncontrolled Narrow-Angle Glaucoma *[see Contraindications]*. **Concomitant Use with Alcohol-**In clinical trials, more patients treated with Savella developed elevated transaminases than did placebo-treated patients [see *Warnings and Precautions*]. Because it is possible that milnacipran may aggravate pre-existing liver disease, Savella should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

ADVERSE REACTIONS: Clinical Trial Data Sources-Savella was evaluated in three double-blind placebo-controlled trials involving 2209 fibromyalgia patients (1557 patients treated with Savella and 652 patients treated with placebo) for a treatment period up to 29 weeks. The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Adverse Reactions Leading to Discontinuation-**In placebo-controlled trials in patients with fibromyalgia, 23% of patients treated with Savella 100 mg/day, 26% of patients treated with Savella 200 mg/day discontinued prematurely due to adverse reactions, compared to 12% of patients treated with placebo. The adverse reactions that led to withdrawal in ≥ 1% of patients in the Savella treatment group and with an incidence rate greater than that in the placebo treatment group were nausea (milnacipran 6%, placebo 1%), palpitations (milnacipran 3%, placebo 1%), headache (milnacipran 2%, placebo 0%), constipation (milnacipran 1%, placebo 0%), heart rate increased (milnacipran 1%, placebo 0%), hyperhidrosis (milnacipran 1%, placebo 0%), vomiting (milnacipran 1%, placebo 0%), and dizziness (milnacipran 1% and placebo 0.5%). Discontinuation due to adverse reactions was generally more common among patients treated with Savella 200 mg/day compared to Savella 100 mg/day. **Most Common Adverse Reactions-**In the placebo-controlled fibromyalgia patient trials the most frequently occurring adverse reaction in clinical trials was nausea. The most common adverse reactions (incidence ≥ 5% and twice placebo) in patients treated with Savella were constipation, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth, and hypertension. Table 2 lists all adverse reactions that occurred in at least 2% of patients treated with Savella at either 100 or 200 mg/day and at an incidence greater than that of placebo. Table 2 in the full PI shows the incidence of common adverse reactions that occurred in at least 2% of patients treated with Savella at either 100 or 200 mg/day and at an incidence greater than that of placebo. **Cardiac disorders:** Palpitations, Tachycardia; **Eye Disorders:** Vision blurred; **Gastrointestinal Disorders:** Nausea, Constipation, Vomiting, Dry mouth, Abdominal pain; **General Disorders:** Chest pain, Chills, Chest discomfort; **Infections:** Upper respiratory tract infection; **Investigations:** Heart rate increased, Blood pressure increased; **Metabolism and Nutrition Disorders:** Decreased appetite; **Nervous System Disorders:** Headache, Dizziness, Migraine, Paresthesia, Tremor, Hypoesthesia, Tension headache; **Psychiatric Disorders:** Insomnia, Anxiety; **Respiratory Disorders:** Dyspnea; **Skin Disorders:** Hyperhidrosis, Rash, Pruitius; **Vascular Disorders:** Hot flush, Hypertension, Flushing. **Weight Changes-**In placebo-controlled fibromyalgia clinical trials, patients treated with Savella for up to 3 months experienced a mean weight loss of approximately 0.8 kg in both the Savella 100 mg/day and the Savella 200 mg/day treatment groups, compared with a mean weight loss of approximately 0.2 kg in placebo-treated patients. **Genitourinary Adverse Reactions in Males-**In the placebo-controlled fibromyalgia studies, the following treatment-emergent adverse reactions related to the genitourinary system were observed in at least 2% of male patients treated with Savella, and occurred at a rate greater than in placebo-treated male patients: dysuria, ejaculation disorder, erectile dysfunction, ejaculation failure, libido decreased, prostatitis, scrotal pain, testicular pain, testicular swelling, urinary hesitation, urinary retention, urethral pain, and urine flow decreased. **Other Adverse Reactions Observed During Clinical Trials of Savella in Fibromyalgia-**Following is a list of frequent (those occurring on one or more occasions in at least 1/100 patients) treatment-emergent adverse reactions reported from 1824 fibromyalgia patients treated with Savella for periods up to 68 weeks. The listing does not include those events already listed in Table 2, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. Adverse reactions are categorized by body system and listed in order of decreasing frequency. Adverse reactions of major clinical importance are described in the *Warnings and Precautions* section. Gastrointestinal Disorders – diarrhea, dyspepsia, gastroesophageal reflux disease, flatulence, abdominal distension; General Disorders – fatigue, peripheral edema, irritability, pyrexia; Infections – urinary tract infection, cystitis; Injury, Poisoning, and Procedural Complications – contusion, fall; Investigations – weight decreased or increased; Metabolism and Nutrition Disorders – hypercholesterolemia; Nervous System Disorders – somnolence, dysgeusia; Psychiatric Disorders – depression, stress; Skin Disorders – night sweats. **Postmarketing Spontaneous Reports-**The following additional adverse reactions have been identified from spontaneous reports of Savella received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to Savella. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include: Blood and Lymphatic System Disorders – leukopenia, neutropenia, thrombocytopenia; Cardiac Disorders – supraventricular tachycardia; Eye Disorders – accommodation disorder; Endocrine Disorders – hyperprolactinemia; Hepatobiliary Disorders – hepatitis; Metabolism and Nutrition Disorders – anorexia, hyponatremia; Musculoskeletal and Connective Tissue Disorders – rhabdomyolysis; Nervous System Disorders – convulsions (including grand mal), loss of consciousness, Parkinsonism; Psychiatric Disorders – delirium, hallucination; Renal and Urinary Disorders – acute renal failure; Reproductive System and Breast Disorders – galactorrhea; Skin Disorders – erythema multiforme, Stevens Johnson syndrome; Vascular Disorders – hypertensive crisis.

DRUG INTERACTIONS: Milnacipran undergoes minimal CYP450-related metabolism, with the majority of the dose excreted unchanged in urine (55%), and has a low binding to plasma proteins (13%). In vitro and in vivo studies showed that Savella is unlikely to be involved in clinically significant pharmacokinetic drug interactions *[see Pharmacokinetics in Special Populations]*. **Monoamine Oxidase Inhibitors** - *[See Contraindications]* **Serotonergic Drugs** - Due to the mechanism of action of SNRIs and SSRIs, including Savella, and the potential for serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)–like reactions, caution is advised when Savella is co-administered with other drugs that may affect the serotonergic neurotransmitter systems. This includes drugs such as triptans, lithium, tryptophan, antipsychotics and dopamine antagonists. Co-administration of Savella with other inhibitors of serotonin re-uptake may result in hypertension and coronary artery vasoconstriction, through additive serotonergic effects. Concomitant use of Savella with other SSRIs, SNRIs, or tryptophan is not recommended [*see Warnings and Precautions*]. **Triptans** - There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Savella with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions*]. **Catecholamines** - Savella inhibits the reuptake of norepinephrine. Therefore concomitant use of Savella with epinephrine and norepinephrine may be associated with paroxysmal hypertension and possible arrhythmia [*see Warnings and Precautions – Effects on Blood Pressure* and *Effects on Heart Rate*]. **CNS-active drugs** - Given the primary CNS effects of Savella, caution should be used when it is taken in combination with other centrally acting drugs, including those with a similar mechanism of action. *Clomipramine:* In a drug-drug interaction study, an increase in euphoria and postural hypotension was observed in patients who switched from clomipramine to Savella. **Clinically Important Interactions with Select Cardiovascular Agents** - Digoxin: Use of Savella concomitantly with digoxin may be associated with potentiation of adverse hemodynamic effects. Postural hypotension and tachycardia have been reported in combination therapy with intravenously administered digoxin (1 mg). Co-administration of Savella and intravenous digoxin should be avoided [*see Warnings and Precautions*]. *Clonidine:* Because Savella inhibits norepinephrine reuptake, co-administration with clonidine may inhibit clonidine's anti-hypertensive effect.

USE IN SPECIFIC POPULATIONS: Pregnancy-Pregnancy Category C. Milnacipran increased the incidence of dead fetuses in utero in rats at doses of 5 mg/kg/day (0.25 times the MRHD on a mg/m^2 basis). Administration of milnacipran to mice and rabbits during the period of organogenesis did not result in embryotoxicity or teratogenicity at doses up to 125 mg/kg/day in mice (3 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis) and up to 60 mg/kg/day in rabbits (6 times the MRHD of 200 mg/day on a mg/m^2 basis). In rabbits, the incidence of the skeletal variation, extra single rib, was increased following administration of milnacipran at 15 mg/kg/day during the period of organogenesis. There are no adequate and well-controlled studies in pregnant women. Savella should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To provide information regarding the exposure to Savella during pregnancy, physicians are advised to recommend that pregnant patients taking Savella enroll in the Savella Pregnancy Registry. Enrollment is voluntary and may be initiated by pregnant patients or their healthcare providers by contacting the registry at 1-877-643-3010 or by email at **registries@kendle.com**. Data forms may also be downloaded from the registry website at **www.savellapregnancyregistry.com**. Nonteratogenic Effects: Neonates exposed to dual reuptake inhibitors of serotonin and norepinephrine, or selective serotonin reuptake inhibitors late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions*]. In rats, a decrease in pup body weight and viability on postpartum day 4 were observed when milnacipran, at a dose of 5 mg/kg/day (approximately 0.2 times the MRHD on a mg/m^2 basis), was administered orally to rats during late gestation. The no-effect dose for maternal and offspring toxicity was 2.5 mg/kg/day (approximately 0.1 times the MRHD on a mg/m^2 basis). **Labor and Delivery-**The effect of milnacipran on labor and delivery is unknown. The use of Savella during labor and delivery is not recommended. **Nursing Mothers-**There are no adequate and well-controlled studies in nursing mothers. It is not known if milnacipran is excreted in human milk. Studies in animals have shown that milnacipran or its metabolites are excreted in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from milnacipran, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. Because the safety of Savella in infants is not known, nursing while on Savella is not recommended. **Pediatric Use-**Safety and effectiveness of Savella in a fibromyalgia pediatric population below the age of 17 have not been established [*see Box Warning* and *Warnings and Precautions*]. The use of Savella is not recommended in pediatric patients. **Geriatric Use-**In controlled clinical studies of Savella, 402 patients were 60 years or older, and no overall differences in safety and efficacy were observed between these patients and younger patients. In view of the predominant excretion of unchanged milnacipran via kidneys and the expected decrease in renal function with age renal function should be considered prior to use of Savella in the elderly [*see Dosage and Administration*]. SNRIs, SSRIs, and Savella, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Warnings and Precautions*].

DRUG ABUSE AND DEPENDENCE: Controlled Substance-Milnacipran is not a controlled substance. **Abuse-**Milnacipran did not produce behavioral signs indicative of abuse potential in animal or human studies. **Dependence-**Milnacipran produces physical dependence, as evidenced by the emergence of withdrawal symptoms following drug discontinuation, similar to other SNRIs and SSRIs. These withdrawal symptoms can be severe. Thus, Savella should be tapered and not abruptly discontinued after extended use [see *Discontinuation of Treatment with Savella*].

OVERDOSAGE: There is limited clinical experience with Savella overdose in humans. In clinical trials, cases of acute ingestions up to 1000 mg, alone or in combination with other drugs, were reported with none being fatal. In postmarketing experience, fatal outcomes have been reported for acute overdoses primarily involving multiple drugs but also with Savella only. The most common signs and symptoms included increased blood pressure, cardio-respiratory arrest, changes in the level of consciousness (ranging from somnolence to coma), confusional state, dizziness, and increased hepatic enzymes. **Management of Overdose-**There is no specific antidote to Savella, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug. An adequate airway, oxygenation, and ventilation should be assured and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Because there is no specific antidote for Savella, symptomatic care and treatment with gastric lavage and activated charcoal should be considered as soon as possible for patients who experience a Savella overdose. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial. In managing overdose, the possibility of multiple drug involvement should be considered. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

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FEATURES

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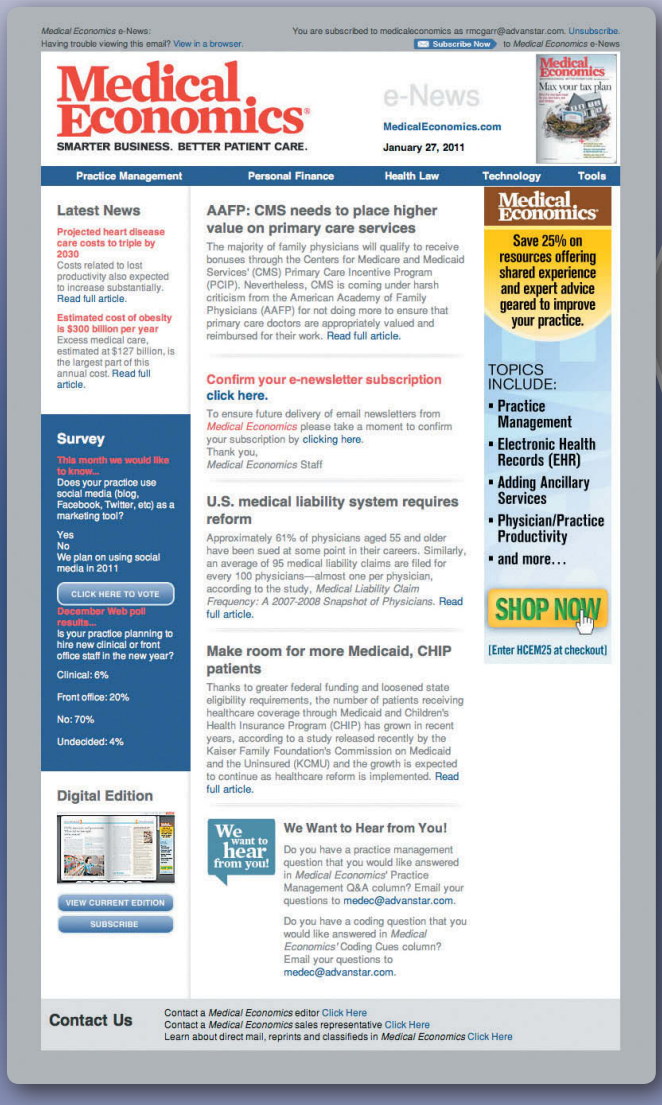

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Latest News

Projected heart disease care costs to triple by 2030
Costs related to lost productivity also expected to increase substantially. Read full article.

Estimated cost of obesity is $300 billion per year
Excess medical care, estimated at $127 billion, is the largest part of this annual cost. Read full article.

Survey

This month we would like to know...
Does your practice use social media (blog, Facebook, Twitter, etc) as a marketing tool?

Yes
No
We plan on using social media in 2011

CLICK HERE TO VOTE

December Web poll results...
Is your practice planning to hire new clinical or front office staff in the new year?

Clinical: 6%
Front office: 20%
No: 70%
Undecided: 4%

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AAFP: CMS needs to place higher value on primary care services

The majority of family physicians will qualify to receive bonuses through the Centers for Medicare and Medicaid Services' (CMS) Primary Care Incentive Program (PCIP). Nevertheless, CMS is coming under harsh criticism from the American Academy of Family Physicians (AAFP) for not doing more to ensure that primary care doctors are appropriately valued and reimbursed for their work. Read full article.

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U.S. medical liability system requires reform

Approximately 61% of physicians aged 55 and older have been sued at some point in their careers. Similarly, an average of 95 medical liability claims are filed for every 100 physicians—almost one per physician, according to the study, *Medical Liability Claim Frequency: A 2007-2008 Snapshot of Physicians.* Read full article.

Make room for more Medicaid, CHIP patients

Thanks to greater federal funding and loosened state eligibility requirements, the number of patients receiving healthcare coverage through Medicaid and Children's Health Insurance Program (CHIP) has grown in recent years, according to a study released recently by the Kaiser Family Foundation's Commission on Medicaid and the Uninsured (KCMU) and the growth is expected to continue as healthcare reform is implemented. Read full article.

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Multitasking: Boon or bane

By **JUDY BEE**

Do you have a busy signal problem? Most practices don't because they have an automatic voice mail if the phone call is not answered after a specified number of rings. So this solves the problem, right? Not really.

Here's the issue: You may not have enough ears to answer the volume of calls you have. If your staff cannot get to the calls the first time, how will they have time to call back (a disappointed caller) while they are supposed to be available to answer the new incoming calls?

Two ears can generally handle two lines simultaneously and give acceptable service. Adding more lines into infinity with the voice mail system gives you the opportunity to irritate more callers simultaneously. It also accounts for front desk/phone burnout and staff turnover.

Technology is great, but it doesn't substitute for having enough qualified staff with "do-able" jobs. Study the types of calls answered, the volume per hour, and the staffing availability to answer before you add more access. There may be other solutions that won't kill the phone staff or turn off good patients.

THESE DAYS, MANY PEOPLE THINK THAT THEY CAN MULTITASK WHILE USING TECHNOLOGY. I AM NOT CONVINCED.

The doctor who is knee-deep in a complex medical case and stops to review emails, text messages, or take phone calls might think that he or she is an all-star multitasker, but this scenario should be avoided whenever possible. Distractions from the case at hand jeopardize the outcome. Even though it's okay to allow a reasonable amount of personal calls for staff, a team member should never be distracted when working with patients and physicians.

These days, many people think that they can multitask while using the computer, driving, and while working. I am not convinced (and using technology while driving is downright unsafe—to the user and others on the road). I recommend that pagers, phones, iPods, or other electronic gear be stored away from staff work areas, placed on silent mode, and accessed only at breaks or mealtimes. Some practices provide a laptop that is not on the practice network for the staff to use while on break.

Technology is an amazing thing, and a well-run practice should embrace it. However, just because you can use technology to cure every ill doesn't mean you always should.

The author is a Medical Economics *editorial consultant and a medical practice management consultant with the Practice Performance Group, La Jolla, California. Read her blog at: MedicalEconomics.com/jbee. Send your feedback to medec@advanstar.com.*

The Pong Principle What happens when a doctor asks a patient for advice? Thomas Ellis, MD, the Grand Prize winner of the 2011 Doctors' Writing Contest shares his experience, when a patient asks what she can do for him. She serves up some home-spun wisdom that forever changes the way that Ellis practices medicine and communicates with his family and patients. **page 22**

DOs AND DON'Ts WITH MIDLEVELS

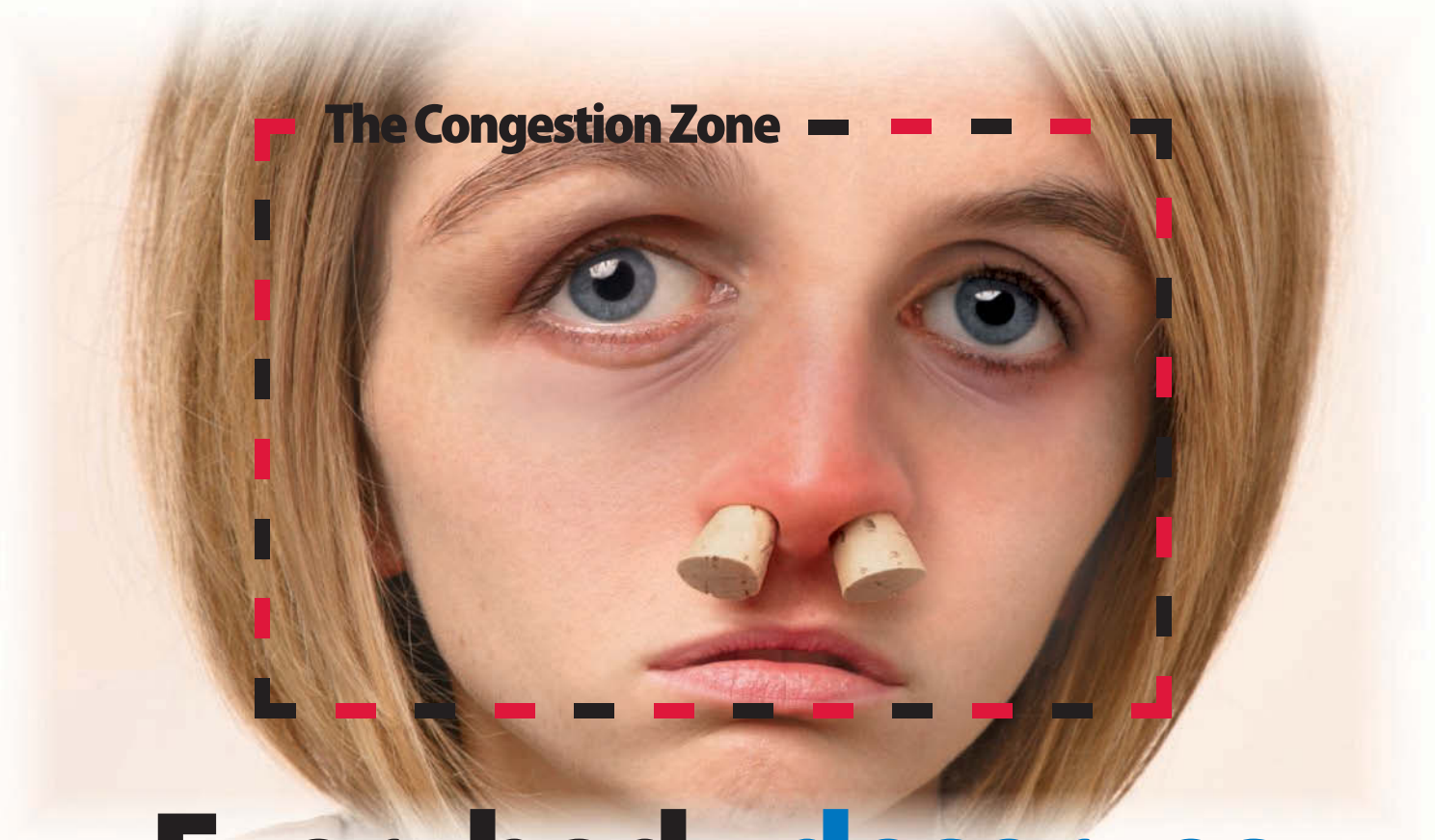
Are you thinking of adding midlevel providers to your practice? If so, benefit from a colleague's experience so that new physician assistants and/or nurse practitioners affect the practice's livelihood, patient access, and patient satisfaction in a positive way. **page 38**

BADMOUTHING CAN BITE YOU

Making negative comments about another doctor could haunt you—and him or her—in several ways. Read why, and find out what to do if another physician makes negative comments about you, in the Malpractice Consult column. **page 70**

NEW OBSERVATION CODES

The 2011 CPT codebook contains three new codes for subsequent outpatient services. Learn how to use them to maximize your reimbursements in the Coding Cues column. Also, learn more about the delayed implementation of CMS PECOS. **page 72**



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'A tenacious advocate'

By **LOIS A. BOWERS**, *Managing Editor*


Steven I. Kern, JD

The legal world lost a great cross-examiner when Steven I. Kern, JD, passed away January 10. As a health law attorney representing numerous physicians, medical societies, and others, Steve was "a tenacious advocate," in the words of one of his sons, Brian S. Kern, JD.

Steve was a tenacious advocate for physicians as a writer and editorial consultant for *Medical Economics*, too. We—and you—always could count on him to address legal and malpractice-related issues of vital importance to you—and to bring his knowledgeable perspective to those issues.

A case in point is a Malpractice Consult column he wrote about the legal ramifications facing you and your colleagues when you apologize for medical errors. Examining two recently published studies, the column appeared in our September 24, 2010, issue. Taken at face value, the results of one of the studies seemed to support apology and disclosure policies as not only ethical requirements but also as a means to reduce the costs of malpractice. As Steve pointed out, however, the rather unique environment of the study setting, as well as the results of the other research reviewed, demonstrated that "physicians continue to face serious exposure if they apologize or even express sympathy for an unexpected adverse result."

The last Malpractice Consult column Steve wrote appeared in our December 3, 2010, issue. We'll miss his insights and are thankful that his legacy lives on in so many ways, including the online archives of *Medical Economics*. To read the contributions he made to *Medical Economics* via feature articles and Malpractice Consult columns, visit MedicalEconomics.com/kern. To read the blog entries he contributed to ModernMedicine.com, a Web site including content from *Medical Economics* and other Advanstar healthcare brands, visit MedicalEconomics.com/kernblog.

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Talk Back

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Required reading

I just read the editorial in a recent issue ("Hope must be part of the formula," [by Gregory A. Hood, MD], January 10 issue). Dr. Hood is *exactly correct*.

This article should be required reading for every member of Congress and every Centers for Medicare and Medicaid Services bureaucrat. I hope it will be circulated as widely as possible.

JOHN MACKEL, MD, MHSA
Cape Girardeau, Missouri

DR. GREGORY A. HOOD'S "ARTICLE SHOULD BE REQUIRED READING FOR EVERY MEMBER OF CONGRESS AND EVERY [CMS] BUREAUCRAT."

EHRs miss the mark

The article by David O'Dell, MD, JD, MBA, MHSM, speaks hopefully of electronic health records (EHRs) benefits ("Avoiding medical negligence claims," January 10 issue). However, in my review of charts where medical malpractice is alleged, I am disappointed at how frequently an EHR will "hang" a physician as well as exonerate him or her.

For example, checking the box on an EHR template for "all other systems reviewed and negative" when the patient has a glass eye, amputation, psoriasis, or any number of readily notable but undocumented abnormalities, indicates an evaluation lacking in rigor and believability. Conversely, an EHR may contain prompts for symptoms associated with a presenting complaint, and those prompts remain blank.

An EHR will never produce the "color" that shows the true nature of a physician-patient interaction. The absence of an actual personal note, either typed, dictated, or handwritten, can be a boon to a plaintiff.

CHARLES A. PILCHER, MD, FACEP
Kirkland, Washington

A shared experience

Wow, I feel as if I could have written the article ("The good, the bad, and the ugly," [by Russell Bacak, MD], December 3 issue) as our stories run pretty parallel.

The only difference in my case is that I skipped the partnership, going straight from a group of 10 to a solo practice (with 6 months of hospitalist work to pay bills while I set up my own practice from scratch). I distinctly remember having conversations in medical school and residency about future plans, and I always said that I'd never be doing the solo practice thing.

Now I am 10 years out of residency and 3 years into my own practice, and I absolutely love it. I have actually found that I enjoy the business side of it, now that it is my business and not just something that I have to go along with.

In answer to your pondering on hiring a physician assistant, I have a suggestion. I hired a nurse practitioner (NP) about 2 years ago, and it has been a fantastic move. I now can take vacations and other days off without worrying about the practice being nonproductive.

My uncle was a solo general practitioner, and I frequently discuss ideas with him. He also thought NPs were a great addition, as long as you hire the right one. I found an NP to whom the patients really respond, and she has built her own patient panel. She can also take the overload from me or run the practice when I'm gone.

If you can find the right person, he or she can be a very helpful addition. I appreciate seeing your article. Maybe it will embolden other people suffering through bad work situations to go "the old-fashioned way." As one of my mentors always said: "Life is too short to not love what you are doing."

DAVID KEUHN, MD
Marshall, Missouri

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Barry B. Cepelewicz, MD, JD HEALTH LAW ATTORNEY

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Are you helping to keep it away?

Despite medical guidelines, millions of at-risk patients remain unprotected by aspirin.[1,2] Aspirin can reduce the risk of recurrent MI by 30%.[3,4] Counsel your patients today.

Say aspirin. Help save lives.

BAYER

MI=myocardial infarction.

References: 1. Ajani UA, Ford ES, Greenland KJ, Giles WH, Mokdad AH. Aspirin use among US adults, behavioral risk factor surveillance system. *Am J Prev Med*. 2006;30(1):74-77. **2.** Cardiovascular disease statistics. American Heart Association Web site. http://www.americanheart.org/presenter.jhtml?identifier=4478. Accessed May 14, 2010. **3.** Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. *Arch Intern Med*. 2002;162:2197-2202. **4.** Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009; 373(9678):1849-1860.

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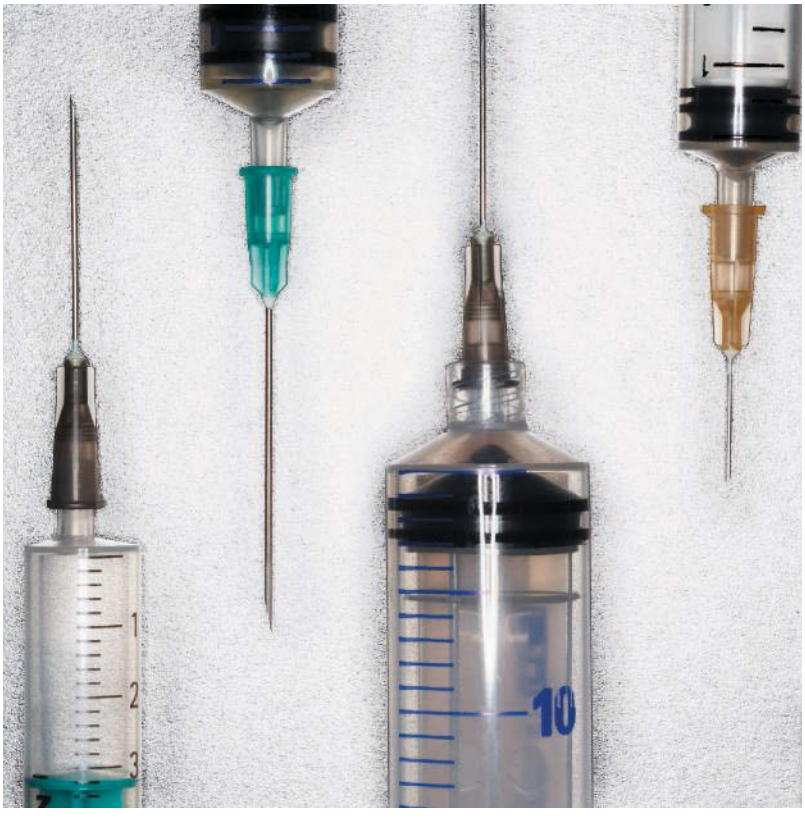

REIMBURSEMENT

AAFP criticizes CMS fee schedule

The Centers for Medicare and Medicaid Services (CMS) is coming under harsh criticism from the American Academy of Family Physicians (AAFP) for not doing more to ensure that primary care doctors are appropriately valued and reimbursed.

Lori Heim, MD, AAFP board chairwoman, wrote in a letter to CMS that primary care doctors are being sold short for the work involved in counseling patients for combination vaccinations, because the relative value units are taken from old CPT coding structures that don't reflect the work associated with counseling. The American Medical Association/Specialty Society Relative Value Update Committee has recommended higher values to these codes.

Three new CPT codes allow primary care doctors to be reimbursed for subsequent observation services in a facility setting but do not go far enough to reflect the recent increase in the need for such services, Heim writes.

MANAGED CARE

STUDY SHOWS LITTLE INSURER COMPETITION

Most commercial health insurance markets in the United States are dominated by one or two health insurers, according to an updated analysis released by the American Medical Association.

The 2010 edition of "Competition in Health Insurance: A Comprehensive Study of U.S. Markets" found that 99% of health insurance markets in the United States are "highly concentrated," based on the 1997 U.S. Department of Justice and Federal Trade Commission Horizontal Merger Guidelines.

In 48% of metropolitan statistical areas, at least one insurer had a market share of 50% or more. In 60% of the areas, the two largest insurers had a combined market share of 70% or greater. In 24 states, the two largest insurers had a combined market share of 70% or more.

PAY FOR PERFORMANCE

QUALITY ORGANIZATION UPDATES PCMH GUIDE

The healthcare quality organization that sets the health insurance industry-accepted criteria for practices being recognized as a Patient-Centered Medical Home (PCMH) released updated guidelines on January 31.

The new criteria from the National Committee for Quality Assurance (NCQA) call on medical practices to be more patient-centered and reinforce federal meaningful use incentives for primary care practices to adopt health information technology.

Practices earn points for meeting PCMH criteria, with more points equating to a higher level of NCQA PCMH recognition. The new version of the recognition directs practices to organize care according to patients' preferences and needs. Standards emphasize access to care during and after office hours and managing care in collaboration with patients and families. Other changes include providing services in patients' preferred languages and helping patients with self-care.

GETTY IMAGES; RADIUS IMAGES

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

OA pain relief patients can stay with[1]

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

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

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

Cardiovascular Risk

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

Gastrointestinal Risk

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

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

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

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

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

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

AstraZeneca

Vimovo™

naproxen/esomeprazole magnesium

delayed-release tablets

BRIEF SUMMARY of Prescribing Information.

Cardiovascular Risk

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

Gastrointestinal Risk

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis

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

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

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

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

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

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

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

CONTRAINDICATIONS

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

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

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

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

WARNINGS AND PRECAUTIONS

Cardiovascular Thrombotic Events

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

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

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

Hypertension

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

Congestive Heart Failure and Edema

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

Gastrointestinal Effects — Risk of Ulceration, Bleeding, and Perforation

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

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

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

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

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

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

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

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

Active Bleeding

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

Renal Effects

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

Advanced Renal Disease

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

Anaphylactoid Reactions

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

Skin Reactions

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

Pregnancy

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

Hepatic Effects

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

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

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

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

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

Hematological Effects

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

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

Preexisting Asthma

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

Concomitant NSAID Use

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

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

Corticosteroid Treatment

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

Bone Fracture

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

Masking of Inflammation and Fever

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

Laboratory Tests

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

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

ADVERSE REACTIONS

Clinical Studies Experience

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

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

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

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

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

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

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

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

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

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

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

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

Postmarketing Experience

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

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

DRUG INTERACTIONS

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

ACE-inhibitors

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

Aspirin

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

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

Cholestyramine

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

Diuretics

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

Lithium

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

Methotrexate

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

Anticoagulants

Naproxen decreases platelet aggregation and may prolong bleeding time.

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

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

Selective Serotonin Reuptake Inhibitors (SSRIs)

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

Other Information Concerning Drug Interactions

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

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

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

Drug/Laboratory Test Interaction

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

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

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

Interactions Related to Absorption

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

Antiretroviral Agents

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

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

Effects on Hepatic Metabolism/Cytochrome P-450 Pathways

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

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

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

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

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

Other Pharmacokinetic-based Interactions

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

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

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

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

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

Labor and Delivery

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

Nursing Mothers

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

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

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

Pediatric Use

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

Geriatric Use

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

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

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

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

Hepatic Insufficiency

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

Renal Insufficiency

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

OVERDOSAGE

There is no clinical data on overdosage with VIMOVO.

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

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

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

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

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

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REGULATION

SENATE APPROVES REPEAL OF TAX REPORTING PROVISION

The U.S. Senate passed an amendment to the healthcare reform legislation to repeal the requirement for small businesses, including physician practices, to file an IRS form 1099 for each vendor from whom they make purchases of $600 or more. The House of Representatives had not voted on the amendment as of mid-February.

The American Medical Association applauded the Senate's vote. AMA President Cecil B. Wilson, MD, says it is estimated that paperwork already takes up as much as a third of a physician's workday, which is "time that could be better spent with patients," and that the requirement would have only increased that burden.

REFORM

ACP: CONTROL COSTS WITH BETTER VALUE

The ability to control healthcare costs depends on providing the best value of care, according to the American College of Physicians (ACP) clinical guidelines committee.

In an attempt to develop clinical practice guidelines, the committee plans to address the possibility of controlling costs while maintaining or improving quality of care, as well as how clinicians can contribute to the delivery of high-value healthcare. A recent report published in *Annals of Internal Medicine* provides recommendations for determining value.

Physicians should use three assessment tools, the committee says. First is to determine the benefits, harms, and costs of the care. Physicians should weigh the potential improvements in the patient's health and quality of life, as well as the potential problems that can arise from the care and whether a test or intervention is necessary.

The second step is to determine costs, taking into consideration the costs of the care itself as well as those that can arise later as a result of the intervention. The final step in assessing value is to use cost-effectiveness analysis, which involves comparing possible treatment strategies and the costs associated with them.

FRAUD

HIGH-RISK PATIENTS TO FALL UNDER MORE SCRUTINY

The government is continuing its commitment to stopping fraud by instituting more advanced screening and prevention techniques as part of the Patient Protection and Affordable Care Act.

Providers wishing to participate in Medicare, Medicaid, and Children's Health Insurance Program will endure more detailed screening, and any enrollees who are identified as high risk for fraud will be scrutinized more closely. A new enrollment process requires states to screen enrollees for past fraud, and any identified offenders will be ineligible to participate.

New software will allow Medicare and states to identify trends among providers and suppliers that could be evidence of fraudulent activity. In addition, the government can temporarily suspend payment to any provider thought to be engaging in fraudulent activity once there is a legitimate allegation.

GETTY IMAGES: PAWEL GAUL

GOVERNMENT PAYERS

MAKE ROOM FOR MORE MEDICAID PATIENTS

Thanks to greater federal funding and loosened state eligibility requirements, the number of patients receiving healthcare coverage through Medicaid and Children's Health Insurance Program (CHIP) has grown in recent years, according to a study released recently by the Kaiser Family Foundation's Commission on Medicaid and the Uninsured (KCMU). The growth is expected to continue as healthcare reform is implemented.

The study found that in 2010, 49 states made changes to their eligibility rules and enrollment procedures to make it easier for residents to enroll in these programs. "Millions of American families have turned to Medicaid and CHIP as incomes have declined after losing jobs and the health insurance that often goes with them," says Diane Rowland, KCMU executive director.

Medicaid enrollment is expected to increase even further in 2014 when, under the Patient Protection and Affordable Care Act of 2010, income eligibility will be expanded to 133% of the federal poverty level, and states will be permitted to enroll nondisabled, nonpregnant adults without dependent children without a waiver. However, the report predicted that the majority of uninsured, low-income adults will not be eligible for Medicaid until 2014.

WORKFORCE

MORE PHYSICIANS DOESN'T INCREASE PATIENT SATISFACTION

Medicare patients living in areas with a larger supply of physicians were no more satisfied with their care than patients living in regions with a smaller physician supply, according to a study by Dartmouth College investigators and the Centers for Medicare and Medicaid Services and published in the February issue of *Health Affairs*.

The study also found that seniors living in areas with a large supply of physicians were no more likely to report having a primary care physician as their personal doctor. In addition, no significant differences were found in numbers of visits to their personal physician in the previous year, amount of time spent with a physician, or access to tests or specialists.

Researchers surveyed 2,515 Medicare patients about their perceptions of access and satisfaction with their health care, and directly compared the relationship between physicians per capita in designated geographic areas and respondents' ratings of the care they received.

While physician supply varied almost 70% across the country, the authors found little evidence that increasing physician supply alone will resolve the problems associated with a physician shortage.

COMPENSATION

DOW JONES SUES TO OPEN MEDICARE DATABASE

The publisher of *The Wall Street Journal* filed court papers in late January to overturn a 31-year-old court injunction that blocks public access to information in the Medicare physician payment database. The filing by Dow Jones & Company, in the U.S. District Court for the Middle District of Florida, seeks to overturn an injunction obtained by the American Medical Association in 1979. The injunction prevents the disclosure of reimbursements for individual doctors from the Medicare program.

Prior to the suit, the *Journal* had requested the reimbursement data for an article series on Medicare spending, but received only a subset of data once it agreed not to disclose physician identities.

PATIENT CARE

MICHIGAN PCMHs SHOW POSITIVE RESULTS

In the first six months of 2010, the Patient-Centered Medical Home program of Blue Cross Blue Shield of Michigan (BCBSM) showed measurable results in improved quality and cost management, according to the health insurer.

Analysis of January to June 2010 claims data show PCMH practices have a 7.4% lower rate of adult high-tech radiology usage than non-PCMH practices, and a per member per month cost that is 4.3% lower.

PCMH practices have a 2.8% lower rate of adult emergency department (ED) visits than non-PCMH practices and a 7% lower rate of pediatric ED visits.

For patients with manageable chronic conditions, PCMH practices have a 25.5% lower rate of adult inpatient admissions than non-PCMH practices, and a 4.2% higher rate of dispensing generic drugs than non-PCMH practices.

In the BCBSM Patient-Centered Medical Home model, physicians receive an enhanced fee for office visits. The program is the largest in the nation, with 1,800 designated doctors in 500 practices across the state. BCBSM says 5,000 doctors have been working toward designation, which could affect 2 million Michigan residents.

TECHNOLOGY

HEALTH IT CHIEF EXITS AFTER TWO-YEAR TERM

After two years on the job, David Blumenthal, MD, announced his resignation as the National Coordinator for Health Information Technology, effective in the spring.

In a memo to Office of the National Coordinator staff and partners, Blumenthal writes that the two-year term was agreed upon before he started the position in 2009. He writes that he plans to return academic life.

Blumenthal writes in his memo that during his tenure the proportion of primary care physicians who adopted a basic electronic health record (EHR) system grew from 19.6% to 29.6%, and 41% of office-based physicians believe they will qualify for meaningful use objectives. He noted also that 38,000 providers have sought assistance with EHR selection and implementation from his office's regional extension centers.

GETTY IMAGES: COMSTOCK

PATIENT RELATIONS

SURVEY: PATIENTS WANT DOCTORS TO LEAD CARE

Although 83% of consumers surveyed want a physician to have primary responsibility for their health care, many are confused about the qualifications of healthcare professionals, according to the results of a survey by the American Medical Association.

Ninety percent of those surveyed said that a medical doctor's additional years of education and training are vital to patient care. The survey found much confusion about the qualifications of healthcare professionals; for instance, 24% indicated uncertainty that an otolaryngologist was a physician. Eighty-seven percent of respondents support legislation that would require advertisements to designate the qualifications of the healthcare professional.

COMPENSATION

STUDY: WOMEN PCPs EARN LESS THAN MEN

Newly trained primary care physicians who are women are being paid significantly lower salaries than their male counterparts, according to a study published in the February issue of *Health Affairs*.

The authors based their conclusions on survey data from physicians exiting training programs in New York state, which is home to 1,073 residency programs, more programs and resident physicians than any other state, according to the Association of American Medical Colleges.

The mean starting salary for family physicians was $139,504 for women and $147,874 for men. For general internal medicine, it was $142,526 for women and $154,900 for men. For geriatrics, the mean starting salary for women was $137,221, but it was $147,881 for men.

The authors identify an unexplained gender gap in starting salaries for all physicians that has been growing steadily since 1999, increasing from a difference of $3,600 in 1999 to $16,819 in 2008. This gap exists even after accounting for gender differences in determinants of salary including medical specialty, hours worked, and practice type, they say.

The number of physicians in the survey sample included 4,918 men and 3,315 women.

BILLING

CALIFORNIA INSURERS DENY 26% OF ALL CLAIMS

Health insurers in California denied 26% of claims submitted in 2009, according to a report released in January from the Institute of Health and Socio-Economic Policy, a research group of the California Nurses Association and National Nurses United.

PacifiCare had the highest percentage of denials, at 44%. Other insurers studied and the claims denial rates included Cigna, 40%; Anthem Blue Cross, 27%; HealthNet, 24%; Blue Shield, 22%; Kaiser Permanente, 20%; and Aetna, 6%

These seven firms, which account for more than three-quarters of all insurance enrollees in California, have rejected 67.5 million claims since 2002, according to report, based on data from the California Department of Managed Care.

Cigna showed the largest rejection rate increase in 2009, 5.3%, and Kaiser Permanente accounted for the biggest drop in denials, 7.4%.

GETTY IMAGES: JOSE LUIS PELAEZ INC

EHR ADOPTION//BY THE NUMBERS

50.7% Office-based physicians with anything from a "basic" to "fully functional" electronic health record (EHR) system.

24.9% Those who reported having a "basic" EHR system, which includes patient history and demographics, physician notes, medications, and more.

10.1% Those who reported having a "fully functional" system, which also includes electronic x-ray, lab orders, and more.

80.2% Office-based doctors in Minnesota reporting any level of EHR adoption, the largest portion in the nation. Kentucky was the lowest, at 38.1%.

Source: National Ambulatory Medical Care Survey by the Centers for Disease Control and Prevention's National Center for Health Statistics, preliminary 2010 results.

Medical Economics
SMARTER BUSINESS. BETTER PATIENT CARE.

Doctors' WRITING CONTEST 2011

By **TARA STULTZ**, *Editor-in-Chief*

It's often said that some of the most valuable meetings at medical conferences take place informally among colleagues in the hallways of conference centers.

Our annual Doctors' Writing Contest, and really, *Medical Economics* itself, is founded on the value of those types of shared experiences—what you've learned about running a business and being a doctor, and what you can learn from other doctors and from practice management and other experts.

Thomas J. Ellis, MD, this year's Grand Prize winner, whose article is based on life-changing advice a patient gave him, had never entered a writing contest before, but he says this one was perfectly timed. After seeing the call for entries shortly after the patient interaction occurred, Ellis said to himself: "Wow, I think I've got a story to tell."

What Ellis wanted to communicate to other doctors in sharing his story was the importance of truly listening to patients. "Those extra seconds you take to really sit down and listen can enhance the interaction," Ellis says. "You're helping the patient more, but you might get something more out of the interaction as well."

The 2011 competition marked some of the strongest entries we've ever received. Our staff and Editorial Board judged the 115 entries using a scoring system based on three criteria: quality of writing, quality of information, and alignment with our editorial mission.

We chose a Grand Prize Winner, an Overall Runner-Up, Best Practice Solution, and co-winners in the New Doctor Award category. We also named 11 excellent Honorable Mention recipients (all winners named at right). The Grand Prize winner will receive $2,000 and a crystal award, plus $500 to donate to a healthcare charity; and the Overall Runner-Up, Best Practice Solution, and New Doctor Award winners will receive $1,000 and a crystal award. Each Honorable Mention will receive a $500 honorarium, publication of his or her article, and a really cool *Medical Economics* mug!

When it comes to value added, these aren't the only winners in the competition. Just wait until you read the articles! ME

And the winners are...

GRAND PRIZE

Thomas J. Ellis, MD
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[†]All studies are multicenter, randomized, placebo-controlled, double-blind, minimum 100 participants and of adequate minimum duration (SAR: 2 weeks or PAR: 4 weeks). Total symptom severity score measured by patient.

References: 1. Data on file, McNeil-PPC, Inc. **2.** Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. *J Allergy Clin Immunol*. 1998;101:638-645.

Doctors' WRITING CONTEST 2011

Grand Prize Winner

One day after Thomas J. Ellis, MD, treated Mrs. Marilyn Love, pictured with him here, he asked whether he could do anything else for her. She said no but responded with: "Now, Dr. Ellis, what can I do for you today?" And so began a dialogue in which the patient taught the doctor about raising teenagers and communicating with patients.

The Pong Principle

LEARNING TO LISTEN: A PATIENT BECOMES THE TEACHER BY SERVING UP LIFE-CHANGING ADVICE

[*By* **THOMAS J. ELLIS**, *MD*]

After nearly 20 years of practicing medicine, I have come to expect patients to ask my advice about everything in their lives, from their most mundane struggles to their darkest secrets. They routinely share with me their most private issues, holding back nothing in an effort to glean new hope that things will get better, reassurance they aren't dying from "that" disease, or simply the comfort of knowing someone is willing to listen.

As a family doctor, I have advised patients on every physical and mental problem imaginable. I have guided

CREDIT: LAURIE CRUTCHFIELD

"ONCE IN A GREAT WHILE, THE EXAM TABLE TURNS DURING A PATIENT ENCOUNTER, AND I FIND MYSELF IN UNFAMILIAR TERRITORY."

patients and their families through a myriad of difficulties, from diabetes to depression. Patients are always asking me why they're gaining weight when they aren't eating anything, and why they're losing weight when they're eating everything in sight. They've sought my wisdom to gain relief from the relentless crying of colic and the unyielding pain of cancer. At this point in my career, I seldom see a problem that I haven't seen before, although every day someone finds a new and interesting way to solicit my input on a familiar float in this endless parade.

Once in a great while, the exam table turns during a patient encounter, and I find myself in unfamiliar territory. I had such an experience about a year ago, and it will forever change the way I practice medicine, the way I parent, and the way I view my most important relationships.

A WELL-TIMED QUESTION

Mrs. Marilyn Love (name used with the patient's permission), a mild-mannered, pleasant, 70-year-old woman, was in for a follow-up visit. She was doing well. No new problems. I was completing her encounter form and rising to escort her out of the room when she turned to me and said, "Now, Dr. Ellis, what can I do for you today?"

She waited expectantly as I tripped over my own thoughts. To say I don't often get this kind of question from a patient would be an understatement. Even my best friends rarely ask me this. I wondered if it was apparent I was struggling with something? And, if it was, might she have something to offer?

Maybe she had read my mind, which was becoming increasingly overwhelmed with the challenges of raising four children between the ages of 10 and 16. I felt my wife and I were treading water to stay on top of their growing bodies, changing ways, and scary thinking.

Transitioning from the smartest dad in the world when they were in elementary school, to a complete dunce as they entered the worlds of middle school and high school, was tough for me. I didn't have a clue how to relate to these creatures living in my house. I was struggling to understand where I might have gone wrong. What kinds of kids was I raising? How was I going to do it? Was there even a right way?

"Umm... do you have any advice on raising teenagers?" I blurted out. Without hesitation, Mrs. Love nodded her head and confidently replied, "Buy a ping pong table."

We laughed and talked a few minutes about how she and her teenage sons had played ping pong for hours at a time, sharing great fun and talks over the table. That evening, I mentioned the exchange to my wife, who was hesitant to give up her garage parking spot for a dinosaur that probably wouldn't hold our kids' interest more than a few days. I didn't give our conversation much thought during the next several days.

CREDIT: LAURIE CRUTCHFIELD

FOLLOW-UP LETTER

A week later I received a hand-written note from Mrs. Love:

"Dr. Ellis:

These are a few things we did with our teenagers that seemed to work. As I mentioned, the ping pong table. This was the best. Worked out a lot of tension. Did you ever play ring-around-the-table with a group? So much fun! If and when you have time, take each child out individually for a treat—ice cream, pizza, etc. Helps you focus on and pay attention to that child and hear what's going on. Family bike rides. These were really great. We rode all over town, sometimes ending up at a pizza or burger place. Family movie night. Children can take turns choosing the movie and pop some popcorn. No phones on! I'm sure you all have your own special things to do. I think your children are really lucky to have you for a father."

Butrans™ (buprenorphine) Transdermal System is indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time.

One Butrans —7 days of analgesic delivery

- **Butrans is a Schedule III, single-entity opioid analgesic**
- **Butrans 5 mcg/hour allows initiation in appropriate opioid-naïve patients**
  - **Individually titrate the dose. Dose may be titrated to the next higher level after a minimum of 72 hours**

DOSAGE AND ADMINISTRATION

Apply Butrans to the upper outer arm, upper chest, upper back or the side of the chest. These four sites (each present on both sides of the body) provide 8 possible application sites. Rotate Butrans among the 8 described skin sites. After Butrans removal, wait a minimum of 21 days before reapplying to the same skin site.

Apply Butrans to a hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped, not shaven. Do not apply Butrans to irritated skin. If the application site must be cleaned, clean the site with water only. Do not use soaps, alcohol, oils, lotions, or abrasive devices. Allow the skin to dry before applying Butrans.

If problems with adhesion of Butrans occur, the edges may be taped with first aid tape. If Butrans falls off during the 7 days dosing interval, dispose of the transdermal system properly and place a new Butrans on at a different skin site.

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, POTENTIAL FOR ABUSE, AND LIMITATIONS OF USE

Proper Patient Selection

Butrans is a transdermal formulation of buprenorphine indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. (1)

Potential for Abuse

Butrans contains buprenorphine which is a mu opioid partial agonist and a Schedule III controlled substance. Butrans can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the abuse potential when prescribing or dispensing Butrans in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9)

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (eg, major depression). Assess patients for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Routinely monitor all patients receiving opioids for signs of misuse, abuse and addiction. (2.2)

Limitations of Use

Do not exceed a dose of one 20 mcg/hour Butrans system due to the risk of QTc interval prolongation. (2.3)

Avoid exposing the Butrans application site and surrounding area to direct external heat sources. Temperature-dependent increases in buprenorphine release from the system may result in overdose and death. (5.11)

Parentheses refer to sections in the Full Prescribing Information.

CONTRAINDICATIONS

- Butrans is contraindicated in patients who have: significant respiratory depression, severe bronchial asthma, or known hypersensitivity to any of its components or the active ingredient, buprenorphine. Butrans is contraindicated in patients who have or are suspected of having paralytic ileus
- Butrans is also contraindicated in the management of: acute pain or in patients who require opioid analgesia for a short period of time, postoperative pain, mild pain, or intermittent pain (eg, use on an as-needed basis [prn])

WARNINGS AND PRECAUTIONS

- **Respiratory Depression**
  Respiratory depression is the chief hazard with Butrans. Use with extreme caution in patients at risk of respiratory depression
- **CNS Depression**
  Butrans may cause somnolence, dizziness, alterations in judgment and alterations in levels of consciousness, including coma. Use with caution in patients who are receiving other central nervous system (CNS) depressants. Additive CNS effects are expected when used with alcohol, benzodiazepines, other opioids, or illicit drugs
- **QTc Prolongation**
  Avoid in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications
- **Head Injury**
  Butrans may worsen increased intracranial pressure and obscure its signs, such as level of consciousness or pupillary signs
- **Hypotensive Effects**
  Butrans may cause severe hypotension. Use with caution in patients at increased risk of hypotension and in patients in circulatory shock
- **Application Site Skin Reactions**
  In rare cases, severe application site skin reactions with signs of marked inflammation including "burn," "discharge," and "vesicles" have occurred
- **Anaphylactic/Allergic Reactions**
  Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience
- **Use in Pancreatic/Biliary Tract Disease and Other Gastrointestinal Conditions**
  Use with caution in patients with biliary tract disease, including acute pancreatitis. Ileus may occur. Monitor for decreased bowel motility

ADVERSE REACTIONS

- Most common adverse reactions (≥5%) included: nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, and application site rash

The first 7-day analgesic delivered in 1 application

Butrans™ C-III

(buprenorphine) Transdermal System

5, 10, and 20 mcg/hour

One Butrans, Once Weekly

Please read Brief Summary of Full Prescribing Information on the following pages.

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PURDUE

Butrans™ Ⓒ III

(buprenorphine) Transdermal System

5, 10, and 20 mcg/hour

for transdermal administration

BRIEF SUMMARY OF PRESCRIBING INFORMATION

(For complete details please see the full prescribing information and Medication Guide.)

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, POTENTIAL FOR ABUSE, AND LIMITATIONS OF USE

Proper Patient Selection

Butrans is a transdermal formulation of buprenorphine indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. (1)

Potential for Abuse

Butrans contains buprenorphine which is a mu opioid partial agonist and a Schedule III controlled substance. Butrans can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the abuse potential when prescribing or dispensing Butrans in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9)

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Assess patients for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Routinely monitor all patients receiving opioids for signs of misuse, abuse and addiction. (2.2)

Limitations of Use

Do not exceed a dose of one 20 mcg/hour Butrans system due to the risk of QTc interval prolongation. (2.3)

Avoid exposing the Butrans application site and surrounding area to direct external heat sources. Temperature-dependent increases in buprenorphine release from the system may result in overdose and death. (5.11)

1 INDICATIONS AND USAGE

Butrans is indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time.

4 CONTRAINDICATIONS

Butrans is contraindicated in:

- patients who have significant respiratory depression
- patients who have severe bronchial asthma
- patients who have or are suspected of having paralytic ileus
- patients who have known hypersensitivity to any of its components or the active ingredient, buprenorphine
- the management of acute pain or in patients who require opioid analgesia for a short period of time
- the management of post-operative pain, including use after out-patient or day surgeries
- the management of mild pain
- the management of intermittent pain (e.g., use on an as needed basis [prn])

5 WARNINGS AND PRECAUTIONS

5.1 Respiratory Depression

Respiratory depression is the chief hazard of Butrans. Respiratory depression occurs more frequently in elderly or debilitated patients as well as those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation, and when opioids, including Butrans, are given in conjunction with other agents that depress respiration.

Profound sedation, unresponsiveness, infrequent deep ("sighing") breaths or atypical snoring frequently accompany opioid-induced respiratory depression.

Use Butrans with extreme caution in patients with any of the following:

- significant chronic obstructive pulmonary disease or cor pulmonale
- other risk of substantially decreased respiratory reserve such as asthma, severe obesity, sleep apnea, myxedema, clinically significant kyphoscoliosis, and central nervous system (CNS) depression
- hypoxia
- hypercapnia
- pre-existing respiratory depression

5.2 CNS Depression

Butrans may cause somnolence, dizziness, alterations in judgment and alterations in levels of consciousness, including coma.

5.3 Interactions with Alcohol, Central Nervous System Depressants, and Illicit Drugs

Hypotension, profound sedation, coma or respiratory depression may result if Butrans is added to a regimen that includes other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, muscle relaxants, other opioids). Therefore, use caution when deciding to initiate therapy with Butrans in patients who are taking other CNS depressants. Take into account the types of other medications being taken, the duration of therapy with them, and the patient's response to those medicines, including the degree of tolerance that has developed to CNS depression. Consider the patient's use, if any, of alcohol and/or illicit drugs that cause CNS depression. If the decision to begin Butrans is made, start with a lower Butrans dose than usual.

Consider using a lower initial dose of a CNS depressant when given to a patient currently taking Butrans due to the potential of additive CNS depressant effects.

5.4 QTc Prolongation

A positive-controlled study of the effects of Butrans on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a Butrans dose of 10 mcg/hour; however, a Butrans dose of 40 mcg/hour (given as two Butrans 20 mcg/hour Transdermal Systems) was observed to prolong the QTc interval *[see Clinical Pharmacology (12.2)]*.

Consider these observations in clinical decisions when prescribing Butrans to patients with hypokalemia or clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Avoid the use of Butrans in patients with a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide).

5.5 Head Injury

The respiratory depressant effects of opioids, including Butrans, include carbon dioxide retention, which can lead to an elevation of cerebrospinal fluid pressure. This effect may be exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Butrans may produce miosis that is independent of ambient light, and altered consciousness, either of which may obscure neurologic signs associated with increased intracranial pressure in persons with head injuries.

5.6 Hypotensive Effects

Butrans may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Buprenorphine may produce orthostatic hypotension in ambulatory patients. Administer Butrans with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

5.7 Misuse, Abuse, and Diversion of Opioids

Butrans contains buprenorphine, a partial agonist at the mu opioid receptor and a Schedule III controlled substance. Opioid agonists have potential for being abused, are sought by drug abusers and people with addiction disorders, and are subject to criminal diversion.

Butrans can be abused in a manner similar to other opioid agonists, legal or illicit. Consider this potential for abuse when prescribing or dispensing Butrans in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Monitor all patients receiving opioids for signs of abuse, misuse, and addiction. Furthermore, assess patients for their potential for opioid abuse prior to being prescribed opioid therapy. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse) or mental illness (e.g., depression). Opioids may still be appropriate for use in these patients; however, they will require intensive monitoring for signs of abuse.

Notwithstanding concerns about abuse, addiction, and diversion, provide proper management of pain. However, all patients treated with opioid agonists require careful monitoring for signs of abuse and addiction, since use of opioid agonist analgesic products carries the risk of addiction even under appropriate medical use *[see Drug Abuse and Dependence (9.2)]*. Data are not available to establish the true incidence of addiction in patients with chronic pain treated with opioids.

Abuse of Butrans poses a significant risk to the abuser that could potentially result in overdose or death *[see Drug Abuse and Dependence (9)]*.

Contact your state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.8 Hepatotoxicity

Although not observed in Butrans chronic pain clinical trials, cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving sublingual buprenorphine for the treatment of opioid dependence, both in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injection drug abuse may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. For patients at increased risk of hepatotoxicity (e.g., patients with a history of excessive alcohol intake, intravenous drug abuse or liver disease), baseline and periodic monitoring of liver function during treatment with Butrans is recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected.

5.9 Application Site Skin Reactions

In rare cases, severe application site skin reactions with signs of marked inflammation including "burn," "discharge," and "vesicles" have occurred. Time of onset varies, ranging from days to months following the initiation of Butrans treatment. Instruct patients to promptly report the development of severe application site reactions and discontinue therapy.

5.10 Anaphylactic/Allergic Reactions

Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the

post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to the use of Butrans.

5.11 Application of External Heat

Advise patients and their caregivers to avoid exposing the Butrans application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system because an increase in absorption of buprenorphine may occur *[see Clinical Pharmacology (12.3)]*. Advise patients against exposure of the Butrans application site and surrounding area to hot water or prolonged exposure to direct sunlight. There is a potential for temperature-dependent increases in buprenorphine released from the system resulting in possible overdose and death.

5.12 Patients with Fever

Patients wearing Butrans systems who develop fever or increased core body temperature due to strenuous exertion should be monitored for opioid side effects and the Butrans dose should be adjusted if necessary *[see Dosage and Administration (2.4)]*.

5.13 Driving and Operating Machinery

Butrans may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Caution patients accordingly.

5.14 Seizures

Butrans, as with other opioids, may aggravate seizure disorders, may lower seizure threshold, and therefore, may induce seizures in some clinical settings. Use Butrans with caution in patients with a history of seizure disorders.

5.15 Special Risk Groups

Use Butrans with caution in the following conditions, due to increased risk of adverse reactions: alcoholism; delirium tremens; adrenocortical insufficiency; CNS depression; debilitation; kyphoscoliosis associated with respiratory compromise; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

5.16 Use in Pancreatic/Biliary Tract Disease and Other Gastrointestinal Conditions

Butrans may cause spasm of the sphincter of Oddi. Use with caution in patients with biliary tract disease, including acute pancreatitis. Opioids, including Butrans, may cause increased serum amylase.

The administration of Butrans may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Use Butrans with caution in patients who are at risk of developing ileus.

5.17 Use in Addiction Treatment

Butrans has not been studied and is not approved for use in the management of addictive disorders.

5.18 MAO Inhibitors

Butrans is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

6 ADVERSE REACTIONS

The following adverse reactions described elsewhere in the labeling include:

- Respiratory Depression *[see Warnings and Precautions (5.1)]*
- CNS Depression *[see Warnings and Precautions (5.2)]*
- QTc Prolongation *[see Warnings and Precautions (5.4)]*
- Hypotensive Effects *[see Warnings and Precautions (5.6)]*
- Application Site Skin Reactions *[see Warnings and Precautions (5.9)]*
- Anaphylactic/Allergic Reactions *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trial Experience

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

A total of 5415 patients were treated with Butrans in controlled and open-label chronic pain clinical trials. Nine hundred twenty-four subjects were treated for approximately six months and 183 subjects were treated for approximately one year. The clinical trial population consisted of patients with persistent moderate to severe pain.

The most common adverse reactions (≥5%) reported by patients in clinical trials comparing Butrans 10 or 20 mcg/hour to placebo are shown in Tables 2, and comparing Butrans 20 mcg/hour to Butrans 5 mcg/hour are shown in Table 3 below:

Table 2: Adverse Events Reported in ≥ 5% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period: Opioid-Naïve Patients

	Open-Label Titration Period	Double-Blind Treatment Period	
	Butrans	Butrans	Placebo
MedDRA Preferred Term	**(N = 1024)**	**(N = 256)**	**(N = 283)**
Nausea	23%	13%	11%
Dizziness	10%	4%	1%
Headache	10%	5%	5%
Application site pruritus	8%	4%	7%
Somnolence	8%	2%	2%
Vomiting	8%	4%	2%
Constipation	7%	4%	1%

Table 3: Adverse Events Reported in ≥ 5% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period: Opioid-Experienced Patients

	Open-Label Titration Period	Double-Blind Treatment Period	
	Butrans	Butrans 20	Butrans 5
MedDRA Preferred Term	**(N = 1160)**	**(N = 219)**	**(N = 221)**
Nausea	15%	12%	8%
Headache	11%	11%	5%
Application site pruritus	9%	13%	5%
Somnolence	6%	5%	2%
Vomiting	5%	5%	2%
Dizziness	5%	5%	2%
Constipation	4%	6%	3%
Application site erythema	3%	10%	5%
Application site rash	3%	9%	6%
Application site irritation	2%	5%	3%

The following table lists adverse events that were reported in at least 2.0% of patients in four placebo/active-controlled titration-to-effect trials.

Table 4: Adverse Events Reported in Titration-to-Effect Placebo/Active-Controlled Clinical Trials with Incidence ≥2%

MedDRA Preferred Term	Butrans (N = 392)	Placebo (N = 261)
Nausea	23%	8%
Dizziness	16%	8%
Headache	16%	11%
Application site pruritus	15%	12%
Constipation	14%	5%
Somnolence	14%	5%
Vomiting	11%	2%
Peripheral edema	7%	3%
Dry mouth	7%	2%
Application site erythema	7%	2%
Application site rash	6%	6%
Fatigue	5%	1%
Hyperhidrosis	4%	1%
Pruritus	4%	1%
Fall	4%	2%
Diarrhea	3%	2%
Pain in extremity	3%	2%
Insomnia	3%	2%
Dyspnea	3%	1%
Dyspepsia	3%	3%
Urinary tract infection	3%	2%
Back pain	3%	2%
Joint swelling	3%	1%
Hypoesthesia	2%	1%
Arthralgia	2%	2%
Stomach discomfort	2%	1%
Rash	2%	1%
Anorexia	2%	1%
Paraesthesia	2%	1%
Tremor	2%	<1%
Confusional State	2%	3%

The adverse events seen in controlled and open-label studies are presented below in the following manner: most common (≥5%), common (≥1% - <5%), and less common (<1%).

The most common adverse events (≥5%) reported by patients treated with Butrans in the clinical trials were nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, and application site rash.

The common (≥1% to <5%) adverse events reported by patients treated with Butrans in the clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class were:

Gastrointestinal disorders: diarrhea, dyspepsia, and upper abdominal pain

General disorders and administration site conditions: fatigue, peripheral edema, application site irritation, pain, pyrexia, chest pain, and asthenia

Infections and infestations: urinary tract infection, upper respiratory tract infection, nasopharyngitis, influenza, sinusitis, and bronchitis

Injury, poisoning and procedural complications: fall

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: back pain, arthralgia, pain in extremity, muscle spasms, musculoskeletal pain, joint swelling, neck pain, and myalgia

Nervous system disorders: hypoesthesia, tremor, migraine, and paresthesia

Psychiatric disorders: insomnia, anxiety, and depression

Respiratory, thoracic and mediastinal disorders: dyspnea, pharyngolaryngeal pain, and cough

Skin and subcutaneous tissue disorders: pruritus, hyperhidrosis, rash, and generalized pruritus

Vascular disorders: hypertension

Other less common adverse events, including those known to occur with opioid treatment, that were seen in <1% of the patients in the Butrans trials include the following in alphabetical order:

Abdominal distention, abdominal pain, accidental injury, affect lability, agitation, alanine aminotransferase increased, angina pectoris, angioedema, apathy, application site dermatitis, asthma aggravated, bradycardia, chills, confusional state, contact dermatitis, coordination abnormal, dehydration, depressed level of consciousness, depressed mood, depersonalization, disorientation, disturbance in attention, diverticulitis, drug hypersensitivity, drug withdrawal syndrome, dry eye, dry skin, dysarthria, dysgeusia, dysmenorrhea, dysphagia, euphoric mood, face edema, flatulence, flushing, gait disturbance, hallucination, hiccups, hot flush, hyperventilation, hypotension, hypoventilation, ileus, insomnia, libido decreased, loss of consciousness, malaise, memory impairment, mental impairment, mental status changes, miosis, muscle weakness, nervousness, nightmare, orthostatic hypotension, palpitations, psychotic disorder, respiration abnormal, respiratory depression, respiratory distress, respiratory failure, restlessness, rhinitis, sedation, sexual dysfunction, syncope, tachycardia, tinnitus, urinary hesitation, urinary incontinence, urinary retention, urticaria, vasodilatation, vertigo, vision blurred, visual disturbance, weight decreased, and wheezing.

7 DRUG INTERACTIONS

7.1 Metabolic Drug Interactions

CYP3A4 Inhibitors

Co-administration of ketoconazole, a strong CYP3A4 inhibitor, with Butrans, did not have any effect on C_{max} and AUC of buprenorphine. Based on this observation, pharmacokinetics of Butrans is not expected to be affected by co-administration of CYP3A4 inhibitors.

However, certain protease inhibitors (PIs) with CYP3A4 inhibitory activity such as atazanavir and atazanavir/ritonavir resulted in elevated levels of buprenorphine and norbuprenorphine following sublingual administration of buprenorphine and naloxone. Patients in this study reported increased sedation, and symptoms of opiate excess have been found in post-marketing reports of patients receiving sublingual buprenorphine and atazanavir with and without ritonavir concomitantly. It should be noted that atazanavir is both a CYP3A4 and UGT1A1 inhibitor. As such, the drug-drug interaction potential for buprenorphine with CYP3A4 inhibitors is likely to be dependent on the route of administration as well as the specificity of enzyme inhibition *[see Clinical Pharmacology (12.3)].*

CYP3A4 Inducers

The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied; therefore it is recommended that patients receiving Butrans be closely monitored for reduced efficacy if inducers of CYP3A4 (e.g. phenobarbital, carbamazepine, phenytoin, rifampin) are co-administered *[see Clinical Pharmacology (12.3)].*

7.2 Non-Metabolic Drug Interactions

Benzodiazepines

There have been a number of reports regarding coma and death associated with the misuse and abuse of the combination of buprenorphine and benzodiazepines. In many, but not all of these cases, buprenorphine was misused by self-injection of crushed buprenorphine tablets. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. Prescribe Butrans with caution to patients taking benzodiazepines or other drugs that act on the central nervous system regardless of whether these drugs are taken on the advice of a physician or are being abused/misused. Warn patients that it is extremely dangerous to self-administer benzodiazepines while taking Butrans, and caution patients to use benzodiazepines concurrently with Butrans only as directed by their physician.

Skeletal Muscle Relaxants

Butrans, like other opioids, may interact with skeletal muscle relaxants to enhance neuromuscular blocking action and increase respiratory depression.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with Butrans in pregnant women. Butrans should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the fetus. In animal studies, buprenorphine caused an increase in the number of stillborn offspring, reduced litter size, and reduced offspring growth in rats at maternal exposure levels that were approximately 10 times that of human subjects who received one Butrans 20 mcg/hour, the maximum recommended human dose (MRHD).

Teratogenic Effects

Studies in rats and rabbits demonstrated no evidence of teratogenicity following Butrans or subcutaneous (SC) administration of buprenorphine during the period of major organogenesis. Rats were administered up to one Butrans 20 mcg/hour every 3 days (gestation days 6, 9, 12, & 15) or received daily SC buprenorphine up to 5 mg/kg (gestation days 6-17). Rabbits were administered four Butrans 20 mcg/hour every 3 days (gestation days 6, 9, 12, 15, 18, & 19) or received daily SC buprenorphine up to 5 mg/kg (gestation days 6-19). No teratogenicity was observed at any dose. Area under the curve (AUC) values for buprenorphine with Butrans application and SC injection were approximately 140 and 110 times that of human subjects who received the MRHD of one Butrans 20 mcg/hour.

Non-Teratogenic Effects

In a peri- and post-natal study conducted in pregnant and lactating rats, administration of buprenorphine either as Butrans or SC buprenorphine was associated with toxicity to offspring. Buprenorphine was present in maternal milk. Pregnant rats were administered 1/4 of one Butrans 5 mcg/hour every 3 days or received daily SC buprenorphine at doses of 0.05, 0.5, or 5 mg/kg from gestation day 6 to lactation day 21 (weaning). Administration of Butrans or SC buprenorphine at 0.5 or 5 mg/kg caused maternal toxicity and an increase in the number of stillborns, reduced litter size, and reduced offspring growth at maternal exposure levels that were approximately 10 times that of human subjects who received the MRHD of one Butrans 20 mcg/hour. Maternal toxicity was also observed at the no observed adverse effect level (NOAEL) for offspring.

8.2 Labor and Delivery

The safety of Butrans given during labor and delivery has not been established.

Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. Butrans is not recommended for use in women immediately prior to and during labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. Have a specific opioid antagonist, such as naloxone or nalmefene, available for reversal of opioid-induced respiratory depression in the neonate.

Neonates whose mothers have been taking opioids chronically may also exhibit withdrawal signs, either at birth and/or in the nursery, because they have developed physical dependence. This is not, however, synonymous with addiction. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts.

8.3 Nursing Mothers

Buprenorphine has been detected in low concentrations in human milk. Breast-feeding is not advised in mothers treated with Butrans.

8.4 Pediatric Use

The safety and efficacy of Butrans in patients under 18 years of age has not been established. Butrans is not recommended for use in pediatric patients.

8.5 Geriatric Use

Of the total number of subjects in the clinical trials (5,415), Butrans was administered to 1,377 patients aged 65 years and older. Of those, 457 patients were 75 years of age and older. In the clinical program, the incidences of selected Butrans-related AEs were higher in older subjects. The incidences of application site AEs were slightly higher among subjects <65 years of age than those ≥ 65 years of age for both Butrans and placebo treatment groups.

In a single-dose study of healthy elderly and healthy young subjects treated with Butrans 10 mcg/hour, the pharmacokinetics and safety outcomes were similar. In a separate dose-escalation safety study, the pharmacokinetics in the healthy elderly and hypertensive elderly subjects taking thiazide diuretics were similar to those in the healthy young adults. In the elderly groups evaluated, adverse event rates were similar to or lower than rates in healthy young adult subjects, except for constipation and urinary retention, which were more common in the elderly. Although specific dose adjustments on the basis of advanced age are not required for pharmacokinetic reasons, use caution in the elderly population to ensure safe use *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].*

8.6 Hepatic Impairment

In a study utilizing intravenous buprenorphine, peak plasma levels (C_{max}) and exposure (AUC) of buprenorphine in patients with mild and moderate hepatic impairment did not increase as compared to those observed in subjects with normal hepatic function. Butrans has not been evaluated in patients with severe hepatic impairment and should be administered with caution *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3)].*

8.7 Renal Impairment

The pharmacokinetics of buprenorphine is not altered during the course of renal failure *[see Clinical Pharmacology (12.3)].*

8.8 Gender Differences

There was no significant gender effect observed for Butrans with respect to either the incidence of adverse events or pharmacokinetics *[see Clinical Pharmacology (12.3)].*

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Butrans contains buprenorphine, a mu opioid partial agonist and Schedule III controlled substance. Butrans can be abused and is subject to misuse, abuse, addiction and criminal diversion.

9.2 Abuse

Abuse of Butrans poses a hazard of overdose and death. This risk is increased with compromise of the Butrans Transdermal System and with concurrent abuse of alcohol or other substances. Butrans has been diverted for non-medical use.

All patients treated with opioids, including Butrans, require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors

influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Opioid drugs are sought by people with substance use disorders (abuse or addiction, the latter of which is also called "substance dependence") and criminals who supply them by diverting medicines out of legitimate distribution channels. Butrans is a target for theft and diversion.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, altering or forging of prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among people with untreated substance use disorders, and criminals who divert controlled substances.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since Butrans may be diverted for non-medical use, careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

The risks of misuse and abuse should be considered when prescribing or dispensing Butrans. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.

Butrans is intended for transdermal use only. Compromising the transdermal delivery system will result in the uncontrolled delivery of buprenorphine and pose a significant risk to the abuser that could result in overdose and death *[see Warnings and Precautions (5.1)]*. The risk of fatal overdose is further increased when buprenorphine is abused concurrently with alcohol or other CNS depressants, including other opioids and benzodiazepines *[see Warnings and Precautions (5.3)]*. Abuse may occur by applying the transdermal system in the absence of legitimate purpose, or by swallowing, snorting or injecting buprenorphine extracted from the transdermal system.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, proper dispensing and correct storage and handling are appropriate measures that help to limit misuse and abuse of opioid drugs. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Physical Dependence and Tolerance

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Tolerance could occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence to an opioid is manifested by characteristic withdrawal signs and symptoms after abrupt discontinuation of a drug, significant dose reduction, or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid analgesic therapy.

The opioid abstinence or withdrawal syndrome in adults is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate *[see Use In Specific Populations (8.2)]*

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms.

In general, opioids should not be abruptly discontinued *[see Dosage and Administration (2.5)]*.

10 OVERDOSAGE

10.1 Symptoms

Acute overdosage with Butrans can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring and death.

Deaths due to overdose have been reported with abuse and misuse of buprenorphine. Review of case reports has indicated that the risk of fatal overdose is further increased when Butrans is abused concurrently with alcohol or other CNS depressants, including other opioids.

10.2 Treatment

In cases of overdose, remove Butrans immediately. It is important to take the pharmacokinetic profile of Butrans into account when treating overdose. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects as opioid continues to be absorbed from the skin. After removal of Butrans, the mean buprenorphine concentrations decrease approximately 50% in 12 hours (range 10-24 hours) with an apparent terminal half-life of approximately 26 hours. Due to this long apparent terminal half-life, patients may require monitoring and treatment for at least 24 hours.

In the treatment of Butrans overdosage, primary attention should be given to the maintenance of a patent airway, and of effective ventilation (clearance of CO_2) and oxygenation, whether by spontaneous, assisted or controlled respiration. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. High doses of naloxone, 10-35 mg/70 kg, may be of limited value in the management of buprenorphine overdose. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride (a respiratory stimulant) has also been used. Since the duration of action of Butrans may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling as needed to maintain adequate respiration. Maintenance of adequate ventilation is essential when managing Butrans overdose and more important than specific antidote treatment with an opioid antagonist such as naloxone.

Do not administer opioid antagonists in the absence of clinically significant respiratory or circulatory depression secondary to buprenorphine overdose. In patients who are physically dependent on any opioid agonist including Butrans, an abrupt partial or complete reversal of opioid effects may precipitate an acute abstinence or withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. See the prescribing information for the specific opioid antagonist for details of its proper use.

17 PATIENT COUNSELING INFORMATION

See MEDICATION GUIDE (including Instructions for Use) as appended at the end of the full prescribing information.

17.1 Information for Patients and Caregivers

Provide the following information to patients receiving Butrans or their caregivers:

1. Advise patients to carefully follow instructions for the application, removal, and disposal of Butrans. Each week, apply Butrans to a different site based on the 8 described skin sites, with a minimum of 3 weeks between applications to a previously used site.
2. Advise patients to apply Butrans to a hairless or nearly hairless skin site. If none are available, instruct patients to clip the hair at the site and not to shave the area. Instruct patients not to apply to irritated skin. If the application site must be cleaned, use clear water only. Soaps, alcohol, oils, lotions, or abrasive devices should not be used. Allow the skin to dry before applying Butrans.
3. Advise the patient to wear Butrans continuously for 7 days.
4. Advise patients to talk to their doctor if they have any pain or bothersome side effects while they are using Butrans. The dose may have to be changed.
5. Advise patients not to increase or decrease the Butrans dose they are using without first speaking to their doctor.
6. Advise patients that Butrans may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
7. Advise patients who are taking Butrans not to drink alcohol. They should also avoid taking sleep aids and CNS depressants, unless a doctor prescribes them.
8. Advise patients that while wearing Butrans, they should avoid exposing the Butrans site to external heat sources, such as heating pads, electric blankets, heat lamps, saunas, hot tubs, heated water beds, etc, because an increase in absorption of buprenorphine may occur that could lead to an overdose or death.
9. Advise women who become pregnant, or who plan to become pregnant, to ask their doctor about the effects that Butrans may have on themselves and their pregnancy.
10. Advise patients that buprenorphine is a drug that some people may abuse. They should use Butrans only as directed, and not give it to anyone other than the individual for whom it was prescribed. Protect it from theft. Be especially careful to keep this medication away from children and pets.
11. Advise patients to tell their doctor if they have a history of serious skin reactions to adhesives, as they may not be able to use Butrans.
12. Advise patients who must stop using Butrans that they should speak with their doctor to manage the transition to other pain medications.

Healthcare professionals can telephone
Purdue Pharma's Medical Services Department
(1-888-726-7535) for information on this product.

CAUTION

DEA Order Form Required.

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Issued: August 2010

302578-0A

THIS PATIENT ENCOUNTER WILL FOREVER CHANGE THE WAY I PRACTICE MEDICINE, THE WAY I PARENT, AND THE WAY I VIEW MY MOST IMPORTANT RELATIONSHIPS.

Wow. A letter *from* a patient with advice for *me!* I was stunned. Scrawled in blue ink across a 3x5 notecard were answers I'd been searching for. I read the note over and over, happy to learn that perhaps I was already doing some things right, and I was encouraged to see specific, tried-and-true suggestions that seemed very doable. I gleaned hope from this patient who had raised teenagers and lived to tell the story. I found reassurance that things would get better and that, just maybe, the experience wouldn't kill me. Once again, I shared Mrs. Love's wisdom with my wife. We both were touched by her compassion for our "plight" and marveled at the time and thought she had invested in encouraging us.

Ellis learned about the importance of listening when he started playing ping pong with his wife, Amy, and their children, from left to right, Philip, 14, Parker, 14, Eve, 11, and Thomas, 16.

CONVERSATION STARTER

Although I wouldn't want it broadcast to my patients, adherence is not my strong suit, so it was still a while before I heeded Mrs. Love's advice about the ping pong table.

Some friends invited our family to spend a long weekend with their family in a cottage on the Outer Banks of North Carolina. Between our two families, there were six kids ranging in age from 10 to 16 years old. Five of the six were boys. My wife and I were a little nervous about how we would keep all the kids entertained in the evenings, especially considering the cottage had no Internet access. But our friends had failed to mention there was a ping pong table in the basement.

Every evening, the kids held ping pong tournaments while the adults enjoyed hours of uninterrupted conversation upstairs. At the end of the weekend, we all knew each other a little better and appreciated each other a little more. I returned from that weekend optimistic, refreshed, and determined to purchase a ping pong table of my own.

Walking through Sam's Club the next weekend, I saw the store was beginning to display seasonal items in preparation for the holidays. On the fringe of all the new gaming systems, big-screen televisions, and computers sat a plain, black-and-white ping pong table, folded up like a forgotten backdrop. I grabbed a ticket from the plastic pocket, practically skipped to customer service, purchased one, strapped it on top of the minivan, and set it up in our garage the same day. Our household hasn't been the same since.

I can't explain the magnetism of the ping pong table. It has drawn neighborhood kids that never hung out at our house before. Even those who don't want to play gather and watch. And they talk. They talk a lot.

My wife has decided her dry parking space has been a small price to pay. When inclement weather recently closed the schools for a couple of days, the kids didn't congregate in the house around video games or lounge on the

POWER POINTS

It's important to look a patient in the eyes when talking and listening.

Body language can give you clues about physical and mental health that words alone don't provide.

The more you interact with a particular patient, the more you can tailor treatment for better outcomes.

Patients have plenty of wisdom to share.

PHOTO BY ERIC JONES

During a ping pong game...	During patient interaction...
You must be face-to-face with your opponent.	It's important to look a patient directly in the eyes when talking and listening to him or her.
All of your focus must be on the game.	You should not be multitasking, writing notes, etc.
Paying attention to your opponent's body language can help you plan your best move.	Paying attention to your patient's body language can give you clues about his or her physical and mental health that words alone don't provide.
There is a back-and-forth exchange of the ball.	Spend as much time listening to the patient as you do talking.
A rhythm develops in the game as two players get to know each others' styles.	The more you interact with a particular patient, the more you can tailor your treatment to that individual in a way that yields better outcomes.
You switch sides to even the playing field.	Sometimes when you interact with a patient, you should give the patient the opportunity to offer you some wisdom and experience.

couch with their iPods. They played ping pong.

Over the past couple of months, we've had some awesome conversations with our three teenage boys and "tween" girl over the ping pong table. I've learned more about the things they're struggling with academically, athletically, socially. I know more about their likes and dislikes, their friends, and their girlfriends.

LIGHT BANTER, SERIOUS DISCOURSE

I'm not sure what it is about ping pong that evokes conversation, but it's becoming our family's platform of choice for light banter as well as serious discourse. Maybe it's that you have to literally face your opponents and give them your undivided attention. It's pretty difficult to check your emails or sign charts during a game of ping pong.

Or maybe the background rhythm the bouncing ball creates serves as some sort of conversational safety net. The focus of ping pong requires certainly seems to chase away the clouds of self-consciousness that tend to settle around teenagers. Our kids don't appear to feel threatened, spotlighted, or grilled when I initiate a discussion with them over a game of pong.

Or perhaps the game simply satisfies some primordial urge to pound something. Better a plastic ball than a sibling.

Anyway, our family relationships are developing a nice new rhythm, too, since we brought home the ping pong table. My heart leaps a little every time one of my kids yells, "Dad, wanna pong?" I don't view this question as a challenge to compete; I see it as an invitation to listen.

My family won't solve the world's problems over the ping pong table. But I have no doubt we'll have many more meaningful conversations over it in the months and, I hope, years, to come. All because of a little 70-year-old patient with a big heart—who, just by listening—showed me how to be a better parent, a better doctor, and a better person.

As much as I would like to think that I have all the answers for every patient I encounter, I don't. Just as I don't have all the answers for the parenting dilemmas I face daily. But I'm trying to develop the habit of talking less and listening more. Your patients, your family—in fact, all the people in your life—will tell you most everything you need to know. You just have to listen.

So... wanna pong? MB

The author is a clinical assistant professor in the Brody School of Medicine at East Carolina University in Greenville, North Carolina. For 14 years he has practiced in their Department of Family Medicine's primary care clinic, Firetower Medical Office, where he serves as medical director. Brody ranks second nationwide for launching graduates into family medicine. Ellis has been actively involved in medical missions to Nicaragua since 2003, often making his trips a family affair. Send your feedback to medec@advanstar.com.

Doctors' WRITING CONTEST 2011

Overall Runner-Up

Jennifer Frank, MD (foreground), regularly evaluates staff members to develop their careers and improve practice efficiency. Shown here are Medical Assistant Sarah Davis (left) and Nurse Practitioner Danielle Vanevenhoven.

Why evaluations matter

LEVERAGE FEEDBACK TO HELP DEVELOP YOUR STAFF—AND YOUR PRACTICE

[*By* **JENNIFER FRANK**, *MD, FAAFP* | *Photos by* **MIKE ROEMER**]

In the military, where I received my residency training and spent the first four years of my medical career as an attending physician, evaluations were sacrosanct. Universally seen as an absolute responsibility of both the evaluator and the person being evaluated, the biannual assessment, review, and narrative summary of performance was the key to your future in the military, your career progression, the next job you would hold, and a measure of your worth to the larger organization.

Evaluations were also required within the first months of a new job or position change, or when you had a new supervisor. While cumbersome at times, the seemingly constant evaluative process served a valuable role in clearly defining roles and expectations at regular intervals and when the supervisor-supervisee relationship changed. It compelled supervisors to review periodically the trajectory of those under their command.

OPPORTUNITY FOR FEEDBACK

These evaluation sessions were opportunities to provide feedback and advice, and to make sure that those things required for successful career advancement were being sought and fulfilled. In the Army, the evaluation system institutionalized this important but often postponed or neglected process.

As a physician leader, it is easy to plead busyness, competing priorities, or a lack of know-how when it comes to completing employee evaluations. However, doing them can provide enormous benefits to your organization. Evaluations are often appreciated by those being evaluated as a way to assess and obtain feedback on their performance, an opportunity to receive the undivided attention of their

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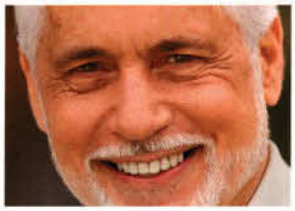


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Effective as monotherapy or in combination[1,2]*

- DBP/SBP reductions of up to -15.3/-29.0 mm Hg for BYSTOLIC when used in combination with HCTZ 25 mg (vs -1.4/-0.2 mm Hg for placebo)†
- DBP/SBP reductions of -9.3/-16.7 and -13.8/-17.6 for BYSTOLIC monotherapy 5 mg and 10 mg, respectively (vs -1.4/-0.2 for placebo)‡

Low incidence of side effects and overall low discontinuation rate[3]

- Discontinuation rate due to adverse events was 2.8% for BYSTOLIC vs 2.2% for placebo[3]

* Results from a 3-month, multicenter, randomized, double-blind, parallel-group, placebo-controlled, multifactorial-design study of BYSTOLIC and hydrochlorothiazide, alone or in combination, for the treatment of mild to moderate hypertension.

† Primary endpoint was sitting DBP at trough. Mean values at baseline: sitting DBP at trough, 102.1 mm Hg; sitting SBP at trough, 158.1 mm Hg (N=240; n=100).

‡ Primary endpoint was sitting DBP at trough. Mean values at baseline: sitting DBP at trough, 100.5 mm Hg; sitting SBP at trough, 158.1 mm Hg (N=240; n=59).

BYSTOLIC is indicated for the treatment of hypertension. BYSTOLIC may be used alone or in combination with other antihypertensive agents.

Important Safety Information

Adverse Reactions

- The most common adverse events with BYSTOLIC versus placebo (approximately ≥1% and greater than placebo) were headache, fatigue, dizziness, diarrhea, nausea, insomnia, chest pain, bradycardia, dyspnea, rash, and peripheral edema. The most common adverse events that led to discontinuation of BYSTOLIC were headache (0.4%), nausea (0.2%), and bradycardia (0.2%).

Contraindications

- BYSTOLIC is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh >B), and in patients who are hypersensitive to any component of this product.

Warnings and Precautions

- Do not abruptly discontinue BYSTOLIC therapy in patients with coronary artery disease. Severe exacerbation of angina, myocardial infarction, and ventricular arrhythmias have been reported following the abrupt discontinuation of therapy with beta blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Caution patients without overt coronary artery disease against interruption or abrupt discontinuation of therapy. As with other beta blockers, when discontinuation of BYSTOLIC is planned, carefully observe and advise patients to minimize physical activity. Taper BYSTOLIC over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, restart BYSTOLIC promptly, at least temporarily.
- BYSTOLIC was not studied in patients with angina pectoris or who had a recent MI.
- In general, patients with bronchospastic diseases should not receive beta blockers.
- Because beta blocker withdrawal has been associated with an increased risk of MI and chest pain, patients already on beta blockers should generally continue treatment throughout the perioperative period. If BYSTOLIC is to be continued perioperatively, monitor patients closely when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene are used. If beta-blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

  The beta-blocking effects of BYSTOLIC can be reversed by beta agonists, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with beta blockers.
- Beta blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Advise patients subject to spontaneous hypoglycemia and diabetic patients receiving insulin or oral hypoglycemic agents about these possibilities.
- Beta blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta blockers in these patients may be followed by an exacerbation of symptoms or may precipitate a thyroid storm.
- Beta blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.
- Because of significant negative inotropic and chronotropic effects in patients treated with beta blockers and calcium channel blockers of the verapamil and diltiazem type, monitor the ECG and blood pressure of patients treated concomitantly with these agents.

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- Aetna Part D
- CIGNA Part D
- Humana Part D
- SilverScript
- MemberHealth/CCRx
- Health Net Part D
- WellPoint Part D

Formulary status information is valid as of October 2010. Coverage is subject to change.

Warnings and Precautions (continued)

- Use caution when BYSTOLIC is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc). When BYSTOLIC is co-administered with an inhibitor or an inducer of CYP2D6, monitor patients closely and adjust the nebivolol dose according to blood pressure response. The dose of BYSTOLIC may need to be reduced. When BYSTOLIC is administered with fluoxetine, significant increases in d-nebivolol may be observed (ie, an 8-fold increase in AUC and a 3-fold increase in C_{max} for d-nebivolol).
- Renal clearance of nebivolol is decreased in patients with severe renal impairment. In patients with severe renal impairment (CICr less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. BYSTOLIC has not been studied in patients receiving dialysis.
- Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. BYSTOLIC has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population.
- Patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine while taking beta blockers.
- In patients with known or suspected pheochromocytoma, initiate an alpha blocker prior to the use of any beta blocker.

Drug Interactions

- Do not use BYSTOLIC with other beta blockers.
- Both digitalis glycosides and beta blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.
- BYSTOLIC can exacerbate the effects of myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide.

Use in Specific Populations

- Use BYSTOLIC during pregnancy only if the potential benefit justifies the potential risk to the fetus. BYSTOLIC is not recommended during nursing.
- The safety and effectiveness of BYSTOLIC have not been established in pediatric patients.
- In a placebo-controlled trial of 2128 patients (1067 BYSTOLIC, 1061 placebo) over 70 years of age with chronic heart failure receiving a maximum dose of 10 mg per day for a median of 20 months, no worsening of heart failure was reported with nebivolol compared to placebo. However, if heart failure worsens, consider discontinuation of BYSTOLIC.

Please see brief summary of full Prescribing Information on last page of this advertisement.

References: 1. Lacourcière Y, Lefebvre J, Poirier L, Archambault F, Arnott W. Treatment of ambulatory hypertensives with nebivolol or hydrochlorothiazide alone and in combination: a randomized, double-blind, placebo-controlled, factorial-design trial. *Am J Hypertens*. 1994;7:137-145. **2.** Data on file. Forest Laboratories, Inc. **3.** BYSTOLIC [package insert]. St. Louis, Mo: Forest Pharmaceuticals, Inc.; 2010. **4.** MediMedia Information Technologies, LLC, as of October 2010. Data is subject to change.

Bystolic®
(nebivolol) tablets
2.5 mg • 5 mg • 10 mg • 20 mg

Effective treatment for hypertension

www.BYSTOLIC.com

BYSTOLIC® (nebivolol) tablets **Rx Only**
Brief Summary of full Prescribing Information
Initial U.S. Approval: 2007

INDICATIONS AND USAGE: Hypertension - BYSTOLIC is indicated for the treatment of hypertension *[see Clinical Studies (14.1)]*. BYSTOLIC may be used alone or in combination with other antihypertensive agents *[see Drug Interactions (7)]*.

CONTRAINDICATIONS: BYSTOLIC is contraindicated in the following conditions: Severe bradycardia; Heart block greater than first degree; Patients with cardiogenic shock; Decompensated cardiac failure; Sick sinus syndrome (unless a permanent pacemaker is in place); Patients with severe hepatic impairment (Child-Pugh >B); Patients who are hypersensitive to any component of this product.

WARNINGS AND PRECAUTIONS: Abrupt Cessation of Therapy - Do not abruptly discontinue BYSTOLIC therapy in patients with coronary artery disease. Severe exacerbation of angina, myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β-blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Caution patients without overt coronary artery disease against interruption or abrupt discontinuation of therapy. As with other β-blockers, when discontinuation of BYSTOLIC is planned, carefully observe and advise patients to minimize physical activity. Taper BYSTOLIC over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, restart BYSTOLIC promptly, at least temporarily. **Angina and Acute Myocardial Infarction** - BYSTOLIC was not studied in patients with angina pectoris or who had a recent MI. **Bronchospastic Diseases** - In general, patients with bronchospastic diseases should not receive β-blockers. **Anesthesia and Major Surgery** - Because beta-blocker withdrawal has been associated with an increased risk of MI and chest pain, patients already on beta-blockers should generally continue treatment throughout the perioperative period. If BYSTOLIC is to be continued perioperatively, monitor patients closely when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. If β-blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. The β-blocking effects of BYSTOLIC can be reversed by β-agonists, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with β-blockers. **Diabetes and Hypoglycemia** - β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. It is not known whether nebivolol has these effects. Advise patients subject to spontaneous hypoglycemia and diabetic patients receiving insulin or oral hypoglycemic agents about these possibilities. **Thyrotoxicosis** - β-blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm. **Peripheral Vascular Disease** - β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. **Non-dihydropyridine Calcium Channel Blockers** - Because of significant negative inotropic and chronotropic effects in patients treated with β-blockers and calcium channel blockers of the verapamil and diltiazem type, monitor the ECG and blood pressure in patients treated concomitantly with these agents. **Use with CYP2D6 Inhibitors** - Nebivolol exposure increases with inhibition of CYP2D6 *[see Drug Interactions (7)]*. The dose of BYSTOLIC may need to be reduced. **Impaired Renal Function** - Renal clearance of nebivolol is decreased in patients with severe renal impairment. BYSTOLIC has not been studied in patients receiving dialysis *[see Clinical Pharmacology (12.4) and Dosage and Administration (2.1)]*. **Impaired Hepatic Function** - Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. BYSTOLIC has not been studied in patients with severe hepatic impairment *[see Clinical Pharmacology (12.4) and Dosage and Administration (2.1)]*. **Risk of Anaphylactic Reactions** - While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions. **Pheochromocytoma** - In patients with known or suspected pheochromocytoma, initiate an α-blocker prior to the use of any β-blocker.

ADVERSE REACTIONS: Clinical Studies Experience - BYSTOLIC has been evaluated for safety in patients with hypertension and in patients with heart failure. The observed adverse reaction profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse reactions reported for each of these patient populations are provided below. Excluded are adverse reactions considered too general to be informative and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population. The data described below reflect worldwide clinical trial exposure to BYSTOLIC in 6545 patients, including 5038 patients treated for hypertension and the remaining 1507 subjects treated for other cardiovascular diseases. Doses ranged from 0.5 mg to 40 mg. Patients received BYSTOLIC for up to 24 months, with over 1900 patients treated for at least 6 months, and approximately 1300 patients for more than one year. HYPERTENSION: In placebo-controlled clinical trials comparing BYSTOLIC with placebo, discontinuation of therapy due to adverse reactions was reported in 2.8% of patients treated with nebivolol and 2.2% of patients given placebo. The most common adverse reactions that led to discontinuation of BYSTOLIC were headache (0.4%), nausea (0.2%) and bradycardia (0.2%). **Table 1** lists treatment-emergent adverse reactions that were reported in three 12-week, placebo-controlled monotherapy trials involving 1597 hypertensive patients treated with either 5 mg, 10 mg, or 20-40 mg of BYSTOLIC and 205 patients given placebo and for which the rate of occurrence was at least 1% of patients treated with nebivolol and greater than the rate for those treated with placebo in at least one dose group. **Table 1.** Treatment-Emergent Adverse Reactions with an Incidence (over 6 weeks) ≥1% in BYSTOLIC-Treated Patients and at a Higher Frequency than Placebo-Treated Patients are listed below in the following order: System Organ Class Preferred Term [Placebo (n = 205), Nebivolol 5 mg (n = 459), Nebivolol 10 mg (n = 461), Nebivolol 20-40 mg (n = 677)] **Cardiac Disorders:** Bradycardia (0, 0, 0, 1); **Gastrointestinal Disorders:** Diarrhea (2, 2, 2, 3); Nausea (0, 1, 3, 2); **General Disorders:** Fatigue (1, 2, 2, 5); Chest pain (0, 0, 1, 1); Peripheral edema (0, 1, 1, 1); **Nervous System Disorders:** Headache (6, 9, 6, 7); Dizziness (2, 2, 3, 4); **Psychiatric Disorders:** Insomnia (0, 1, 1, 1); **Respiratory Disorders:** Dyspnea (0, 0, 1, 1); **Skin and Subcutaneous Tissue Disorders:** Rash (0, 0, 1, 1). Listed below are other reported adverse reactions with an incidence of at least 1% in the more than 4300 patients treated with BYSTOLIC in controlled or open-label trials except for those already appearing in **Table 1**, terms too general to be informative, minor symptoms, or adverse reactions unlikely to be attributable to drug because they are common in the population. These adverse reactions were in most cases observed at a similar frequency in placebo-treated patients in the controlled studies. **Body as a Whole:** asthenia. **Gastrointestinal System Disorders:** abdominal pain. **Metabolic and Nutritional Disorders:** hypercholesterolemia. **Nervous System Disorders:** paraesthesia. **Laboratory Abnormalities** - In controlled monotherapy trials of hypertensive patients, BYSTOLIC was associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol and platelet count. **Postmarketing Experience** - The following adverse reactions have been identified from spontaneous reports of BYSTOLIC received worldwide and have not been listed elsewhere. These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to BYSTOLIC. Adverse reactions common in the population have generally been omitted. Because these adverse reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to BYSTOLIC exposure: abnormal hepatic function (including increased AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, atrioventricular block (both second- and third-degree), bronchospasm, erectile dysfunction, hypersensitivity (including urticaria, allergic vasculitis and rare reports of angioedema), myocardial infarction, pruritus, psoriasis, Raynaud's phenomenon, peripheral ischemia/claudication, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vertigo, and vomiting.

DRUG INTERACTIONS: CYP2D6 Inhibitors - Use caution when BYSTOLIC is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.) *[see Clinical Pharmacology (12.5)]*. **Hypotensive Agents** - Do not use BYSTOLIC with other β-blockers. Closely monitor patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, because the added β-blocking action of BYSTOLIC may produce excessive reduction of sympathetic activity. In patients who are receiving BYSTOLIC and clonidine, discontinue BYSTOLIC for several days before the gradual tapering of clonidine. **Digitalis Glycosides** - Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. **Calcium Channel Blockers** - BYSTOLIC can exacerbate the effects of myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects, Category C - Decreased pup body weights occurred at 1.25 and 2.5 mg/kg in rats, when exposed during the perinatal period (late gestation, parturition and lactation). At 5 mg/kg and higher doses (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance. In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5 and 10 times the MRHD), and small reversible delays in sternal and thoracic ossification associated with the reduced fetal body weights and a small increase in resorption occurred at 40 mg/kg/day (10 times the MRHD). No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD). **Labor and Delivery** - Nebivolol caused prolonged gestation and dystocia at doses ≥5 mg/kg in rats (1.2 times the MRHD). These effects were associated with increased fetal deaths and stillborn pups, and decreased birth weight, live litter size and pup survival rate, events that occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation). No studies of nebivolol were conducted in pregnant women. Use BYSTOLIC during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** - Studies in rats have shown that nebivolol or its metabolites cross the placental barrier and are excreted in breast milk. It is not known whether this drug is excreted in human milk. Because of the potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia, BYSTOLIC is not recommended during nursing. **Pediatric Use** - Safety and effectiveness in pediatric patients have not been established. Pediatric studies in ages newborn to 18 years old have not been conducted because of incomplete characterization of developmental toxicity and possible adverse effects on long-term fertility *[see Nonclinical Toxicology (13.1)]*. **Geriatric Use** - Of the 2800 patients in the U.S.-sponsored placebo-controlled clinical hypertension studies, 478 patients were 65 years of age or older. No overall differences in efficacy or in the incidence of adverse events were observed between older and younger patients. **Heart Failure** - In a placebo-controlled trial of 2128 patients (1067 BYSTOLIC, 1061 placebo) over 70 years of age with chronic heart failure receiving a maximum dose of 10 mg per day for a median of 20 months, no worsening of heart failure was reported with nebivolol compared to placebo. However, if heart failure worsens consider discontinuation of BYSTOLIC.

OVERDOSAGE: In clinical trials and worldwide postmarketing experience there were reports of BYSTOLIC overdose. The most common signs and symptoms associated with BYSTOLIC overdosage are bradycardia and hypotension. Other important adverse reactions reported with BYSTOLIC overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse reactions associated with β-blocker overdose include bronchospasm and heart block. The largest known ingestion of BYSTOLIC worldwide involved a patient who ingested up to 500 mg of BYSTOLIC along with several 100 mg tablets of acetylsalicylic acid in a suicide attempt. The patient experienced hyperhidrosis, pallor, depressed level of consciousness, hypokinesia, hypotension, sinus bradycardia, hypoglycemia, hypokalemia, respiratory failure, and vomiting. The patient recovered. Because of extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance. If overdose occurs, provide general supportive and specific symptomatic treatment. Based on expected pharmacologic actions and recommendations for other β-blockers, consider the following general measures, including stopping BYSTOLIC, when clinically warranted: *Bradycardia:* Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary. *Hypotension:* Administer IV fluids and vasopressors. Intravenous glucagon may be useful. *Heart Block (second- or third-degree):* Monitor and treat with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary. *Congestive Heart Failure:* Initiate therapy with digitalis glycosides and diuretics. In certain cases, consider the use of inotropic and vasodilating agents. *Bronchospasm:* Administer bronchodilator therapy such as a short-acting inhaled β_2-agonist and/or aminophylline. *Hypoglycemia:* Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required. Supportive measures should continue until clinical stability is achieved. The half-life of low doses of nebivolol is 12-19 hours. Call the National Poison Control Center (800-222-1222) for the most current information on β-blocker overdose treatment.

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supervisor to discuss their goals, plans, and professional future, and a chance to share concerns, worries, or problems.

Methods for completing evaluations range from the very formalized to the extremely unstructured. What follows are some general tips to make this part of your job an enjoyable and successful one:

Conduct evaluations at least once a year.

Yearly reviews afford an opportunity to evaluate your employee through the entire cycle of his or her job. Creating an "anniversary" of sorts will allow the staff member to create a set of goals, have sufficient time to achieve or modify them, and be able to summarize what he or she completed, what went well, and what needs improvement. Spring and fall are good seasons to conduct evaluations as they tend not to compete with other stressful or busy times, such as summer vacations or holidays. Depending on the number of staff members you evaluate, you may choose to group all of the evaluations in a single month or conduct them on the anniversary of the employee's date of hire.

Evaluate in times of change or stress.

Even if informal, evaluations can help in situations such as the first year of the employee's hire, significant changes in job demands or responsibilities, or in times of organizational chaos or disruption. A new employee often values and needs more frequent feedback to know if he or she is meeting job expectations, and to have the opportunity to ask questions or voice concerns.

Use the employee's professional degree or title on evaluation comments.

Avoid using "Jane" and instead use Jane Smith, RN, BSN. While this may feel awkward, particularly with employees you know well, it is important to emphasize their professional role by using their professional title. It demonstrates that, while you may be friendly, your relationship is primarily a professional one. Furthermore, it emphasizes that you are evaluating their job-specific function, not just commenting on their personality.

Schedule an appropriate amount of time.

Usually plan for an uninterrupted hour to conduct the evaluation. Your time, especially uninterrupted time, is one of the most valuable things you can offer your staff. By offering it to your staff member, you send the message that he or she and the evaluation are a priority for you. The performance review is primarily a service to the person being evaluated. As such, you want to afford adequate time and your full attention to provide feedback and to address concerns. Allotting sufficient time will also assist you both in developing the conversation beyond a surface review of general job functions.

Ask the staff member to do homework, such as completing a self-assessment form, before the evaluation session.

Very few of us could list all of our accomplishments from the past year without thinking it through carefully. Additionally, some staff members, particularly the high performers, may look at accomplishments as just "part of my job." Using a self-assessment form ensures that the time you've allotted to the review is used well. Also, it will assist both of you in objectively evaluating performance goals and achievements.

Don't use a formal evaluation session to "surprise" the staff member with negative feedback.

A performance review is a summary of performance over a set period of time. While using specific examples to explain both areas of excellence and areas of concern is a good idea, these examples should already be familiar to the staff member. Feedback of any kind should take place as close to the event as possible. It is understandable that a staff member will feel blindsided if he or she is hearing for the first time about an issue that could affect his or her evaluation adversely. Performance reviews are not feedback sessions.

Look for opportunities to facilitate promotions, pay raises, or professional development.

It is unfortunate but true that when it comes to performance, too often no news is good news. If a staff member does not receive any feedback, the assumption is that it's because he or she is doing a fine job. Weeks or months can pass before you realize that your star employee may not know he's a star. Many organizations have official ways of recognizing professional excellence beyond just a good performance review. Bonuses, step increases, promotions, awards, and pay raises should be used judiciously to reward outstanding achievement and to make a statement about an employee's potential to continue to do great things. An excellent performance evaluation should prompt you to identify other ways to recognize your employee.

The summary is vital.

Numerical rating scales are not nearly as helpful as a few carefully chosen and relevant summary sentences. A good summary of the staff member's performance can drive home the point that he or she is valued, respected, and doing a great job. Give specific examples of strengths and accomplishments. Describe how the staff member contributes to the success of the organization. Emphasize potential for growth and particular interests he or she might have in returning to school, earning a certification, or changing duties.

Physicians are often leaders of clinics and other organizations. While you may not have much training in human resources or practice administration, you have a lot of experience analyzing, explaining, summarizing, and documenting. Use these skills to excel in one of the most important areas of staff development—the performance review process. MEC

The author is a family physician in private practice in Neenah, Wisconsin. Send your feedback to medec@advanstar.com.

"Every silver cloud has a dark lining," says Michael T. Beckham, MD, right, who is convinced that midlevel providers such as Kristin Conrey, left, add value to a medical practice. He learned the hard way the mistakes to avoid when adding their services.

A dozen years with midlevels

TAKE-HOME LESSONS ABOUT WHAT WENT RIGHT, WHAT WENT WRONG

[*By* **MICHAEL T. BECKHAM**, *MD* | *Photos by* **HARRISON MCCLARY**]

After years of hard work, you've finally arrived. Gone are the days spent waiting for the next patient to wander in, when your patients consisted of nothing but uninsured follow-up appointments from the emergency room, other doctors' charges, and drug-seekers. You are 5, 10, or 20 years into your practice and are seeing as many patients a day as you want. You've earned the respect of nurses and doctors in your community, and you're flattered by all the new patients referred to you by existing patients. It's what you dreamed of when starting medical school, and you are hitting your stride.

And so it went for me. Yet, suddenly, I had a different problem. I had more patients than I could handle. Patients were waiting 4 or 5 weeks to get

HARRISON MCCLARY/BLACKSTAR

"[ADDING MIDLEVELS] BROUGHT GREAT BENEFITS TO MY PRACTICE, AND I AM A FIRM BELIEVER THAT NPs AND PAs OFFER HOPE FOR THE FUTURE OF PRIMARY CARE."

an appointment and more than 4 months for a physical exam. I started my workday earlier and shortened my lunch time, but I still couldn't keep up. The paperwork piled up, and I spent precious minutes returning more and more calls. After-hours calls increased.

What could I do to avoid working myself to death and still spend enough time with patients without losing revenue? A cardiologist friend jokingly suggested I clone myself.

My solution, like an increasing number of practices in the United States, was to add midlevel providers. Doing so brought great benefits to my practice, and I am a firm believer that nurse practitioners (NPs) and physician assistants (PAs) offer hope for the future of primary care.

Every silver cloud has a dark lining, however. The mistakes I made related to midlevel providers partially contributed to my losing my solo practice. Here I share with you advice to make the use of midlevel providers work in your practice, based on what I have done right and what I have done wrong in 12 years of supervising NPs and PAs.

TAKE THESE STEPS

Midlevels can add much value to your practice—for you and your patients—if you remember these points:

Use midlevel providers in all areas of your practice.

We needed a way to allow patients greater access to the practice, including same-day appointments, and I needed help in reducing my hours and my patient calls. The use of midlevel providers served as a solution to all these issues. With time, one of my midlevel providers even offered more help, serving as a disease management specialist and running a diabetes and cholesterol "clinic" within my practice. And one of my NPs helped me on rounds in the hospital and cut my hospital time in half. By covering part of overhead and increasing visits, the midlevel providers helped increase my net revenue and saved me time.

Hire top-quality midlevel providers.

Initially, I had the luxury of hiring midlevel providers with whom I had previously worked, one from my former group and another from the hospital. I knew they possessed the essential traits I needed in a midlevel: intelligence, a strong work ethic, honesty, and great people skills. I'd recommend against hiring midlevels fresh out of school. I'd suggest hiring PAs or NPs with years of clinical experience, either in a nursing role or as a midlevel. When hiring, dig deep. Don't just speak with references. Get permission to speak with all previous employers. Get to know the real person through co-workers. Interview the candidate both in the office and in an informal setting, where you have a better chance of revealing important character traits. And don't forget to run a criminal background check.

Train them extensively.

This was the single most important factor in my success. I initially reviewed all of the midlevels' charts, giving them daily feedback. I made it clear that the medical practice was mine and that there were certain ways we did things such as check medication lists, provide preventive care, and prescribe antibiotics. The texts we used for defining the scope of practice on paper were rather general, but I was very specific when it came to daily patient interactions. By investing time at the beginning, you ensure uniform practice standards.

Convince your patients that the midlevels really are an extension of you.

Accomplishing this task also was vital to the success of my experience, and doing so was not as difficult as one might think. First, we gave each patient a handout describing the midlevel provider's role and background. We reassured each patient that if seeing the midlevel wasn't acceptable to him or her, then he or she could see the doctor if willing to wait. Most patients acquiesced when given the choice between a same-day appointment with a midlevel or seeing the doctor a few days later. Next, in many cases, I would stick my head in the exam room and give the PA/ NP my support in person. I made myself available for a quick visit if necessary. My midlevels assisted in such instances by including me whenever a patient seemed even a little upset about not seeing the doctor. Before long, many of my patients grew very fond of the NPs and PAs and were requesting specific midlevels by name.

POWER POINTS

Hire experienced midlevels, train them, and use them in all areas of your practice.

Encourage questions from your midlevels, and be open to learning from them.

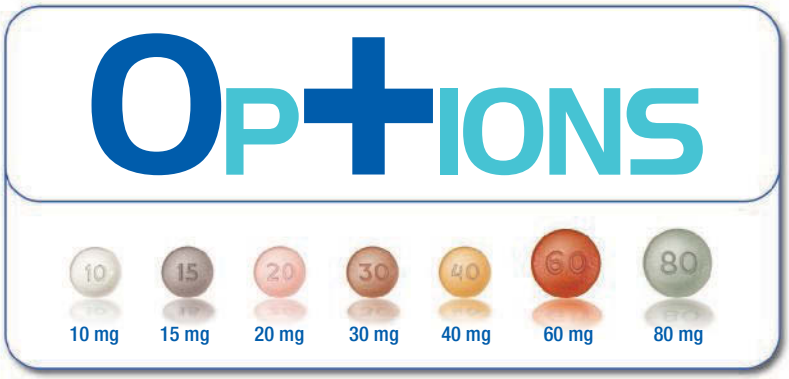
Be supportive of your midlevels in front of patients; convey that the midlevels are an extension of you.

Market-rate compensation will help your midlevels stay motivated.

For moderate to severe pain when a continuous, around-the-clock (ATC) opioid analgesic is needed for an extended period of time

OxyContin® (II)

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS



Tablets are actual size.

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE

OxyContin contains oxycodone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (9)

OxyContin can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9.2)

OxyContin is a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

OxyContin is not intended for use on an as-needed basis. (1)

Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer. OxyContin 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in opioid-tolerant patients, as they may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory-depressant or sedating effects of opioids. (2.7)

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. (2.2)

OxyContin must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone. (2.1)

The concomitant use of OxyContin with all cytochrome P450 3A4 inhibitors such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse effects and may cause potentially fatal respiratory depression. Patients receiving OxyContin and a CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (7.2)

Please read Brief Summary of Full Prescribing Information on the following pages and Contraindications on adjacent page.

Learn more about OxyContin® at **www.PurdueHCP.com/OxyContin**

Because different patients with pain have different treatment needs

- Q12h dosing with as few as 2 tablets per day
- When converting from other opioids, the 7 OxyContin® Tablet strengths enable you to more closely approximate the calculated conversion dose
- OxyContin® is a single-entity opioid
- Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days

Indications and Usage

OxyContin® is a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Usage

OxyContin® is not intended for use on an as-needed basis.

As used here, "moderate" and "moderate to severe" pain do not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort.

OxyContin® is not indicated for the management of pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin® is indicated for postoperative use following the immediate postoperative period only if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

OxyContin® is not indicated for preemptive analgesia (preoperative administration for the management of postoperative pain).

OxyContin® is not indicated for rectal administration.

OxyContin® is contraindicated in

- Patients who have significant respiratory depression
- Patients who have or are suspected of having paralytic ileus
- Patients who have acute or severe bronchial asthma
- Patients with known hypersensitivity to any of its components or the active ingredient, oxycodone

OXYCONTIN® CII
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
Q12h

Purdue is firmly committed to maintaining the highest standards of sales and marketing practices in the industry while continuing to advance the proper treatment of patients. If Purdue's sales and marketing practices fail to meet this standard, we urge you to contact us at 1-888-726-7535.

OxyContin® CII

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

10 mg | 15 mg | 20 mg | 30 mg

40 mg | 60 mg* | 80 mg*

***60 mg and 80 mg tablets for use in opioid-tolerant patients only**

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details please see the full prescribing information and Medication Guide.)

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE

OxyContin contains oxycodone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (9)

OxyContin can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9.2)

OxyContin is a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

OxyContin is not intended for use on an as-needed basis. (1)

Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

OxyContin 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in opioid-tolerant patients, as they may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory-depressant or sedating effects of opioids. (2.7)

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. (2.2)

OxyContin must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone. (2.1)

The concomitant use of OxyContin with all cytochrome P450 3A4 inhibitors such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse effects and may cause potentially fatal respiratory depression. Patients receiving OxyContin and a CYP3A4 inhibitor should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (7.2)

1 INDICATIONS AND USAGE

OxyContin is a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Usage

OxyContin is not intended for use on an as-needed basis.

OxyContin is not indicated for the management of pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is indicated for postoperative use following the immediate post-operative period only if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

OxyContin is not indicated for pre-emptive analgesia (preoperative administration for the management of post-operative pain).

OxyContin is not indicated for rectal administration.

4 CONTRAINDICATIONS

OxyContin is contraindicated in:

- patients who have significant respiratory depression
- patients who have or are suspected of having paralytic ileus
- patients who have acute or severe bronchial asthma
- patients who have known hypersensitivity to any of its components or the active ingredient, oxycodone.

5 WARNINGS AND PRECAUTIONS

5.1 Information Essential for Safe Administration

OxyContin tablets must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.

OxyContin 60 mg and 80 mg Tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in opioid-tolerant patients. Use of these doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Instruct patients against use by individuals other than the patient for whom OxyContin was prescribed, as such inappropriate use may have severe medical consequences, including death.

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

5.2 CNS Depression

OxyContin may cause somnolence, dizziness, alterations in judgment and alterations in levels of consciousness, including coma.

5.3 Interactions with Alcohol, CNS Depressants and Illicit Drugs

Hypotension, profound sedation, coma or respiratory depression may result if OxyContin is added to a regimen that includes other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). Therefore, use caution when deciding to initiate therapy with OxyContin in patients who are taking other CNS depressants. Take into account the types of other medications being taken, the duration of therapy with them, and the patient's response to those medicines, including the degree of tolerance that has developed to CNS depression. Consider the patient's use, if any, of alcohol and/or illicit drugs that cause CNS depression. If the decision to begin OxyContin is made, start with a lower OxyContin dose than usual. *[see Drug Interactions (7.3)]*

Consider using a lower initial dose of a CNS depressant when given to a patient currently taking OxyContin due to the potential of additive CNS depressant effects.

5.4 Respiratory Depression

Decreased respiratory drive resulting in respiratory depression is the chief hazard from the use or abuse of opioid agonists, including OxyContin. The risk of opioid-induced respiratory depression is increased, for example, in elderly *[see Use In Specific Populations (8.5)]* or debilitated patients; following large initial doses in any patient who is not tolerant to the respiratory-depressant or sedating effects of opioids; or when opioids are given in conjunction with other agents that either depress respiratory drive or consciousness.

Use OxyContin with extreme caution in patients with any of the following:

- significant chronic obstructive pulmonary disease or cor pulmonale
- other risk of substantially decreased respiratory reserve
- hypoxia
- hypercapnia
- pre-existing respiratory depression

Respiratory depression induced by opioids typically follows a pattern entailing first a shift in CO_2 responsiveness of the CNS respiratory drive center, which results in a decrease in the urge to breathe, despite the presence of hypercapnia. The increase in brain CO_2 can result in sedation that can accentuate the sedation from the opioid itself. Profound sedation, unresponsiveness, infrequent deep ("sighing") breaths or atypical snoring frequently accompany opioid-induced respiratory depression. Eventually, hypoxia ensues. In addition to further decreasing consciousness, hypoxia, along with hypercapnia, can predispose to life-threatening cardiac arrhythmias.

5.5 Seizures

Oxycodone, as with other opioids, may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Use OxyContin with caution in patients with a history of seizure disorders.

5.6 Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention, which can lead to an elevation of cerebrospinal fluid pressure. This effect may be exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone may produce miosis that is independent of ambient light, and altered consciousness, either of which may obscure neurologic signs associated with increased intracranial pressure in persons with head injuries.

5.7 Hypotensive Effect

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Administer OxyContin with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

5.8 Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of OxyContin, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations.

The expected clinical results with CYP3A4 inhibitors would be an increase in oxycodone plasma concentrations and possibly increased or prolonged opioid effects. The expected clinical results with CYP3A4 inducers would be a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone.

If co-administration is necessary, caution is advised when initiating OxyContin treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved. *[see Drug Interactions (7.2) and Clinical Pharmacology (12)*]

5.9 Interactions with Mixed Agonist/Antagonist Opioid Analgesics

It is generally not advisable to administer mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) to a patient receiving OxyContin. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect and may precipitate withdrawal symptoms in these patients.

5.10 Use in Pancreatic/Biliary Tract Disease and Other Gastrointestinal Conditions

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in the serum amylase.

The administration of OxyContin may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Use OxyContin with caution in patients who are at risk of developing ileus.

5.11 Tolerance

Tolerance to opioids is demonstrated by the need for increasing doses to maintain adequate analgesic effect (in the absence of disease progression or other external factors). If tolerance develops, or if pain severity increases, a gradual increase in dose may be required. The first sign of tolerance is usually a reduced duration of effect. Tolerance to different effects of opioids may develop to varying degrees and at varying rates in a given individual. There is also inter-patient variability in the rate and extent of tolerance that develops to

various opioid effects, whether the effect is desirable (e.g., analgesia) or undesirable (e.g., nausea).

5.12 Special Risk Groups

Use OxyContin with caution in the following conditions, due to increased risk of adverse reactions: alcoholism; delirium tremens; adrenocortical insufficiency; CNS depression; debilitation; kyphoscoliosis associated with respiratory compromise; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

5.13 Driving and Operating Machinery

OxyContin may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Caution patients accordingly.

5.14 Use in Addiction Treatment

OxyContin has no approved use in the treatment of addiction. Its proper usage in individuals with drug or alcohol addiction (substance dependence), either active or in remission, is for the management of pain requiring opioid analgesia.

5.15 Laboratory Monitoring

Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative". Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and use caution in interpreting results.

6 ADVERSE REACTIONS

The following adverse reactions described elsewhere in the labeling include:

- Respiratory depression *[see Boxed Warning, Warnings and Precautions (5.1, 5.4) and Overdosage (10)]*
- CNS depression *[see Warnings and Precautions (5.1, 5.2) and Overdosage (10)]*
- Hypotensive effects *[see Warning and Precautions (5.7) and Overdosage (10)]*
- Drug abuse, addiction, and dependence *[see Drug Abuse and Dependence (9.2, 9.3)]*
- Paralytic ileus *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

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

The safety of OxyContin was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

OxyContin may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock *[see Overdosage (10)]*.

The most common adverse reactions (>5%) reported by patients in clinical trials comparing OxyContin with placebo are shown in Table 2 below:

TABLE 2: Common Adverse Reactions (>5%)

Adverse Reaction	OxyContin (n=227)	Placebo (n=45)
	(%)	(%)
Constipation	(23)	(7)
Nausea	(23)	(11)
Somnolence	(23)	(4)
Dizziness	(13)	(9)
Pruritus	(13)	(2)
Vomiting	(12)	(7)
Headache	(7)	(7)
Dry Mouth	(6)	(2)
Asthenia	(6)	—
Sweating	(5)	(2)

In clinical trials, the following adverse reactions were reported in patients treated with OxyContin with an incidence between 1% and 5%:

Gastrointestinal disorders: abdominal pain, diarrhea, dyspepsia, gastritis, hiccups

General disorders and administration site conditions: chills, fever

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: twitching

Psychiatric disorders: abnormal dreams, anxiety, confusion, dysphoria, euphoria, insomnia, nervousness, thought abnormalities

Respiratory, thoracic and mediastinal disorders: dyspnea, hiccups

Skin and subcutaneous tissue disorders: rash

Vascular disorders: postural hypotension

The following adverse reactions occurred **in less than 1% of patients** involved in clinical trials:

Blood and lymphatic system disorders: lymphadenopathy

Ear and labyrinth disorders: tinnitus

Eye disorders: abnormal vision

Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, stomatitis

General disorders and administration site conditions: withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema

Injury, poisoning and procedural complications: accidental injury

Investigations: ST depression

Metabolism and nutrition disorders: dehydration

Nervous system disorders: syncope, migraine, abnormal gait, amnesia, hyperkinesia, hypesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perversion

Psychiatric disorders: depression, agitation, depersonalization, emotional lability, hallucination

Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention

Reproductive system and breast disorders: impotence

Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration

Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of controlled-release oxycodone. Because these events 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: abuse, addiction, overdose, death, amenorrhea, symptoms associated with an anaphylactic or anaphylactoid reaction, cholestasis, dental caries, increased hepatic enzymes, muscular hypertonia, hyponatremia, ileus, palpitations (in the context of withdrawal), seizures, syndrome of inappropriate antidiuretic hormone secretion, and urticaria.

In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

7 DRUG INTERACTIONS

7.1 Neuromuscular Junction Blocking Agents

OxyContin may enhance the neuromuscular blocking action of true skeletal muscle relaxants (such as pancuronium) and produce an increased degree and/or duration of respiratory depression.

7.2 Agents Affecting Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4:

Since the CYP3A4 isoenzyme plays a major role in the metabolism of OxyContin, drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations. A published study showed that the co-administration of the antifungal drug, voriconazole, increased oxycodone AUC and C_{max} by 3.6 and 1.7 fold, respectively. Although clinical studies have not been conducted with other CYP3A4 inhibitors, the expected clinical results would be increased or prolonged opioid effects. If co-administration with OxyContin is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP450 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved. *[see Clinical Pharmacology (12.3)]*

Inducers of CYP3A4:

CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone (oral) AUC and Cmax by 86% and 63%, respectively. If co-administration with OxyContin is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

Inhibitors of CYP2D6:

Oxycodone is metabolized in part to oxymorphone via cytochrome CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not been shown to be of clinical significance during oxycodone treatment.

7.3 CNS Depressants

Start OxyContin at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other CNS depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate. *[see Warnings and Precautions (5.2)]*

7.4 Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should generally not be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as OxyContin. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and may precipitate withdrawal symptoms in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category B:

There are no adequate and well-controlled studies of oxycodone use during pregnancy. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. In animal reproduction and developmental toxicology studies, no evidence of fetal harm was observed. Because animal reproduction studies are not always predictive of human response, oxycodone should be used during pregnancy only if clearly needed.

Teratogenic Effects

The effect of oxycodone in human reproduction has not been adequately studied. Studies with oral doses of oxycodone hydrochloride in rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 0.5 and 15 times an adult human dose of 160 mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone. In a pre- and postnatal toxicity study, female rats received oxycodone during gestation and lactation. There were no long-term developmental or reproductive effects in the pups. *[see Nonclinical Toxicology (13)]*

Non-Teratogenic Effects

Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4-times an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. OxyContin is not recommended for use in women immediately prior to and during labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. Have a specific opioid antagonist, such as naloxone or nalmefene, available for reversal of opioid-induced respiratory depression in the neonate.

Neonates whose mothers have been taking opioids chronically may also exhibit withdrawal signs, either at birth and/or in the nursery, because they have developed physical dependence. This is not, however, synonymous with addiction *[see Drug Abuse and Dependence (9.3)]*. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts.

8.3 Nursing Mothers

Oxycodone has been detected in breast milk. Instruct patients not to undertake nursing while receiving OxyContin. Do not initiate OxyContin therapy while nursing because of the possibility of sedation or respiratory depression in the infant.

Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.4 Pediatric Use

Safety and effectiveness of OxyContin in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% *[see Clinical Pharmacology (12.3)]*. Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride controlled-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received oxycodone hydrochloride controlled-release tablets. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. However, reduce the starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients. Respiratory depression is the chief risk in elderly or debilitated patients, usually the result of large initial doses in patients who are not tolerant to opioids, or when opioids are given in conjunction with other agents that depress respiration. Titrate the dose of OxyContin cautiously in these patients.

8.6 Hepatic Impairment

A study of OxyContin in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function. Therefore, in the setting of hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Follow a conservative approach to dose initiation and adjust according to the clinical situation *[see Clinical Pharmacology (12.3)]*.

8.8 Gender Differences

In pharmacokinetic studies with OxyContin, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OxyContin contains oxycodone, which is a Schedule II controlled substance with an abuse liability similar to morphine. OxyContin, like morphine and other opioids used for analgesia, can be abused and is subject to criminal diversion.

9.2 Abuse

Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances.

With parenteral abuse, the tablet excipients can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Opioid drugs are sought by people with substance use disorders (abuse or addiction, the latter of which is also called "substance dependence") and criminals who supply them by diverting medicines out of legitimate distribution channels. OxyContin is a target for theft and diversion.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, altering or forging of prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among people with untreated substance use disorders, and criminals who divert controlled substances.

The risks of misuse and abuse should be considered when prescribing or dispensing OxyContin. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.

Compromising an extended or controlled-release delivery system will result in the uncontrolled delivery of oxycodone and pose a significant risk to the abuser that could result in overdose and death *[see Warnings and Precautions (5.1)]*. The risk of fatal overdose is further increased when oxycodone is abused concurrently with alcohol or other CNS depressants, including other opioids *[see Warnings and Precautions (5.3)]*. Abuse may occur by taking intact tablets without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation.

Drug addiction is characterized by compulsive abuse, repeated use for non-medical purposes, loss of control over intake, craving of psychic effects and continued abuse despite harm or risk of harm in medical, social, legal or occupational domains. There is a potential for drug addiction to develop following exposure to opioids, including oxycodone. Drug addiction is a treatable disease, but relapse is common.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by intentional misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin has been diverted for non-medical use.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, proper dispensing and correct storage and handling are appropriate measures that help to limit misuse and abuse of opioid drugs. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Physical dependence to an opioid is manifested by characteristic withdrawal signs and symptoms after abrupt discontinuation of a drug, significant dose reduction or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome in adults is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. *[See Use In Specific Populations (8.2)]*

In general, opioids should not be abruptly discontinued *[see Dosage and Administration (2.9)]*.

10 OVERDOSAGE

Acute overdosage with OxyContin can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring and death.

It is important to take the pharmacokinetic profile of OxyContin into account when treating overdose. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects as opioid continues to be absorbed from ingested tablets.

Deaths due to overdose have been reported with abuse and misuse of whole OxyContin tablets, and with abuse and misuse by ingesting, inhaling, or injecting crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of OxyContin overdosage, primary attention should be given to the maintenance of a patent airway, and of effective ventilation (clearance of CO_2) and oxygenation, whether by spontaneous, assisted or controlled respiration. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Since the duration of action of OxyContin may exceed that of the antagonist, especially when the overdose involves intact tablets, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling as needed to maintain adequate respiration. Do not administer opioid antagonists in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin, an abrupt partial or complete reversal of opioid effects may precipitate an acute abstinence (or withdrawal) syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. See the prescribing information for the specific opioid antagonist for details of its proper use.

17 PATIENT COUNSELING INFORMATION

See MEDICATION GUIDE as appended at the end of the full prescribing information

17.1 Information for Patients and Caregivers

Provide the following information to patients receiving OxyContin or their caregivers:

- Advise patients that OxyContin contains oxycodone, which is a morphine-like substance.
- Advise patients that OxyContin is designed to work properly only if swallowed whole. Taking cut, broken, chewed, crushed, or dissolved OxyContin Tablets can result in a fatal overdose.
- Advise patients that OxyContin tablets should be taken one tablet at a time.
- Advise patients not to pre-soak, lick or otherwise wet the tablet prior to placing in the mouth.
- Advise patients to take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth.
- Advise patients to report adverse experiences, and episodes of increased or incident pain occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
- Advise patients not to adjust the dose of OxyContin without consulting the prescribing professional.
- Advise patients that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
- Advise patients not to combine OxyContin with alcohol or other central nervous system depressants (e.g. sedatives, hypnotics) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
- Advise women of childbearing potential who become, or are planning to become, pregnant to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
- Advise patients that OxyContin is a drug with known abuse potential. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
- Advise patients that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. If tapering is appropriate, their prescriber can provide a dose schedule to gradually discontinue the medication.
- Advise patients to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

CAUTION
DEA Order Form Required.

Purdue Pharma L.P.
Stamford, CT 06901-3431

U.S. Patent Numbers 5,508,042; 6,488,963; 7,129,248; 7,674,799; 7,674,800 and 7,683,072

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"MY PA CONTINUES TO PROVIDE GREAT VALUE BY INCREASING PATIENT ACCESS TO THE PRACTICE AND WORKING IN SAME-DAY APPOINTMENTS."

Encourage questions.

I made it clear to the midlevels that we were part of a team and that I expected to be called in if they had any doubts when they were delivering care. I really had to demonstrate that there were no dumb questions; I could not afford to have providers afraid to seek my advice or counsel.

Humble yourself.

Just as when working with medical students, I often found that I learned as much from the midlevels as they learned from me. Their questions forced me to go back to the books or the Web to refresh my memory time and time again. By having to support my recommendations with evidence, I became a better doctor.

AVOID THESE MOVES

Mistakes related to midlevels can affect patient satisfaction and your livelihood, so be sure to avoid these ones:

Fail to provide financial incentives.

Any good businessperson knows that employees respond to financial rewards, but I overlooked this important issue. In the beginning, we all worked hard, and I paid my midlevel providers well above market average. After a few years, however, the midlevels showed a tendency to slow down some, and because I failed to research standard benchmarks, I failed to find ways to motivate them, and profits declined. A related mistake I made was failing to ask for more help regarding expectations. In retrospect, I should have obtained information related to workload expectations from consultants and the Medical Group Management Association. In my subsequent practice, this was taken care of, and I had one of the hardest-working PAs around.

Hire when money is tight.

Things were going well for me and my three midlevels (one full-time and two part-time) in my 6-year-old solo practice until I took some risks that proved to be disastrous. I expanded into a large office and nearly tripled my rent. Soon after, I lost money after buying and failing to implement an unworkable electronic health record system, and I lost a physician employee 8 months after hiring her. Out of desperation, I hired another PA to replace the doctor and was surprised when patients left the practice. I was saddled with tremendous overhead, too many mouths to feed, and not enough revenue. As the recession deepened, banks were unwilling to lend money.

Become overdependent on midlevel providers.

As my practice grew and my supervisory role expanded, I found myself personally seeing fewer patients. I was tempted to let a work-in patient see the PA when I could have seen the patient myself. Distracted by the stresses of running a solo practice, my patient visits fell. An unintended effect was that patients started to complain about never seeing me. And worse still, numerous patients changed doctors without letting the practice know, presumably because they felt abandoned. In losing the physician employee and hiring the PA I didn't need, a perfect storm was created. Overhead expenses climbed while revenues dropped. Sensing a crisis, one of my NPs left for greener pastures, and I had no choice but to cut my losses and join another primary care group.

At this point in my career, I am grateful for all that I have learned through managing midlevel providers. My PA continues to provide great value by increasing patient access to the practice and working in same-day appointments. She spends a little more time with patients and gives them a bit more TLC than I could give.

I know that the care provided through our model of delivery, by incorporating proper training and close physician supervision, far exceeds that of the clinics that are popping up. This is a great model for the changes in healthcare delivery coming our way. ME

The author is a board-certified internist who has practiced in the Nashville, Tennessee, area for more than 16 years. Send your feedback about this article to medec@advanstar.com.

ModernMedicine NETWORK

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Learn how benchmarking data can keep your practice operationally healthy at MedicalEconomics.com/compare

MODERNMEDICINE BOX CREDIT: MIKE FENDER

Doctors' WRITING CONTEST 2011

New Doctor Award

Robert Rhodes, MD, says he has derived great satisfaction from helping women through pregnancy and delivering nearly 1,000 babies.

Saving Grace

AN EMERGENCY CESAREAN DELIVERY AND ITS SURPRISING AFTERMATH SHAPE A DOCTOR'S CAREER PATH

[*By* **ROBERT B. RHODES**, *MD, FAAFP*]

That morning, the sun had painted a beautiful array of colors over the town, but they fell behind me as I drove into the cavernous gray hospital parking garage. By the time my shift was over, I would be yearning to be outside again to get some warmth on my face, soak in the colors, and heal the coldness in my hands and my heart.

It had been a sleepless night for me. I was newly married, living in a new town and just beginning my residency—all insecure places to be, and my tired mind was adding to my body's fatigue. I went into morning rounds with a full slate of patients on the labor and delivery floor.

Thankfully, everything was going well at first, but the routine seemed colorless. No two days are the same when you're a resident, but as the time ticks away, you realize if there were 25 hours in a day, more would be demanded of you. It's not easy being at the beck and call of a nurse or attending physician. Even janitors seemed to have more clout and direction than a resident.

I found myself in room 440, helping an attending doctor deliver a beautiful baby boy. The mother's tears of pain and then the family's tears of joy filled the room. The healthy newborn's vital signs were proud "tales of the tape," which included 9 pounds, 21 inches and excellent APGAR (activity, pulse, grimace, appearance, and respiration) scores of 9, 9, and 9.

PHOTO COURTESY OF SAINT ELIZABETH REGIONAL MEDICAL CENTER

When the delivery was completed, the attending, Dr. Lane* and I discussed how well it had gone. He left the hospital, while I finished up some paperwork, grabbed a much-needed coffee, and found myself in the hallway talking to the family. We proceeded into the room to make sure everything was going well with postpartum care and the newborn baby.

Suddenly, I was paged overhead and urgently ushered to the room next door, where I found the polar opposite of a happy birth. Upon entering the room, I immediately noted panic on the face of the head nurse, Diane.

As I looked over to the bed, I saw a 29-year-old first-time expectant mother in what appeared to be a full tonic-clonic seizure. I looked at her vitals on the monitor, assessed the conditions, and knew the situation was not good. Her skin was pale, and her face was blue even though oxygen had been initiated. I asked Diane what had happened. She said the mother, Beth, had been doing fine, when she had suddenly rolled her eyes back, gasped, and then appeared to be having a seizure.

CODE BLUE

My mind rapidly made decisions, while outwardly I tried to remain calm. In what seemed like a slow-motion blur, but was really only a few seconds, I called a full code blue. (Later on I would find out that many colleagues responding to the code were not sure if it was accurate, because codes aren't supposed to be called on the labor and delivery floor.) The nurses phoned the patient's attending physician, but he was 15 minutes out, far too long to help.

I had the clarity of mind to call Dr. Lane back to the hospital, even though he had not been involved in the care of this mother. The nurses and I began initial CPR with oxygen and chest compressions, which seemed especially complex because the pregnant abdomen and muscular uterus were pushing back.

There was a cold and surreal feeling about the whole situation. Faceless bodies flooded the room to offer help. I had never seen anything like this before. Dr. Lane arrived, and I updated him. It had been only four minutes since the code had been called. Oxygen, IV epinephrine, lidocaine, and CPR were in full swing, but we needed to make a radical decision. Should we try to save the baby, the mom, or both?

It became obvious the patient was deteriorating. The cardiac monitor flat-lined, and we administered more alternating shocks, followed by more medications. Dr. Lane took off his dress shirt and threw a green scrub top over his T-shirt. He reached for the gloves and scalpel and we started a cesarean delivery right there in the room on a standard hospital bed.

"THERE WAS NO TIME TO MOVE HER"

In a perfect world, cesarean deliveries are performed in sterile operating suites. In this case, however, with Beth's life in a delicate balance, there was no time to move her. The situation already was out of our control and about to surprise us with more chaos. I assisted Dr. Lane as best I could, also helping with CPR. We delivered the baby in 12 seconds.

Neonatal intensive care doctors and staff swiftly took the small, crying infant, and we attempted to finish the C-section. The patient had lost a great deal of blood. In between stitches, as we sutured the uterus closed, we administered shocks and stepped back from the table, making sure to lay down our tools so we would not be affected by the voltage. At some point, I thought the family had to be in the room, and wondered what was going through their minds. Then I remembered seeing Joe, the father of the child, being escorted out early in the code setting.

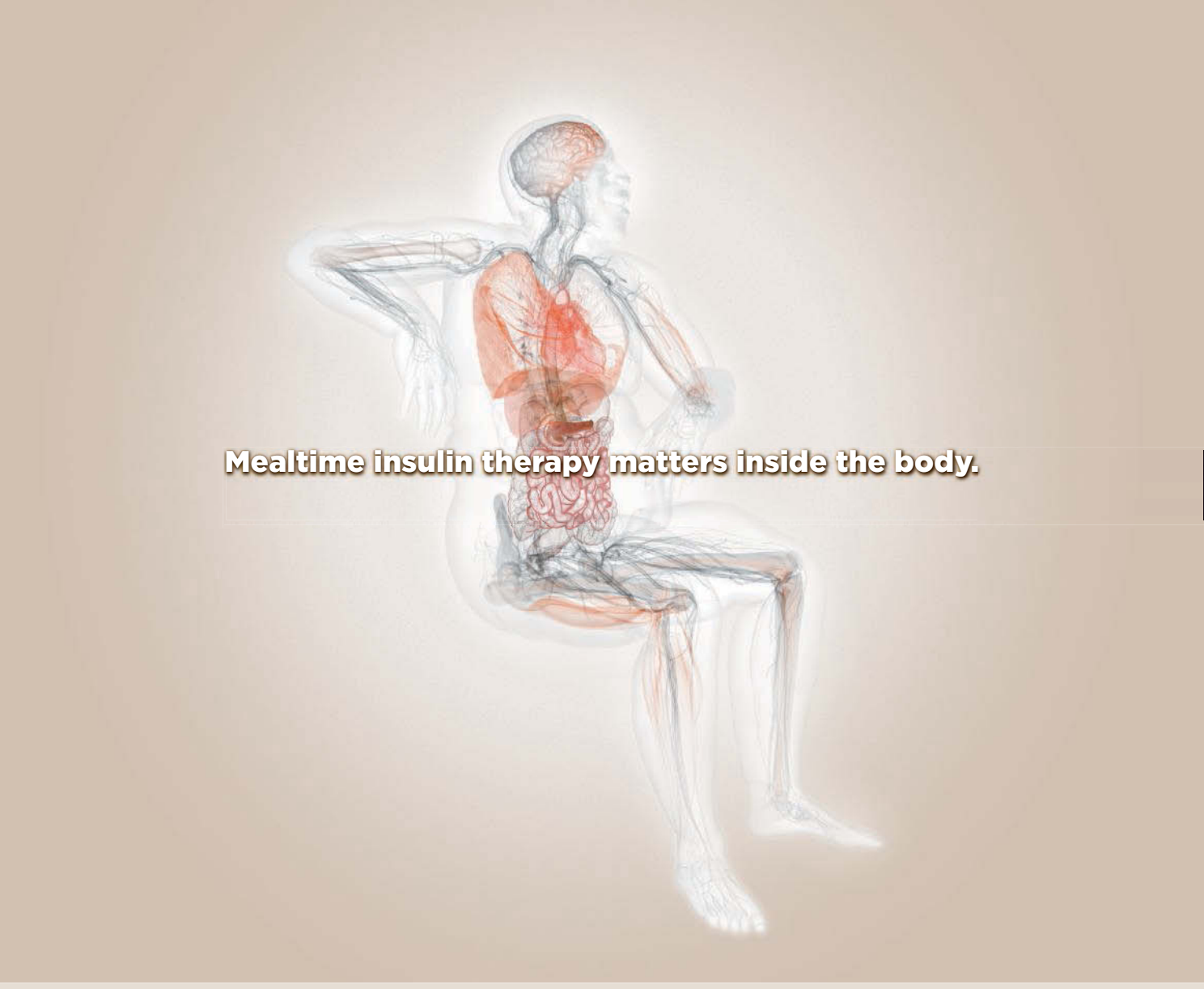
LOSING THE MOTHER—BUT SAVING THE BABY

Despite our efforts and 30 minutes of CPR post-delivery, it became obvious that even with the most skilled emergency, intensivist, and anesthesiology interventions, we had lost Beth. But we saved baby Grace.

Several numb hours later as my shift ended, many solemn faces were still looking to each other for support, for a touch, or some other type of reassurance. For the next several days, other things didn't seem so important. I tried to talk about what had happened with friends and family, but I was not able to share with them the deep emotion of this life-changing situation. I found myself pretending the entire incident was all in a normal day's activities for a doctor.

It was difficult to grasp the enormity of events. This family had lost a loved one. What an eerie feeling to know that a young mother had come into the hospital in joy to deliver a baby, but left in a hearse. I told myself that at least we had saved her baby.

Hospital administrators contacted me over the next several days. After investigating, they concluded that most likely the patient died of a rare condition called an amniotic fluid embolus. In the ensuing weeks, hospital staff conducted more investigations. Now, on top of having to deal with the trauma of the event itself, we had to worry whether we would be found negligent. I thought I had done everything right, but who knows? Those of us on the scene used every bit of training we had to do what we thought was right. I was amazed that our intentions were



Achieving mealtime control takes more than insulin alone. That's why the maker of Humalog provides a combination of products, pens, and tools designed to help fit mealtime insulin therapy into your patient's life.

To find out more, visit www.Humalog.com.

Indication

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

Important Safety Information

Contraindications

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

Important Safety Information, continued

Warnings

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

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

Glucose monitoring is recommended for all patients with diabetes.

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

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Important Safety Information, continued

Warnings, continued

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

Hypoglycemia

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

Other Side Effects

Other potential side effects associated with the use of insulins include: hypokalemia, weight gain, lipodystrophy, and hypersensitivity. Systemic allergy is less common, but may be life-threatening. Because of the difference in action of Humalog, care should be taken in patients in whom hypoglycemia or hypokalemia may be clinically relevant

Important Safety Information, continued

Other Side Effects, continued

(eg, those who are fasting, have autonomic neuropathy or renal impairment, are using potassium-lowering drugs, or taking drugs sensitive to serum potassium level).

For additional safety profile and other important prescribing considerations, see the accompanying Brief Summary of full Prescribing Information.

Humalog®

insulin lispro injection (rDNA origin)

Lilly

HUMALOG®

INSULIN LISPRO INJECTION (rDNA ORIGIN)

BRIEF SUMMARY: Consult package insert for complete prescribing information.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

HOW SUPPLIED:

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

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

[1] MiniMed® and Polyfin® are registered trademarks of MiniMed, Inc.

[2] Disetronic®, H-TRONplus®, D-TRON®, and Rapid® are registered trademarks of Roche Diagnostics GMBH.

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

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

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

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

Literature revised December 7, 2009

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

being questioned, but that's the way it is when you're in medicine. You do your best, and sometimes people still don't think you've done enough.

The case continued to throw us twists and turns. After Grace was born, paternity had to be proven, because Beth hadn't named the baby's father on the admission papers. Blood tests revealed that Joe wasn't Grace's father. This created a whole new aspect to the situation that no one had anticipated, as well as an emotional blow that took its toll on Joe.

OUT OF CHAOS, DETERMINATION

Joe could have walked away, but out of chaos came a fervent determination on his part to love and care for baby Grace. He claimed Grace for his own, spending countless hours in the neonatal intensive care unit getting to know the staff and this beautiful baby girl. Grace's family members and other loved ones made daily visits too, but there was a high level of tension between them and Joe.

I guess it was understandable. They hadn't even known Beth was pregnant. Watching them was like watching a soap opera unfold before our eyes. Through all that time, however, one fact kept hitting me in the gut: Grace had many visitors—but none of them would ever be her mother.

LITIGATION ENSUES

The hospital contacted me again to give my deposition, because they believed Beth's death most likely would result in litigation. Sure enough, all the attorneys who represented the hospital, as well as some of the doctors who had attended the code that day, and I were named in a lawsuit by Beth's mother, who was understandably devastated at the loss of her daughter—and frustrated that she wasn't getting the visitation privileges she wanted. Even though the pathology report at autopsy confirmed that Beth died of an amniotic fluid embolus and we could not save her, we were still named in the lawsuit.

Grace didn't know or care about any of that. Through countless hours of nursing and doctor care in the neonatal intensive care unit (NICU), she moved from one level of the nursery to another, eventually making her way into the general nursery. After countless fearful hours watching over Grace in the NICU, Joe and one of the staff nurses found a special connection. Many months later, they became involved in a relationship, eventually marrying and giving birth to a second child of their own.

Joe fought Beth's parents for custody and became Grace's adopted father. Because Grace's adopted mother worked at the hospital, I received regular updates on her progress, complete with photographs and stories. It was gratifying to know that through the process of this emotional loss many precious things were gained.

CASE DISMISSED

Finally, the hospital and its staff were cleared of any wrongdoing. The only known causes for an amniotic fluid embolus other than natural causes were the use of pitocin and external fetal scalp monitoring, and we had done neither. The investigators concluded that the doctors and nurses delivered excellent care. The situation would have happened no matter what actions we had taken, because of the rarity of the embolus. The judge ruled it to be a natural cause of death, and dismissed the case.

I was relieved, but even without having to endure a malpractice battle, the experience changed me forever. I was surprised to find that the death of Beth and Grace's birth had affected me so deeply. It was a perfect lesson, early in my career, that doctors too often must learn over and over: No matter how good a clinician you are, sometimes things still go wrong. People will sue you, and you can still come out of court in one piece.

I learned it's important to trust your training, believe in yourself, not be too proud to get help when you need it, document well, be available to talk with each family after a tragedy, and get counseling when something like this happens, especially if you are a resident.

More importantly, the experience led me to examine my motives for being a doctor, and question whether I wanted to deliver babies as a family doctor. Had I not been there that day, I would not have had the honor of experiencing firsthand the very reason I wanted to practice medicine.

Like the deepening of Joe's devotion to Grace, I found a determination to do what I can to make THE difference in people's lives during times of chaos and uncertainty. No longer were the stresses of a new marriage, a new town, and a new residency so intimidating. No longer did the hospital seem gray and colorless. My future path now was clear. ME

* Names have been changed

The author is a family physician practicing in Lincoln, Nebraska. Send your feedback to medec@advanstar.com.

ModernMedicine NETWORK

NEWS & UPDATES

A recent study suggests cesarean deliveries should be performed only when medically necessary. See details at MedicalEconomics.com/cesarean

The effects of a malpractice suit can linger long after the case is dismissed. Read one doctor's experience at MedicalEconomics.com/linger

GETTY IMAGES: IMAGEMORE CO., LTD.

Patients' life stories "challenge me to reassess what I consider valuable in my own life," says Yolanda Wong, MD, right. She and her husband are parents to a 10-month-old daughter and 2-year-old son, left.

A bittersweet taste of perspective

A PATIENT ENCOUNTER LEADS TO A NEW OUTLOOK ON LIFE

[*By* **YOLANDA WONG**, *MD*]

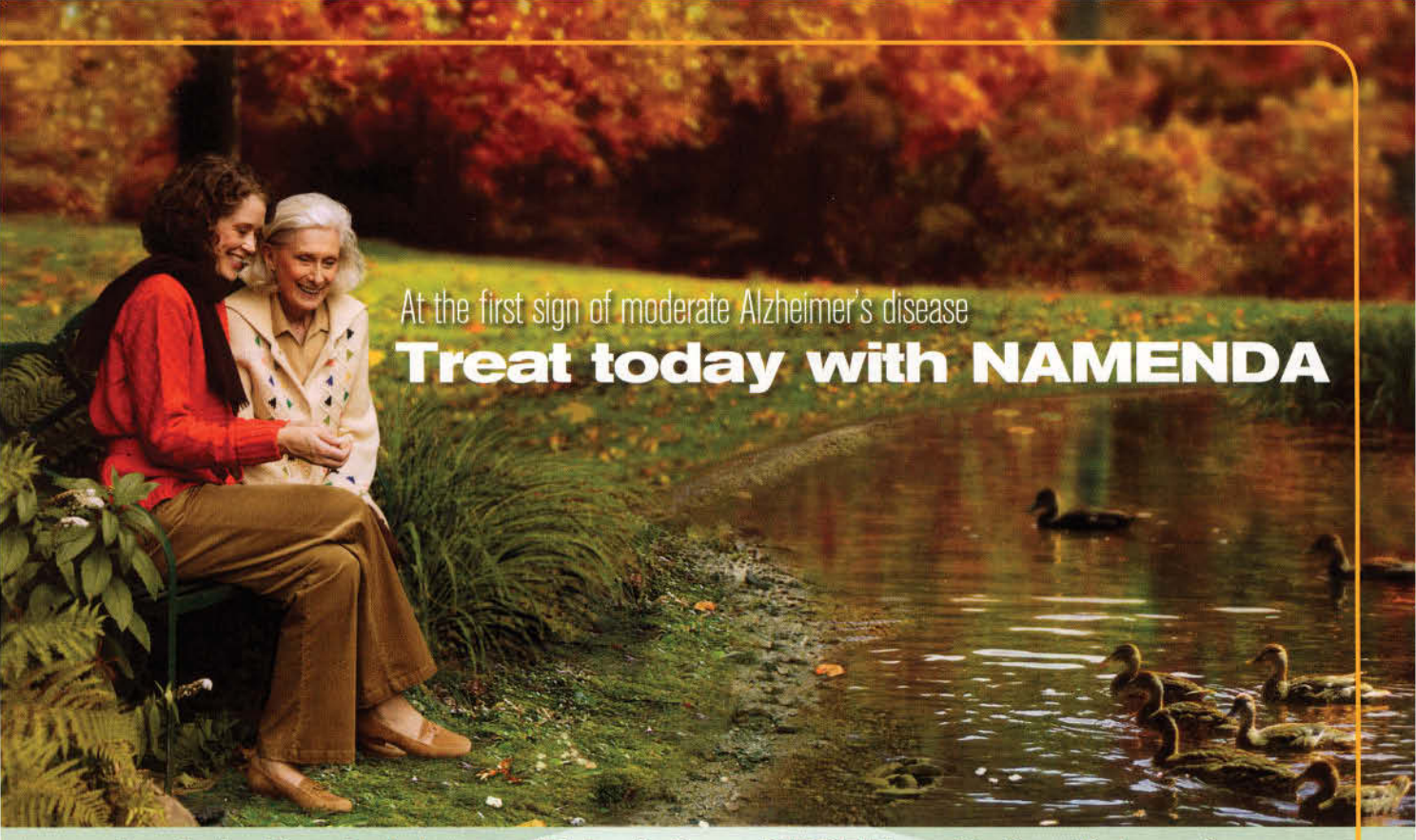
In the movie "Ratatouille," cynical food critic Anton Ego challenges the whiskered chef to whip him up some perspective.

"That's it. I'd like some fresh, clear, well-seasoned perspective," he says. "Can you suggest a good wine to go with that?"

I had been craving some well-seasoned perspective myself. I had finished residency not long before. I had a baby and had just returned to work. My career and identity as a pediatrician were yet to be defined, but the culture of medical school and residency already had deeply ingrained in me a desire for recognition.

Bills, chores, and little nagging things-to-do seemed to multiply and regenerate before my eyes each day. Life once had seemed relatively simple and straightforward, but a creeping discontent and

PHOTO COURTESY OF YOLANDA WONG, MD



In patients with moderate to severe Alzheimer's disease, NAMENDA in combination with donepezil (5 mg and 10 mg):

- Offers benefits in cognition, function, and behavior[1]
- Improves overall global function[1]
- Delivers proven efficacy with a low incidence of side effects[1-3]
  — Low risk of gastrointestinal side effects and drug-drug interactions

Available on 99% of Commercial Health Plan and Medicare Part D formularies[2]

NAMENDA® (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

Namenda® (memantine HCl) tablets
5 mg and 10 mg

Important Safety Information

Contraindications

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

Precautions

- Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and about dose escalation (minimum interval of one week between dose increases)
- NAMENDA has not been systematically evaluated in patients with a seizure disorder
- NAMENDA should be used with caution under conditions that raise urine pH (including alterations by diet, drugs and the clinical state of the patient). Alkaline urine conditions may decrease the urinary elimination of memantine, resulting in increased plasma levels
- A dosage reduction is recommended in patients with severe renal impairment
- NAMENDA should be administered with caution to patients with severe hepatic impairment

Adverse Reactions

- In clinical trials, the most common adverse events occurring in at least 5% of patients treated with NAMENDA and at a greater frequency than placebo-treated patients were dizziness (7% vs 5%), confusion (6% vs 5%), headache (6% vs 3%) and constipation (5% vs 3%)

References: 1. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I, for the Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA*. 2004;291:317-324. **2.** Data on file. Forest Laboratories, Inc. **3.** NAMENDA® (memantine HCl) Prescribing Information. Forest Pharmaceuticals, Inc., St Louis, Mo.

Forest Pharmaceuticals, Inc.

For more details, please visit **www.namenda.com**.
Please see brief summary of Prescribing Information on the adjacent page.

Namenda
memantine HCl

Tablets/Oral Solution
Rx Only

Brief Summary of Prescribing Information.

For complete details, please see full Prescribing Information for Namenda.

INDICATIONS AND USAGE
Namenda (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS
Namenda (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

PRECAUTIONS
Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

Neurological Conditions
Seizures: Namenda has not been systematically evaluated in patients with a seizure disorder. In clinical trials of Namenda, seizures occurred in 0.2% of patients treated with Namenda and 0.5% of patients treated with placebo.

Genitourinary Conditions
Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

Special Populations
Hepatic Impairment
Namenda undergoes partial hepatic metabolism, with about 48% of administered dose excreted in urine as unchanged drug or as the sum of parent drug and the N-glucuronide conjugate (74%). No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Namenda should be administered with caution to patients with severe hepatic impairment.

Renal Impairment
No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in Full Prescribing Information).

Drug-Drug Interactions
N-methyl-D-aspartate (NMDA) antagonists: The combined use of Namenda with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effects of Namenda *on substrates of microsomal enzymes: In vitro* studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effects of inhibitors and/or substrates of microsomal enzymes on Namenda: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: Coadministration of Namenda with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of donepezil alone.

Drugs eliminated via renal mechanisms: Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of Namenda and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the antihyperglycemic drug Glucovance® (glyburide and metformin HCl) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance®.

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

Carcinogenesis, Mutagenesis and Impairment of Fertility
There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m^2 basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro S. typhimurium* or *E. coli* reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the *in vivo* mouse micronucleus assay. The results were equivocal in an *in vitro* gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Pregnancy
Pregnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m^2 basis.

There are no adequate and well-controlled studies of memantine in pregnant women. Memantine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether memantine is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

Pediatric Use
There are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children.

ADVERSE REACTIONS
The experience described in this section derives from studies in patients with Alzheimer's disease and vascular dementia.

Adverse Events Leading to Discontinuation: In placebo-controlled trials in which dementia patients received doses of Namenda up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the Namenda group as in the placebo group. No individual adverse event was associated with the discontinuation of treatment in 1% or more of Namenda-treated patients and at a rate greater than placebo.

Adverse Events Reported in Controlled Trials: The reported adverse events in Namenda (memantine hydrochloride) trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ. Table 1 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with Namenda than for those treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Namenda and at a Higher Frequency than Placebo-treated Patients.

Body System Adverse Event	Placebo (N = 922) %	Namenda (N = 940) %
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

Other adverse events occurring with an incidence of at least 2% in Namenda-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, abnormal gait, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

Vital Sign Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with Namenda. A comparison of supine and standing vital sign measures for Namenda and placebo in elderly normal subjects indicated that Namenda treatment is not associated with orthostatic changes.

Laboratory Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Namenda treatment.

ECG Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with Namenda treatment.

Other Adverse Events Observed During Clinical Trials
Namenda has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day. Patients received Namenda treatment for periods of up to 884 days, with 862 patients receiving at least 24 weeks of treatment and 387 patients receiving 48 weeks or more of treatment.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using WHO terminology, and event frequencies were calculated across all studies.

All adverse events occurring in at least two patients are included, except for those already listed in Table 1, WHO terms too general to be informative, minor symptoms or events unlikely to be drug-caused, e.g., because they are common in the study population. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events- those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Namenda treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole: *Frequent:* syncope. *Infrequent:* hypothermia, allergic reaction.

Cardiovascular System: *Frequent:* cardiac failure. *Infrequent:* angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.

Central and Peripheral Nervous System: *Frequent:* transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. *Infrequent:* paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia, involuntary muscle contractions, stupor, cerebral hemorrhage, neuralgia, ptosis, neuropathy.

Gastrointestinal System: *Infrequent:* gastroenteritis, diverticulitis, gastro-intestinal hemorrhage, melena, esophageal ulceration.

Hemic and Lymphatic Disorders: *Frequent:* anemia. *Infrequent:* leukopenia.

Metabolic and Nutritional Disorders: *Frequent:* increased alkaline phosphatase, decreased weight. *Infrequent:* dehydration, hyponatremia, aggravated diabetes mellitus.

Psychiatric Disorders: *Frequent:* aggressive reaction. *Infrequent:* delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paroniria, delirium, depersonalization, neurosis, suicide attempt.

Respiratory System: *Frequent:* pneumonia. *Infrequent:* apnea, asthma, hemoptysis.

Skin and Appendages: *Frequent:* rash. *Infrequent:* skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria.

Special Senses: *Frequent:* cataract, conjunctivitis. *Infrequent:* macula lutea degeneration, decreased visual acuity, decreased hearing, tinnitus, blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment.

Urinary System: *Frequent:* frequent micturition. *Infrequent:* dysuria, hematuria, urinary retention.

Events Reported Subsequent to the Marketing of Namenda, both US and Ex-US
Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in labeling: aspiration pneumonia, asthenia, atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, colitis, deep venous thrombosis, depressed level of consciousness (including loss of consciousness and rare reports of coma), dyskinesia, dysphagia, encephalopathy, gastritis, gastroesophageal reflux, grand mal convulsions, intracranial hemorrhage, hepatitis (including increased ALT and AST and hepatic failure), hyperglycemia, hyperlipidemia, hypoglycemia, ileus, increased INR, impotence, lethargy, malaise, myoclonus, neuroleptic malignant syndrome, acute pancreatitis, Parkinsonism, acute renal failure (including increased creatinine and renal insufficiency), prolonged QT interval, restlessness, sepsis, Stevens-Johnson syndrome, suicidal ideation, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, thrombocytopenia, and hallucinations (both visual and auditory).

ANIMAL TOXICOLOGY
Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 6 times the maximum recommended human dose on a mg/m^2 basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: Memantine HCl is not a controlled substance.

Physical and Psychological Dependence: Memantine HCl is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE
Signs and symptoms associated with memantine overdosage in clinical trials and from worldwide marketing experience include agitation, confusion, ECG changes, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2.0 grams in a patient who took memantine in conjunction with unspecified antidiabetic medications. The patient experienced coma, diplopia, and agitation, but subsequently recovered.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

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"WITH PERSPECTIVE COMES THE DISCOMFORT AND DANGER OF VULNERABILITY, SO IT OFTEN IS EASIER TO BACK AWAY AND LET IT BE A PRETTY CONCEPT ON THE SHELF TO ADMIRE AND APPLAUD."

uncertainty weighed on me. I wondered: Am I doing enough? Am I good mom? Am I good doctor? What do I live for?

I woke up one Friday morning tired and disoriented, like any other morning. I was tempted to press the snooze button just one more time. The week had wiped me out. My son still wasn't sleeping through the night. I'm a pediatrician, I thought. Shouldn't I be a pro at this kind of stuff?

Even before getting out of bed, I was grumbling at the day ahead, which held charting that I hadn't finished from the day before; at my husband, who had this incredible ability to sleep through our baby's wailing; and at my son, who apparently didn't read the textbook on soothing himself back to sleep. What I didn't expect that morning was that I would get a taste of some much-needed perspective.

PRACTICE BRINGS CHANCE TO SEE LIFE'S UPS AND DOWNS

Perspective is elusive in the practice of medicine. On one hand, the opportunity to see into the lives of so many people, witnessing their hurts and fears, provides a broad perspective on life. From a person's triumphant joys to his or her most menial struggles, there is no generic story.

On the other hand, lives are messy. Emotions are inconvenient. With perspective comes the discomfort and danger of vulnerability, so it often is easier to back away and let it be a pretty concept on the shelf to admire and applaud. And besides, that pesky thing called productivity prefers a nice tidy SOAP note, a quick scribble of a signature, and a terse pat on the back.

LIFE CHANGES WITH THE INTRODUCTION OF A QUIET BOY

My first patient that morning was a quiet, slender 5-year-old boy with a thick mess of hair that begged to be tousled. I had seen him for the first time a few days before for his school physical, and his parents mentioned a concern about the way he walked.

Suspecting muscular dystrophy, I later looked up his name at the hospital on a whim to see whether any evaluations had been performed in the past. Parents often have poor recollection of a child's medical history. After all, it's hard enough being a parent. I was stunned, however, when I came across a neurology report stating my patient's diagnosis of Duchennes muscular dystrophy.

I was even more speechless as I glanced at the date of the report: more than 1 year ago. Here was a boy with a serious diagnosis that already had been made, and yet the family still had no clue. A language barrier led to an unfortunate miscommunication between the specialist and the mother, whose first language was Spanish, and a poorly timed lapse in insurance coverage then resulted in the loss of follow-up. Now this sweet family sat patiently in my office, thinking I had called them in to "start" an evaluation, whereas I already had an answer for them.

I knew it would be difficult to break the news, but I wasn't prepared for my reaction: my voice cracked, and I found myself trembling. I looked down at the young boy pushing a white toy truck in circles on the floor, then up at his parents. As our eyes met, the father seemed to know that this was no ordinary visit, and he instinctively placed his hand on the mother's knee.

Even before I could finish, the tears already had begun to fall down their faces. They held each other and wept, shoulders shaking uncontrollably. I reached out my hand and took the mother's hand in mine, and my tears began to flow, too. There was nothing left to say for quite some time.

Meanwhile, the young boy continued to play quietly with a few toys on the floor, not a care in the world. He looked up puzzled at the distress on his mother's face and crawled to her feet, hugging her leg tenderly.

The rest of the day was a blur. As I drove home that day, I still found myself crying. The tears would not stop.

CAUGHT OFF-GUARD IN FAMILIAR TERRITORY

This isn't the first time I have had to give bad news, yet I was shaken and heartbroken like never before, even more so than the time I had to declare the death of a patient. Perhaps it was because I was a mother now. I saw my own son in the eyes of this young boy and his love of trucks. Or perhaps it was the thought of the hard and long journey that remained ahead for

both the boy and his parents. Perhaps I simply was caught off-guard with the realization that this family was no different from my own. Their tears were no different than mine. Their dreams for their son were no less hopeful than mine. Love and despair translate quite clearly no matter the differences in language, culture, or socioeconomic status.

But mostly, I suspect I was especially shaken by the realization of how utterly blind and ungrateful I had been. I was humbled as I saw my lack of perspective. When had I lost it?

Despite what I saw and knew, I had been taking everything for granted. I had grown discontent and was obsessing over trivial details. I often felt entitled to more, forgetting what I already had. I had lost sight of what mattered most to me for the sake of following what others defined as successful and worthwhile.

I recalled all the times, even just yesterday, that I complained about what a headache it was that my son was running circles around me. Shame burned on my cheeks at the irony as I explained the course of muscular dystrophy to the parents. Most parent don't envision a wheelchair among the necessities of raising a child.

How quickly I had lost sight of the precious value of my son and the days we have together. How easily I had fretted about the opinions of others rather than boldly following my heart and beliefs. I had questioned my decision to work part-time and secretly had desired to be more respected and admired by the medical community.

I had wondered whether more money would make life easier. I had been annoyed that I was not the multitasking superwoman I thought I used to be.

When I was at home with the kids, I felt as if I couldn't keep up with the working world; when I was at work, I felt as if I couldn't keep up with my family. Chasing after these images of success had shifted my focus from all the joy of living my life and appreciating it just as it is, no less and no more.

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A REMINDER TO CHERISH THOSE WE LOVE

That morning, the parents of this young boy and I were reminded that the worth of a person and the life that he lives does not rest on his abilities, accomplishments, or the number of his days. We were reminded to cherish those we love.

No matter the diagnosis, it didn't change who this boy was to his parents, and who they were to him. No matter the prognosis, they still could make the most of each day to show their son just how special he was.

Human worth stems from the simple but wondrous gift of being loved. It can't be taught, demanded, or bought. And although disease and death may try to do so, human worth also cannot be stolen.

As I held my son in my arms that night, I looked down at his face and contemplated the unknowns of the future. I thought about all of the hopes and dreams I have for him. I thought about all the things I hoped to teach him and all the ways I wanted to protect him.

As I savored the warmth of his head resting on my chest, I realized that all of those thoughts would be pointless if he did not know his worth. Suddenly, I just wanted my son to simply understand the incredible extent to which he is loved.

MEETING, CARING FOR PATIENTS REVEALS TRUE IDENTITY

I have completed years of higher education and take great pride in my medical training. I speak of all that I have accomplished and hope to accomplish in life. I even think I'm an awfully nice person. But at the end of the day, I am like anyone else. I wrestle with fear. I seek identity. I want immediate answers and instant gratification. I want to be in control, and I often fool myself into thinking I am.

Then I go to work, and my patients give me a fresh dose of humility. Their life stories challenge me to reassess what I consider valuable in my own life. They remind me that people still matter. They help to fight back the insistent tide of cynicism and apathy that sometimes blind my eyes to the beauty in even the simplest everyday moments.

As our lives briefly intersect, I am amazed to this day how the interaction can change my self-absorbed heart and unveil my preconceptions of what happiness is all about. Meeting and caring for my patients clarifies my muddied perspective and gives me an honest glimpse of myself. As bittersweet as perspective may be, I cannot live without it. ME

The author works part-time as a general pediatrician at Linda Vista Health Care Center in San Diego, California. She enjoys writing and sharing musings on being a mother and physician at blaggieplaggie.blogspot.com Send your feedback about this article to medec@advanstar.com.

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Secrets of great staffs

10 PROVEN STRATEGIES TO BUILD YOUR DREAM TEAM

[*By* **JUDY BEE**]

When it comes to managing staff, doctors who have been around for a while and have learned from experience often wish they knew back then what they know now. Here are 10 proven strategies based on others' trials and tribulations that can guide you in developing your ideal team:

1 "JOB-HOPPERS" MAY MAKE GOOD EMPLOYEES

Many physicians reviewing resumes of job applicants dismiss candidates who move from job to job as undesirable. Actually, these "job-hoppers" might make good employees.

What's really important is what potential employees know and can do in your office, not how long they might stay. It's better to have an A+ worker for a year or two than to endure the services of a C- staff member for his or her whole career. Actually, when presented with two receptionists with 6 years' experience, the better candidate might be the one who has held three jobs rather than only one. She will have more varied experience, all else being equal.

2 EMPLOYEE TURNOVER ISN'T NECESSARILY BAD

Actually, a change of personnel offers the practice a chance to bring in some new ideas to solve work problems. Some employees, no matter how valuable they are, get tired doing the same old thing and become stale.

An office manager we know left a practice to work at the hospital for 9 years. Then she returned to her old job to find that nothing had changed in her absence. She says, "It was like deja vu. The same people were doing things the same way—no progress."

Sure, bringing on new employees is disruptive. They require training and more supervision. We're not recommending you encourage turnover. But it's nothing to panic over, either. You just might benefit from it.

3 TRAINING NEW STAFF IS WORTH THE INVESTMENT

Home Depot founders Bernard Marcus and Arthur Blank spent a lot of time personally visiting their stores. They used the time to train personally every

"THE PRACTICES THAT WILL SUCCEED IN THE NEXT DECADE WILL NOT BE THE ONES WITH ORDINARY, ACCEPTABLE WORKERS."

assistant manager in the chain. Quite a testimony to how much value they place on training. If these guys weren't too busy to train workers, you should think about doing the same in your practice.

The nurses, techs, and medical assistants who work with patients all will benefit from direct training by the physicians in the practice. So will the manager, who needs to know what you consider important. And who better than a physician to teach receptionists the questions they should ask patients (and what the answers mean) to schedule a smoothly running office session?

Most physicians are skilled teachers. And taking the time to train your team has a collateral benefit: It cements loyalty to the practice in a new employee. Nearly all employees value training by the physician, and it's done so rarely that you will create a solid impression of commitment to the new worker's success.

4 EMPLOYEE LOYALTY MUST BE EARNED

Well, of course it's nice when your staff members are loyal. Having loyal employees is something every boss wants. The mistake is in thinking that loyalty is something people bring to the job.

Loyalty is created—earned—by the employer. Treating employees respectfully, giving them the tools and training they need to do the job, acknowledging them when they do it well, and insisting on achievement of a reasonable standard are all ways that employers earn loyalty. And when employees are disloyal, it's usually because of something the employer did or failed to do.

5 IT'S OKAY TO BE SELECTIVE WHEN HIRING

For instance, if your office is open on Saturdays, it's not unfair to rule out a job applicant who can't work those days. Or consider two employees who want the same promotion. One, with more seniority, thinks she should get the advancement. But the other is more qualified. What would be fair? The first consideration should always be: "What will be best for the practice, the doctor(s), and the patients?"

6 GIVING A REFERENCE ISN'T OFF LIMITS

An employer who knowingly gives out false information can be sued. But even then, the number of reference-related lawsuits is miniscule.

Obtain the exiting employee's permission (in writing) to give references. Stick to facts that you can prove when giving a reference. Don't provide a reference in writing, and be sure you know whom you're talking to. Answer questions that you feel you can answer fairly, but don't take the lead in the conversation.

Remember, you're really helping both the prospective employer and your former employee to make a good decision, one that will benefit them both. If you feel angry or malicious toward the ex-employee, stay off the phone.

7 BENEFITS PACKAGES MAY NEED REVISION

Sure, you can revise your benefits package, and you may need to do so as times get tougher in some areas. Practices that provide health insurance for the employee's family, dental insurance, 3 weeks of vacation after 3 years, and birthdays off may wish they hadn't been so generous when the economy is down.

"But," you may ask, "taking away benefits we've promised is like welshing on a contract, isn't it?"

True, if employees stick with an employer for three years with the expectation of getting three weeks' vacation, it would be wrong to change the rules after 30 months.

However, with proper advance notice and consideration, employees usually will understand if you need to make reasonable modifications to your benefit policy to reduce costs.

8 IT'S NOT OKAY TO BE ORDINARY

Most physicians—in fact, most rational people—don't like to terminate employees. So this unpleasant chore gets avoided unless an employee does something spectacularly wrong, insubordinate, or dangerous. The practices that will succeed in the next decade, however will not be the ones with ordinary, acceptable workers. It's going to take enthusiastic, motivated, positive, upbeat, friendly, talented people in every job to thrive in the current environment. In a word, your employees need to be special if you intend to stay ahead of the curve.

Of course, terminating workers can be a legal

'HIRING'S IMPOSSIBLE THESE DAYS'

A physician asked recently: "How do you find and hire truly top-notch personnel? Sometimes, it seems almost impossible. Want ads and agencies seem to bring out only the sub-par."

He's right that the market is more competitive than ever. That means it's important to revisit the competitiveness of your pay and benefits package to attract the high-intellect workers who will be able to cope with the detail and ambiguity of most medical office jobs. And creating an inviting and supportive work team will appeal to many workers unhappy working in big, impersonal environments.

Finally, expand your recruiting beyond the traditional want ads and agencies. Remember, many of the best workers aren't out of work or even looking for a job change. That means you'll want to engage the widest possible word-of-mouth network and consider smart and creative workers from other industries. A waitress who can keep nine tables happy during a busy lunch rush might have just what you need at your front desk, for example. And nearly every bank has midlevel, educated executives to whom you may be able to offer better work, pay, and benefits.

Recruiting good workers isn't more difficult for physicians than anyone else in business. The key is to never give up and to take the time needed to ensure you're making the right decision for your practice.

minefield, so you will need to be fair. But why not let your competition have the ordinary employees?

9 HOURLY IS THE WAY TO GO

Unfortunately, this one isn't a matter of opinion to be decided by the owner of the business. Hourly workers have to be paid hourly and are not exempt from the overtime (and the record-keeping) provisions of the federal and state wage and hour laws.

So who are these hourly workers? They are just about everyone who works in a medical office except the physicians and, in some cases, the manager. Nurses, bookkeepers, billers, techs, and all the other positions all are hourly.

Another advantage to complying with this law is that it makes the attendance aspect of supervision easier. When an employee is manipulating the employer by arriving late or leaving early, the principal damage is not the wasted payroll. It's the loss of respect for the employer by the other employees who know it's going on. It's a demotivator.

Any record of the hours worked will do, from a time sheet or diary kept by the worker to a timecard punched in a time clock. Our recommendation: Get a time clock to keep an accurate and indisputable record of arrivals and departures. While you're at it, get one that will calculate the elapsed time and cumulative hours worked. It's the computer age, after all.

You may need to put a positive spin on the idea with your employees, who may have come to enjoy a more relaxed, less supervised approach. Tell them it is unfair not to pay them for each and every hour they actually work, and the time clock will make that process easier. Besides, the law requires it and there are sanctions for employers who fail to keep good records.

10 EXPERIENCE COUNTS, BUT SO DO OTHER ATTRIBUTES

It's best to hire the most qualified candidate, even if he or she is from outside the practice. Sure, you should allow your current employees to apply for openings in the practice that they consider advancements. But they should win the job based on their skills, knowledge, and experience compared with the other candidates.

The criteria for advancement should be expected ability to do the new job, not performance in the current job. The appropriate reward for a job well done is a bonus or raise. Advancement to a new job is not.

In fact, you should memorialize this principle in your employee handbook: "We pay for performance and promote for ability." This avoids the famous Peter Principle problem: People tend to be promoted to their level of incompetence. The gorilla hair on your neck should stand up when people start spouting conventional wisdom. Sure, experience counts. But don't fall prey to rigid thinking that inhibits progress. ME

POWER POINTS

It's better to have an A+ worker for a year or two than to endure the services of a C- staff member for his or her whole career.

Staff members who work with patients will benefit from direct training by the physicians in the practice.

Loyalty is created by the employer.

Stick to facts that you can prove when giving a reference.

The author is a principal management consultant with Practice Performance Group, La Jolla, California, and a Medical Economics *editorial consultant Since entering consulting practice in 1977, she has focused on the medical sector exclusively, consulting with more than 250 medical practices representing more than 1,100 physicians in 40 states. Send your feedback to medec@advanstar.com.*

Steve Dudley, DVM, MD, reflects on his career as a family physician with concern, pride, and optimism for his son, a pre-med student, who hopes to follow in his father's footsteps.

An open letter to my son, who is a pre-med student

A FAMILY PHYSICIAN AND FATHER OFFERS WORDS OF WARNING AND ENCOURAGEMENT TO HIS ASPIRING DOCTOR SON

[*By* **STEVE DUDLEY**, *DVM, MD*]

Dear Daniel,

To borrow a line from the Beatles, "I read the news today, oh boy...and though the news was rather sad. Well, I just had to laugh." There it was, another article detailing that physicians experience a higher prevalence of depression, burnout, suicidal ideation and a lower quality of life than age-matched members of the general population.

Yep, my son, you're in for a long haul. Are you sure you don't want to reconsider? After all, there are easier ways to make a buck, wouldn't you agree? It's not too late to put on the brakes and redirect your

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many talents. And, yes, just like the song, I just have to laugh as it hurts too much to cry, reflecting on the path laid out before you.

No doubt about it, life in medicine can be difficult. I think back to my own years of training. It was tough then—perhaps a tad tougher, because you had just been born and I had to juggle being a husband and parenting two small children with the demands of medical school and residency. My supervising residents and attendings had little regard for my life outside of the hospital, nor could they give a rip about my child who had just taken sick with a fever at Miss Laurie's Daycare.

Speaking of that, I learned a new word the other day: "presenteeism." Great word. It means showing up to work when you are sick. I once worked with an emergency room physician who had caught an intestinal virus. He talked one of the nurses into hooking him up to a bag of IV fluid, which he wheeled around on a little pole from room to room so he could continue seeing patients. He wasn't about to let a little nausea and diarrhea stand in his way.

Any rational person might ask who wants to put up with all this? The years of study? Delayed gratification? Living at poverty level for so long? Putting marriage and relationships at risk while you pursue the dream of medicine? And then after you have tackled all of the above issues, you come out ill-prepared to fight new foes: mastering the ICD-9, soon to be ICD-10, codes, insurance companies, paperwork, running a business. It's downright daunting.

So why do I stick with it? Well, simply put, it's about the best darned gig around, that's why. In the face of doctor burnout, isolation and the stresses of running an office, there is nothing to rival the satisfaction of being a doctor. I may come home weary and burdened from seeing so many hurting people, but an inner peace suffuses me, often the most intensely on my roughest days. It comes from being able to stand back and reflect on my day, resting in the calm assurance that I am indeed doing some good out there, one patient at a time.

Where do I begin? Well, for starters, there's Frankie, a strapping 7-year-old who used to burst into tears every time I walked into the room when he was a toddler. Today, he high-fives me and calls me the best doctor in the world. His baby sister just had a febrile seizure and he's confident that I'll take good care of her. There's Gert. At 104, she's my oldest patient. With the twinkle in her eye and that smile of hers, she always lifts my spirits. Mr. Connors just had a stroke. At 51, this wasn't supposed to happen, but it did. Even though he's well-connected with his neurologist, he leans on me to help him navigate the maze of health challenges that have hit him like a freight train.

Time and again, I step into the room and quietly close the door. After some friendly banter about important matters such as this year's lousy tomato crop, good fishing holes, bicycle riding, and how my beloved Washington State Cougars are doing (usually not very well), I segue into the reason for the visit.

"What's going on today?"

That's when the magic happens. Time stops (or at least it should). I'm honored that patients entrust their health to me, putting faith in my ability to help them along the road to wellness. It's a humbling feeling to be in that position. And, at the end of the day, I can look back and say, yes indeed I did a little good in my corner of the primary care world. It's neither glamorous nor flashy to lance abscesses, treat toenail fungus, or battle with hypertension and diabetes, but it's a necessary calling and one that I am proud to be part of.

And when I reflect on your aspirations to enter medicine, I am filled with pride that you have chosen this career. I know you have the compassion and the talent to be an excellent and caring physician. I think of the time you took care of the burn on my back after my shirt caught fire (how was I to know the candle was so close?). You meticulously cleaned the wound, carefully extracting the shards of burnt shirt from flesh with the care and patience of a seasoned professional. I sensed your healing touch, even then. And when you decided to stuff a silly fish you found on the beach, you took to suturing his belly closed like an attending surgeon.

Of course, that's not to say that things aren't going to be tough. You've got many years of hard work and sleepless nights ahead of you. I reflect back to my own years of training when the alarm rang, signaling the beginning of another day. Yes, it was time to get up and do it all over again, tired or not.

You'll be very good at what you do, no doubt about it. Your love of learning will be rewarded in a career in which there will always be new frontiers to explore (we call it CME). I look forward to standing back and watching you as you develop into the fine young doctor you are called to be and welcome you as a future colleague.

I'll never be famous, and I doubt you will either. But I can promise you that your life in medicine will be one that is equally challenging, stimulating, and rewarding. What more could someone ask of a career?

Godspeed, Daniel. You'll do well. Of that, I am certain.

Love, Dad ME

The author is a family physician in Seattle, Washington. Send your feedback to medec@advanstar.com.

Solving the narcotics dilemma

FOLLOW THESE TIPS WHEN DECIDING WHETHER A PATIENT TRULY NEEDS PRESCRIPTION PAINKILLERS

[*By* **PAUL DIBBLE**, *MD*]

"I need another script for my Vicodin because I accidentally dropped my pills in the toilet." "I'm going out of town for 2 weeks; I need my Oxycontin early." No doubt you have heard these kinds of requests for early refills. As physicians, we roll our eyes and exchange knowing looks with our staff every time we hear them, and groan every time a narcotic refill request crosses our desk.

If you write any narcotic prescriptions at all, it can seem as though everyone is a druggie and that every patient taking them is out to pull a fast one on you. It is even worse if you manage chronic narcotic use. It's hard not to get cynical.

On the other hand, some people have real pain, and narcotics can provide real relief. So how should we manage narcotics, particularly chronic narcotic use? What principles can help us to prescribe narcotics appropriately?

Before going any further, I will make a disclaimer. This article is not meant to be an authoritative guide to managing chronic pain or chronic narcotic use. You can find guidelines and protocols for doing that elsewhere. I can, however, offer a few useful tips that I have learned as a family physician in my struggle to find the best way to manage chronic narcotic use.

THE EMOTIONAL APPROACH

Here is one approach that may *not* be the best. "You have pain? Nothing but Vicodin works? You look sincere. Here's your prescription. I put refills on that script as well." Unfortunately, I have seen this approach commonly (though not always to that extreme). The perceived sincerity or desperation of the patient is the primary consideration for determining pain treatment. I call it the emotional approach to narcotics management since feelings, or gut instincts, make the decision. For these doctors, maintaining pleasant feelings by avoiding confronta-

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"IF YOU WRITE ANY NARCOTIC PRESCRIPTIONS AT ALL, IT CAN SEEM AS THOUGH EVERYONE IS A DRUGGIE AND THAT EVERY PATIENT TAKING THEM IS OUT TO PULL A FAST ONE ON YOU. . . . IT'S HARD NOT TO GET CYNICAL."

tion or disagreement is important. Often, a narcotics prescription is the least painful means to end an office visit for a pain complaint. While this approach avoids confrontation or disagreement, it will ensure that many narcotic scripts are written.

Perhaps this approach comes naturally to us. We go into medicine because we want to help others. Our training reinforces our listening and empathy skills. After several years of this kind of training, we are ready to believe anything our patients tell us. Usually that's a good idea, but occasionally it is not. While those who actually need narcotics probably will get them from the emotional prescriber, those same patients may misuse them due to the lack of restraint in prescribing.

Narcotic abusers will also find it easy to get prescriptions. Moreover, since the emotional prescriber prefers a narcotic prescription as the path of least resistance, many patients may miss out on potentially more effective, non-narcotic options.

THE CYNICAL APPROACH

Rarely prescribing narcotics is another way of avoiding conflict, but that practice doesn't help the patient with a clinical indication for the drugs. I call it the cynical approach to narcotic management since it seems to be based on universal suspicion. Physicians who deal with narcotics this way probably have been burned before by some clever abusers. Since these physicians have discovered that they can't always trust their own feelings, they prefer to avoid the issue altogether. Commonly, they refer the patient to a specialist, often a pain specialist, who often will put the patient on narcotics anyhow. But at least the referring physician didn't have to try to sort out which person's pain was real.

Of course, the methods presented above are at the extremes, but they illustrate poor ways of managing chronic narcotic use. So what is a better way? The following ideas may help you to navigate the difficult waters of narcotics management.

■ **Be consistent.**

If seeing old records is important for you to verify prior narcotic use, always at least try to get them. If checking a controlled substance database is part of how you monitor narcotic use, do it consistently. I could talk about many specific ways to control or monitor narcotic use, but that is not the purpose here. Rather, I wish to emphasize that whatever tools you use, use them consistently.

Think of how you manage other chronic illnesses, such as diabetes. You have a set schedule for labs and office visits. You have pre-determined goals for hemoglobin A_{1C}, blood pressure, and cholesterol. You may tailor the plan slightly, as appropriate, but you consistently apply the same standard to all of your diabetic patients. Do the same thing for chronic narcotic users.

■ **Use objective criteria.**

It is hard to be objective when dealing with pain, but you can find many useful guides. Some guidelines suggest using indicators such as functional status, point scales, or pictorial methods as ways of assessing pain and pain control. Whichever method you use, that going by gut instinct alone won't work. Narcotics abusers are better actors than you are a detective. Even patients who are not trying to abuse narcotics don't all describe or display their pain in the same way.

■ **Accept that you'll get fooled sometimes.**

No matter how good your instincts, how consistent your standards, or how rigorous your controls, some

continued on page 69

POWER POINTS

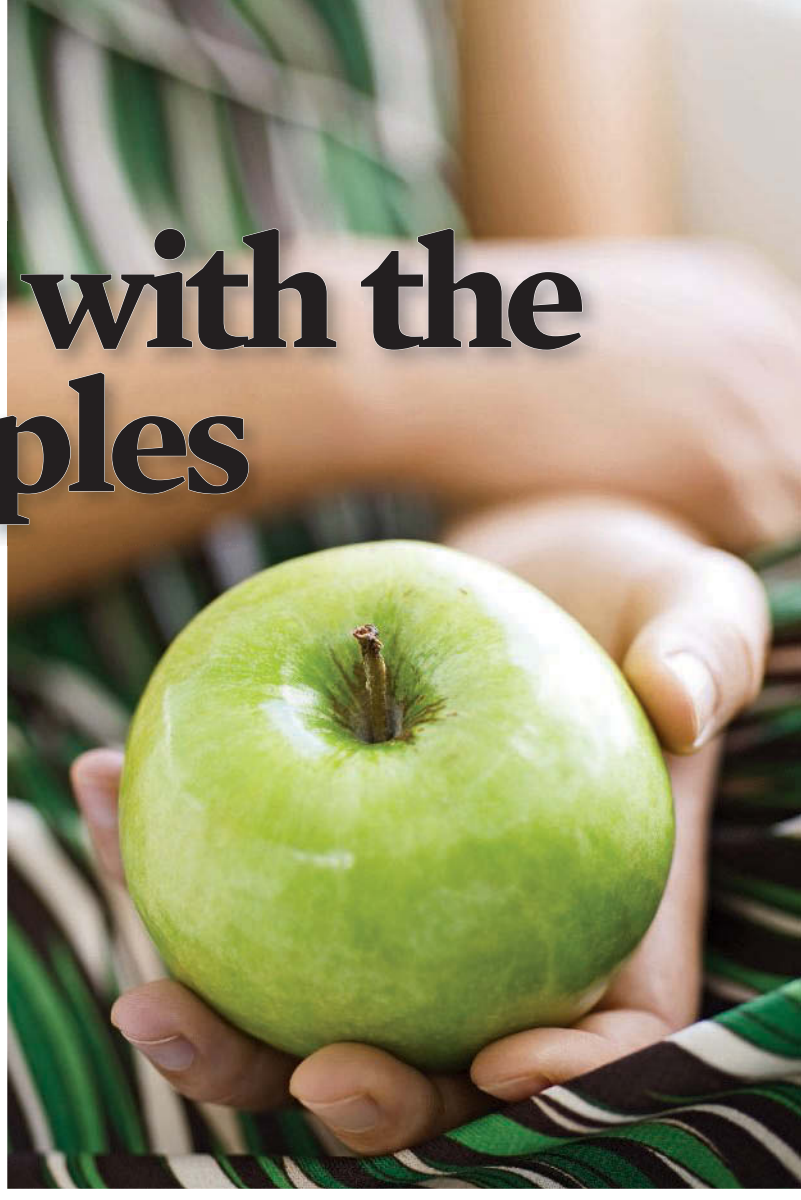
Don't go on gut feeling alone as the basis for prescribing a narcotic.

Use the same criteria for every patient when making prescription decisions.

Communicate your expectations to patients regularly and honestly.

Focus on the long-term interests of the patient.

The lady with the green apples



A GERIATRIC PATIENT SERVES AS A REMINDER TO TREAT THE WHOLE PERSON, NOT JUST THE DISEASE

[*By* **TASNEEM BADER-OMARALI**, *MD*]

I first met Mrs. Smith (not her real name) in a grocery line at a local farmers' market. She was in front of me, and her bag of green Granny Smith apples had just slipped out of her hands, sending them rolling down the smooth pavement. I helped her collect them, one by one, and while I was bent over, my face close to her ankles, I noticed that her ankles were swollen the size of the grapefruits that I was carrying in my own bag.

"You need to see your doctor," I told her as I stood up, handing her back her apples. It was one of my habits: offering medical advice to strangers about something that seemed clearly ominous. "Those ankles need to be looked at."

She was in her 70s, gray hair in wisps and coils that hung randomly about an aging, gentle face weathered by the deep lines of time. But one feature shone as sharp as freshly cut emeralds: her bright-green eyes.

Those eyes stared at me curiously as if trying to recognize a face. Then, as if in resignation, she shrugged and paid the cashier.

A SURPRISE VISIT

It was my first month in practice out of internal medicine residency. My husband and I were newlyweds, and we had just moved to a sunny northern California suburb. The area was affluent, surrounded by renowned university hospitals such as Stanford, and I wondered how long it would take me to get busy enough to make a salary to help support our new mortgage.

I looked out in my waiting room, which was empty except for one patient. It was the lady with the green apples.

"Her name is Mrs. Smith," my secretary informed me in a brisk voice. "She has not had a doctor in several years."

Mrs. Smith had found me through my photo advertisement in the town newspaper. She had recognized me from the farmers' market.

Now 75 years old, she had not seen a doctor since her husband died 10 years prior from metastatic colon cancer. She was disillusioned with the medical system. Her husband's diagnosis had been delayed despite a series of complaints he had expressed about abdominal pain. He had waited a year for a CT scan, by which time it was too late.

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The medical bills were astronomical because he had no secondary insurance to pick up what Medicare could not cover. They had no children, and there was no money left over to afford home healthcare, so she had to be his sole caregiver.

So now, Mrs. Smith, despite swollen legs and progressive shortness of breath, had refused to see a doctor. She had come that day only because I had seemed like a "nice young woman." But she really did not care for doctors. She just wanted to give me, in her own words, "a small chance."

AN APPARENT NIGHTMARE

This situation would be a nightmare to many doctors, and I was no exception.

Mrs. Smith appeared to be a nonadherent, stubborn patient on the verge of depression. But I was new to the world of medicine, and my enthusiasm not only was fresh but also was strong.

I plunged into performing a work-up. I ordered chest radiographs, an electrocardiogram, an echocardiogram, and lab tests, and I prescribed diuretics.

Mrs. Smith had congestive heart failure with an ejection fraction of 30% and aortic stenosis due to a bicuspid aortic valve. After much discussion, she agreed to take diuretics and aspirin. She refused to take digoxin or anti-depressants, or to see a cardiologist, or even to get a mammogram. Her mother had had an anaphylactic reaction to digoxin, and Mrs. Smith was certain this reaction was related to an allergy to the foxglove plant. She thought the mammogram would be too painful; she knew that breast cancer was even more painful but was willing to take that chance.

A GLIMMER OF HOPE

At first, I grappled with the idea of discharging Mrs. Smith as a patient because of her nonadherence to recommendations regarding medications and referrals. She appeared nothing short of a liability.

I searched for any relatives that I could talk to, to convince her to adhere to prescribed therapy. She had nobody, she told me. She had agreed to part of the medical plan, however; this agreement, I told myself, could provide a path toward more comprehensive health management.

As time, went on, I began to give Mrs. Smith credit for her decisions and soon accepted her choices of medical management just as she had accepted them herself. She declared she had lived a good life. She had run a clothing business on Market Street in San Francisco for 30 years with her husband. He was from Ecuador, and they knit lovely children's sweaters with brightly colored yarn from that country.

They also imported leather accessories. Such accessories had become a popular fashion statement in the city by the bay, and the couple's business flourished.

Mrs. Smith had gone back to college and earned a degree in history. She and her husband traveled to Italy and to the south of Spain and even to Morocco. She kept a journal and often would tell me about the magnificent Al Hambra fortress in Spain, the granite pillars of the Pantheon, and the ancient palaces of Marrakech.

The Smiths were self-employed and paid for their own health insurance. In the 1990s, when work in the apparel industry was outsourced to other countries, their business began to wind down. Few could afford the Smiths' fine wool sweaters. They sold their house and moved into a small mobile home a few yards away from the local farmers' market. They qualified for Medicare but could not afford secondary insurance and could not qualify for Medicaid.

Mr. Smith had been her companion for 40 years. After his death, Mrs. Smith volunteered in the senior center, driving the bus that would take seniors to doctors' appointments. Her health began to fail, however, and the senior center asked her to see a doctor or stay at home. She decided to do the latter only.

PERPLEXING UPS AND DOWNS

Mrs. Smith came to see me regularly, and her health began to improve. Her edema resolved, and she had more energy. She was vibrant and laughed with all my staff over silly "knock-knock" jokes. She even baked a pie with Granny Smith apples for me that Thanksgiving. As a new physician, in my quest for self-fulfillment, I began to feel proud that I had taken on a sick and nonadherent patient and had made a difference.

Then, exactly a year after her first appointment with me, Mrs. Smith called me early one morning. She was short of breath, and her legs were heavy as lead. I told her to go to the emergency room (ER). She refused. Frustrated, I told her to meet me in my office. There, I gave her oxygen and increased her dose of diuretics. I administered some sample diuretic tablets in the office and let her rest in an exam room. Her condition improved, and she went home.

The following week, the same incident recurred. Her edema had returned, worse than I had

"I HAD CROSSED THE FORMALITY OF PROFESSIONAL BARRIERS AND KNOCKED ON HER DOOR, UNINVITED. BY DOING SO, I HAD DISCOVERED A CRITICAL FACTOR OF MY PATIENT'S LIFE THAT HELPED ME CONTRIBUTE TO SOME QUALITY IN HER REMAINING YEARS."

ever seen before. Her breathing was labored. Her echocardiogram still showed an ejection fraction of 30%, and the aortic gradient had not changed. She refused hospitalization, knowing that doing so would put her at risk of death.

I asked her whether she had adhered to her medication schedule. She did not reply.

I decided that she was depressed and perhaps wished to stop all medications. My stomach churned. But then, I thought, why would she call and continue to see me?

AGAIN A DILEMMA

Mrs. Smith had again become a dilemma for me. I sat across from her and solemnly told her that if she did not take her medications or allow me to prescribe antidepressants, then she was not allowing me to do my job as a doctor, in which case I no longer could be of service to her.

She was silent, but in the corners of her clear, green eyes, I could see sparkling tears. After that day, I did not hear from her for a week. I called her home, and there was no response. The local hospital relayed that she had not been admitted.

I was driving home after work one day when the answering service sent me a text. Mrs. Smith was short of breath. I pulled over the side of the road and, using my smartphone, logged on to my electronic health record.

Mrs. Smith's house was just a mile down the road at a nearby senior mobile home facility. On an impulse, I made a U-turn and drove to her house.

Mrs. Smith opened the door and was taken aback. She invited me in. I was surprised that the house was immaculate. The décor was South American.

Just as before, her breathing was labored, and her steps were heavy due to three-plus pitting edema up to her knees. Her lungs had rales bilaterally, and her pulse was irregular, probably in atrial fibrillation.

I told her she needed to go to the hospital. She shook her head in defiance. I asked her where her medications were. "I don't have them," she told me.

"Why?" I asked her. "Your pharmacy has been delivering them to you every month." She pointed to her bedroom and told me to go there. Inside, on a shag rug, was a German Shepherd, curled up, his large head on his paws. He tried to open his eyes for me but could not. His breathing was shallow, saliva streamed down the side of his mouth.

Mrs. Smith did have all her medicine bottles, but they were just lying next to her dog, half empty. She had been feeding them to her dog. She told me that her husband had adopted Rufus from a shelter, and he had been just 5 years old when Mr. Smith died. Two months ago, the veterinarian had diagnosed the same condition of congestive heart failure in the 15-year-old dog, and she no longer could afford to pay the vet's bills. So she had been crushing up her own pills and feeding them to Rufus in water.

"You asked me once if I had any living relatives," she said, sadly. "I really do not. After my Fred died, this dog is the only relative I have and the best one ever. And I will do what I can for him. Even if I have to die first."

RELIEF SETS IN

I actually was relieved. I authorized an early refill on her medications and began to make daily house calls to make sure she was taking her diuretics. She even agreed to take an antidepressant.

Since the day I met Mrs. Smith's dog at her home, she trusted me more. Even though the dog had a small supply of her medications to take for his own ailment, I called the vet, who decided to see the dog under a payment plan.

Unfortunately, Rufus only lived for another month. As for Mrs. Smith, she lived for another 3 years before her ejection fraction slowly declined. She passed away at home with hospice care.

A LASTING LESSON

Occasionally, I pass by the local farmers' market and see the green Granny Smith apples. I think of

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the gray coils of hair hanging about a weathered face and those glittering green eyes.

Angry at her stubborn refusals and frustrated at myself for feeling this way, I nearly had discharged this patient, a woman already feeling discouraged and unhappy with the medical system. Ultimately, I was glad I had stayed with her to the end, but not because I had done anything heroic for her; she would not allow me to do that. Rather, having run out of options, I had crossed the formality of professional barriers and knocked on her door, uninvited. By doing so, I had discovered a critical factor of my patient's life that helped me contribute to some quality in her remaining years.

Our patients are not just limited to waiting rooms and exam rooms or dreaded phone calls. Once they leave our offices, they have other lives that often are mysteries to us. For this reason, we must treat the whole patient and not just the disease. Mrs. Smith was a testament to this simple fact. ME

The author practices internal medicine in Pleasanton, California. This article received an honorable mention in our 2011 Doctors' Writing Contest. Send your feedback about this article to medec@advanstar.com.

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patients will fool you. If you let these few get to you, you will become cynical about everyone. Instead, trust in the consistency of your processes to weed out abusers, and stay focused on the ones you are helping.

Let patients know your expectations right from the beginning. Physicians often find themselves writing recurrent narcotic scripts for what started as an acute condition. Then, they find themselves in the uncomfortable position of not knowing what to do since, as their patients inevitably will tell them, "Vicodin is the *only* thing that works."

As soon as you begin writing recurrent narcotic prescriptions or sense that a chronic pain syndrome is developing, have a frank discussion with your patient. Talk about chronic pain, the options for treatment, the limitations and the dangers of chronic narcotics, and the means by which you will regulate their use.

This approach can help prevent misunderstandings; sometimes it also heads off abusers looking for easy targets. Equally important in this early discussion is letting patients know that you will work with them to control their pain.

The discussion above works best if the patient is your patient. What happens when you inherit patients from your partners—especially the emotional prescribers? What about those new patients arriving with their desperate pleas for refills? In those cases, it is best to choose your battles carefully. The 88-year-old taking two Vicodin a day for her knee arthritis may not be your first "attack."

CLEAR EXPECTATIONS

Still, try to make your expectations clear. Even though you may have done things differently, you may be able to live with some variations.

Try to weigh risks and benefits. What are the risks of abuse or misuse? What is the risk of future problems or conflicts? In the balance of things, is this regimen helping the patient? Again, an early, frank discussion is very helpful.

My last suggestion is, don't become cynical.

"I knew it!" you say when you find out one of your patients was getting narcotics scripts on the sly from another provider. Remember that there are real people with real pain. When we help them live better, more functional lives through the appropriate use of narcotics, we have made the world a better place. ME

The author is a family physician practicing in Wyoming, Michigan. This article received an honorable mention in our 2011 Doctors' Writing Contest. Send your feedback to medec@advanstar.com.

GETTY IMAGES: ANDREA BRICCO

By **LEE J. JOHNSON**, *JD*

'Badmouthing' another doctor never a good idea

"Badmouthing" another physician is never a good idea, regardless of how tempted you might be in some instances.

For example, you may be frustrated because you think another doctor's care resulted in a bad clinical outcome, and you just want to say what you think. Or a patient has experienced a bad result with another physician and is "fishing" for commentary to determine whether to sue.

Refrain from making negative comments about another medical professional, however, for several reasons:

■ **You may make enemies in the medical community.** Your actions could affect the referrals you receive, if the other doctor is a referral source. Regardless, when word of your remarks gets around—and it will get around—the resulting animosity will create a stigma for you similar to that associated with a physician becoming a plaintiff's expert.

■ **If the patient sues, you also may be named in the lawsuit.** The plaintiff's attorney likely will want to include you as a way to get free expert testimony. The shotgun approach to naming defendants covers the plaintiff in case it later turns out that you did something wrong. If the other doctor starts to defend himself or herself by blaming you, then the work is done for the plaintiff's attorney. And if the physician who has been blamed has to testify against you and you have made negative comments, it would be difficult for him or her to be objective.

■ **The other doctor may file a lawsuit against you**, claiming damage to his or her reputation with resultant loss of patients, patient referrals (many patients refer their friends and family), and, therefore, income.

RAMIFICATIONS ARE VARIED

The ramifications are various for the physician about whom negative comments have been made.

If the commentary occurs in a hospital or clinic setting—or even in a group setting—other providers and staff members (such as office managers, administrative assistants, and receptionists) may worry that their reputations could become tainted. Other doctors, nurses, staff members, administrators, and, of course, other patients, may not want to work with the physician whose reputation has been tarnished. An administrator who is looking for a new job may not want to take a chance to go to work for a doctor whose reputation now is in question. A covering physician may not want to work with the one who has been badmouthed.

WHAT IF YOU ARE THE ONE WHO IS BADMOUTHED?

What should you do if another doctor makes negative comments about you?

■ **Take an active stance.** Such a stance may involve contact with the offending colleague and should include as much contact with the patient and/or the patient's significant others as you can arrange.

■ **Don't joust in the medical record.** If any blame can be assigned, it does not belong in the record. The record is a durable business document that will become evidence at the time of trial. Plaintiffs' attorneys are the ones who benefit from finger-pointing in the medical record.

WHY DOES IT HAPPEN?

Often, when one physician makes negative comments about another doctor to a patient, it could signal an ego problem. Badmouthing may arise from professional jealousy, envy, or grandiosity. In such cases, in the perpetrator's mind, his or her standing may be elevated when the other person is disparaged.

Using more primitive psychological

POWER POINTS

If you make negative comments about another doctor, you may harm your practice or may be named in a lawsuit.

Badmouthing can make it difficult for a physician to hire new staff or find a doctor to provide coverage.

If another physician badmouths you, take an active stance, and don't include negative comments in the medical record.

The author is a health law attorney in Mt. Kisco, New York, and a *Medical Economics* consultant. This column was co-authored by Paul Gordon, MD, a psychopharmacologist practicing in Goshen, New York. Malpractice Consult deals with questions on common professional liability issues. Unfortunately, we cannot offer specific legal advice. If you have a general question or a topic you would like to see covered here, send it to medec@advanstar.com.

» Most patients don't access their medical records electronically

Eighty-six percent of patients don't access their medical records electronically despite vast investments in electronic health records (EHR) systems and high hopes that consumers will use EHRs to participate in shared medical decision-making, according to research conducted by PwC's Health Research Institute in conjunction with its "Top Health Industry Issues of 2011" report.

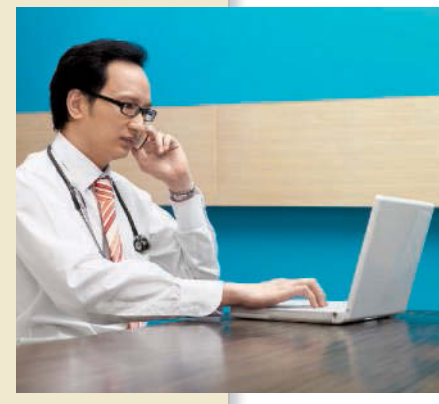
In addition, the report says that record spending on health information technology (HIT) this year is likely to increase demand for skilled HIT professionals, expand roles for chief information officers, and increase merger and acquisition activity among organizations looking to share the cost and benefits of HIT integration. The use of mobile health and wireless technologies also is expected to continue surging.

» Telemonitoring aids blood pressure control in diabetic patients

A fully automated cell phone-based telemonitoring system that involves patients in their care significantly improved blood pressure control among patients who had diabetes and uncontrolled systolic hypertension, according to a study by Alexander G. Logan, MD, of the University of Toronto, and colleagues.

Patients received pre-programmed cell phones that automatically transmitted readings from Bluetooth-enabled home blood pressure monitors to the application server. Patients received instant feedback on their cell phones, including their current blood pressure readings and messages ranging from congratulatory words to prompts to take additional readings over a certain period of time to obtain reliable overall readings.

If blood pressure values were too high, patients were asked to make follow-up appointments with their physicians. If 3-day or 2-week averages exceeded pre-determined goals, the patients' doctors were notified. Doctors could review the results of blood pressure readings on a Web-based server.



At 12 months, systolic blood pressure had decreased by 9.1 mm Hg in the telemonitoring group and by 1.6 mm Hg in those monitoring their blood pressure in the standard manner. Blood pressure control was achieved in 37% of the patients in the phone-based telemonitoring group and in 14.2% of the controls.

» More office-based doctors plan to achieve meaningful use

Forty-one percent of office-based physicians plan to achieve meaningful use of EHRs and apply for government incentive payments, according to a survey by the National Center for Health Statistics (NCHS) and discussed by David Blumenthal, MD, MPP, national coordinator for HIT, in a posting on his blog. Blumenthal says the survey numbers are a reversal of the low interest in EHR adoption in previous years. "I believe we are seeing the tide turn toward widespread and accelerating adoption and use of HIT," he says.

The survey also found that 32.4% of office-based physicians expect to enroll during Stage 1 of the federal incentive programs. Fourteen percent said they were not planning to apply for meaningful use incentives.

Additional survey data from the NCHS show that the number of primary care physicians who already have adopted a basic EHR increased from 19.8% in 2008 to 29.6% in 2010. Most physicians would need to further upgrade their EHR systems or their use of the systems to qualify for meaningful use incentive payments.

New Web site provides tools for meaningful use

The Healthcare Information and Management System Society has launched Meaningful Use OneSource, an online repository of documents, tools, and links to other knowledge available online. The site is designed to help individuals and organizations prepare for meaningful use certification criteria and standards regulations. The site explains:

- how to meet and use meaningful use certification criteria,
- how to receive Medicare and Medicaid incentive funding and avoid penalties,
- how to implement meaningful use in a healthcare organization, and
- how to access updates on federal and state laws and regulations.

Information on the site appears in three categories: 1) the basics, 2) qualifying for meaningful use and funding, and 3) putting meaningful use into practice. View the site at himss.org.

GETTY IMAGES: IMAGE SOURCE

HER FIRST OSTEOPOROTIC FRACTURE COULD LEAD TO ANOTHER

FORTEO® (teriparatide [rDNA origin] injection) SELECT SAFETY INFORMATION

Prescribe FORTEO only for patients for whom the potential benefits are considered to outweigh the potential risks. FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma, including those with Paget's disease of bone, unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy. Additionally, patients with bone metastases or a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or pre-existing hypercalcemia should not receive FORTEO.

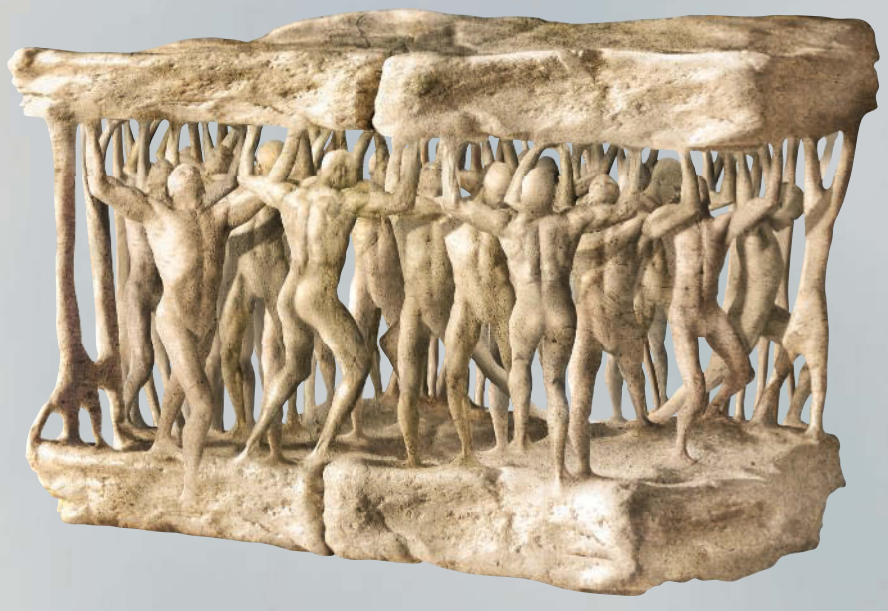
Use of FORTEO for more than 2 years during a patient's lifetime is not recommended.

FORTEO CONNECT OFFERS PERSONALIZED SUPPORT TO HELP PATIENTS THROUGHOUT THEIR TREATMENT

- Patients can choose to sign up for insurance investigation, training, and/or ongoing support

Find out how FORTEO forms new bone at www.FORTEOhcp.com

NOW IS THE TIME FOR ANABOLIC ACTION



FORTEO IS INDICATED:

- For the treatment of postmenopausal women with osteoporosis at high risk for fracture
- To increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
- For the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy at high risk for fracture

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® (teriparatide [rDNA origin] injection) only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

Please see Important Safety Information and Brief Summary of Prescribing Information on adjacent pages.

FORTEO™
teriparatide (rDNA origin) injection
ANABOLIC ACTION FOR NEW BONE

Lilly

IMPORTANT SAFETY INFORMATION

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

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CONTRAINDICATIONS

Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

The following categories of patients have increased baseline risk of osteosarcoma and therefore should not be treated with FORTEO: Paget's disease of bone, pediatric populations and young adults with open epiphyses, or prior external beam or implant radiation therapy.

Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org.

Osteosarcoma occurs in about 4 out of every million older adults each year. Cases of bone tumor and osteosarcoma have been reported rarely in people taking FORTEO in the post-marketing period. The causality to FORTEO use is unclear.

Use of FORTEO for more than 2 years during a patient's lifetime is not recommended.

Patients with the following conditions also should not receive FORTEO: bone metastases or a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or hypercalcemic disorders.

FORTEO may increase serum calcium, urinary calcium, and serum uric acid.

Use with caution in patients with active or recent urolithiasis because of risk of exacerbation. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered.

Transient orthostatic hypotension may occur with initial doses of FORTEO. In short-term clinical pharmacology studies, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. FORTEO should be administered initially under circumstances where the patient can sit or lie down if symptoms of orthostatic hypotension occur.

Patients receiving digoxin should use FORTEO with caution because FORTEO may transiently increase serum calcium and hypercalcemia may predispose patients to digitalis toxicity.

FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal studies, FORTEO may cause fetal harm.

It is not known whether teriparatide is excreted in human milk. Breastfeeding mothers should discontinue nursing or FORTEO, taking into account the importance of treatment to the mother.

ADVERSE REACTIONS

The most common adverse reactions in clinical trials include: arthralgia (10.1 FORTEO vs. 8.4 placebo), pain (21.3 FORTEO vs. 20.5 placebo), and nausea (8.5 FORTEO vs. 6.7 placebo). Other adverse reactions include: dizziness, leg cramps, joint aches, and injection site reactions.

INSTRUCTIONS FOR FORTEO USE

FORTEO is provided as a fixed-dose, prefilled delivery device that can be used for up to 28 days, including the first injection. The delivery device contains 28 daily doses of 20 mcg each. Do not transfer the contents of the delivery device into a syringe. The FORTEO Delivery Device should be stored under refrigeration at 36° to 46° F (2° to 8° C) at all times. Do not use FORTEO if it has been frozen.

Please see Brief Summary of Prescribing Information on adjacent pages.

FORTEO™
teriparatide (rDNA origin) injection
ANABOLIC ACTION FOR NEW BONE

Lilly

FORTEO® (teriparatide [rDNA origin] 20 mcg for injection)

Brief Summary. Consult the package insert for complete prescribing information.

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton).

INDICATIONS

FORTEO is indicated: for the treatment of postmenopausal women with osteoporosis at high risk for fracture; to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; for the treatment of men and women with osteoporosis associated with sustained, systemic glucocorticoid therapy at high risk for fracture.

CONTRAINDICATIONS

Do not use FORTEO in patients with Hypersensitivity to teriparatide or to any of its excipients. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

Osteosarcoma In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. FORTEO should not be prescribed for patients at increased baseline risk of osteosarcoma. These include Paget's disease of bone (unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone); pediatric and young adult patients with open epiphyses; prior external beam or implant radiation therapy involving the skeleton. Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Enrollment information can be obtained by calling 1-866-382-6813, or by visiting www.forteoregistry.rti.org. **Treatment Duration** The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patients' lifetime is not recommended. **Bone Metastases and Skeletal Malignancies** Patients with bone metastases or a history of skeletal malignancies should not be treated with FORTEO. **Metabolic Bone Diseases** Patients with metabolic bone diseases other than osteoporosis should not be treated with FORTEO. **Hypercalcemia and Hypercalcemic Disorders** FORTEO has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with FORTEO because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with FORTEO. **Urolithiasis or Pre-existing Hypercalciuria** In clinical trials, the frequency of urolithiasis was similar in patients treated with FORTEO and placebo. However, FORTEO has not been studied in patients with active urolithiasis. If active urolithiasis or pre-existing hypercalciuria are suspected, measurement of urinary calcium excretion should be considered. FORTEO should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition. **Orthostatic Hypotension** FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur. In short-term clinical pharmacology studies with teriparatide, transient episodes of symptomatic orthostatic hypotension were observed in 5% of patients. Typically, an event began within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment. **Drug Interactions** Hypercalcemia may predispose patients to digitalis toxicity. Because FORTEO transiently increases serum calcium, patients receiving digoxin should use FORTEO with caution.

ADVERSE REACTIONS

Clinical Trials Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. *Treatment of Osteoporosis in Men and Postmenopausal Women* The safety of FORTEO in the treatment of osteoporosis in men and postmenopausal women was assessed in two randomized, double-blind, placebo-controlled trials of 1382 patients (21% men, 79% women) aged 28 to 86 years (mean 67 years). The median durations of the trials were 11 months for men and 19 months for women, with 691 patients exposed to FORTEO and 691 patients to placebo. All patients received 1000 mg of calcium plus at least 400 IU of vitamin D supplementation per day. The incidence of all cause mortality was 1% in the FORTEO group and 1% in the placebo group. The incidence of serious adverse events was 16% in FORTEO patients and 19% in placebo patients. Early discontinuation due to adverse events occurred in 7% of FORTEO patients and 6% of placebo patients. **Percentage of Patients with Adverse Events Reported by at Least 2% of FORTEO-Treated Patients and in More FORTEO-Treated Patients than Placebo-Treated Patients from the Two Principal Osteoporosis Trials in Women and Men Adverse Events are Shown Without Attribution of Causality(FORTEO, N=691, Placebo, N=691):** *Body as a Whole:* Pain (21.3%, 20.5%), Headache (7.5%, 7.4%), Asthenia (8.7%, 6.8%), Neck Pain (3.0%, 2.7%); *Cardiovascular:* Hypertension (7.1%, 6.8%), Angina Pectoris (2.5%, 1.6%), Syncope (2.6%, 1.4%); *Digestive System:* Nausea (8.5%, 6.7%), Constipation (5.4%, 4.5%), Diarrhea (5.1%, 4.6%), Dyspepsia (5.2%, 4.1%), Vomiting (3.0%, 2.3%), Gastrointestional disorder (2.3%, 2.0%), Tooth disorder (2.0%, 1.3%); *Musculoskeletal:* Arthralgia (10.1%, 8.4%), Leg cramps (2.6%, 1.3%); *Nervous System:* Dizziness (8.0%, 5.4%), Depression (4.1%, 2.7%) Insomnia (4.3%, 3.6%), Vertigo (3.8%, 2.7%); *Respiratory System:* Rhinitis (9.6%, 8.8%), Cough increased (6.4%, 5.5%), Pharyngitis (5.5%, 4.8%), Dyspepsia (3.6%, 2.6%), Pneumonia (3.9%, 3.3%); *Skin and Appendages:* Rash (4.9%, 4.5%), Sweating (2.2%, 1.7%). Immunogenicity In the clinical trial, antibodies that cross-reacted with teriparatide were detected in 3% of women (15/541) receiving FORTEO. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions or allergic reactions among these patients. Antibody formation did not appear to have effects on serum calcium, or on bone mineral density (BMD) response. *Laboratory Findings* **Serum Calcium:** FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4 to 6 hours after FORTEO administration was increased from 2% of women and none of the men treated with placebo to 11% of women and 6% of men treated with FORTEO. The number of patients treated with FORTEO whose transient hypercalcemia was verified on consecutive measurements was 3% of women and 1% of men. **Urinary Calcium:** FORTEO increased urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with FORTEO and placebo. **Serum Uric Acid:** FORTEO increased serum uric acid concentrations. In clinical trials, 3% of FORTEO patients had serum uric acid concentrations above the upper limit of normal compared with 1% of placebo patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis. **Renal Function:** No clinically

FORTEO® (teriparatide [rDNA origin] 20 mcg for injection) PA 097 FSAM00

important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment. *Studies in Men and Women with Glucocorticoid-Induced Osteoporosis* The safety of FORTEO in the treatment of men and women with glucocorticoid-induced osteoporosis was assessed in a randomized, double-blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥ 5mg per day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to FORTEO and 214 patients exposed to oral daily bisphosphonate (active control). All patients received 1000 mg of calcium plus 800 IU of vitamin D supplementation per day. The incidence of all cause mortality was 4% in the FORTEO group and 6% in the active control group. The incidence of serious adverse events was 21% in FORTEO patients and 18% in active control patients, and included pneumonia (3% FORTEO, 1% active control). Early discontinuation because of adverse events occurred in 15% of FORTEO patients and 12% of active control patients, and included dizziness (2% FORTEO, 0% active control). Adverse events reported at a higher incidence in the FORTEO group and with at least a 2% difference in FORTEO-treated patients compared with active control-treated patients were: nausea (14%, 7%), gastritis (7%, 3%), pneumonia (6%, 3%), dyspnea (6%, 3%), insomnia (5%, 1%), anxiety (4%, 1%), and herpes zoster (3%, 1%), respectively. **Postmarketing Experience:** The following adverse reactions have been identified during postapproval use of FORTEO. 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. **Osteosarcoma**: Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing. **Hypercalcemia**: Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use. Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following: *Allergic Reactions*: Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria; *Investigations:* Hyperuricemia; *Respiratory System*: Acute dyspnea, chest pain; *Musculoskeletal*: Muscle spasms of the leg or back; *Other*: Injection site reactions including injection site pain, swelling and bruising; oro-facial edema.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C. There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At doses ≥ 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings. In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses ≥120 times the human dose (based on surface area, mcg/m2). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively. Exposure multiples were normalized based on body surface area (mcg/m2). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day). **Nursing Mothers:** It is not known whether teriparatide is excreted in human milk. Because of the potential for tumorigenicity shown for teriparatide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** The safety and efficacy of FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses. **Geriatric Use:** Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** No studies have been performed in patients with hepatic impairment. **Renal Impairment:** In 5 patients with severe renal impairment (CrCl<30 mL/min), the AUC and T1/2 of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased.

OVERDOSAGE

Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur. In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) of the FORTEO delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported. Overdose Management There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

DOSAGE FORMS AND STRENGTHS

Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg.

PATIENT COUNSELING INFORMATION

Patients should read the FDA-approved *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with FORTEO and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

12/13/2010

PLEASE SEE FULL PRESCRIBING INFORMATION FOR ADDITIONAL INFORMATION.

Literature revised December 13, 2010

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defense mechanisms, one physician who speaks negatively about another doctor may be projecting his or her own insecurities and/or past mistakes on to others. If you are on the receiving end of such behavior, consider that a professional may not like you simply because you remind him or her of someone he or she dislikes.

A CASE IN POINT

In a case involving the co-author of this column, psychiatrist Paul Gordon, MD, an emergency room (ER) physician reportedly was badmouthing Gordon to a patient's spouse when the patient arrived in a coma to the ER. The ER doctor, according to the spouse, had told the spouse that Gordon's treatment was "like putting a gun to the patient's head." Gordon had written the patient a prescription for 300 pills, but the patient overdosed, and subsequently died, from another substance, not from the prescription.

Gordon's reason for giving the prescription for the large quantity of pills was expressly to prevent overdosing. His opinion is that it is safer to prescribe some medications in low strengths, necessitating that a large number of pills be taken to reach the prescribed dosage, than to prescribe a higher-strength pill that would require the patient to take fewer pills to reach the dosage amount.

In this case, the first order of business for Gordon was to contact the ER doctor, explain the reasoning behind the prescription being written the way it was written, and ask him not to repeat his earlier comments. The second step was to send a sympathy card to the patient's spouse.

In such cases, consider offering bereavement counseling at no charge. The more contact, the less likely a lawsuit.

By RENEE STANTZ

Three codes introduced for observation

Q: *Can you explain the changes to the observation codes?*

A: The 2011 CPT codebook contains three new codes for subsequent outpatient care services: 99224, 99225, and 99226. A great deal of confusion has occurred in the past, so these codes are welcome additions that clarify and simplify how to code for these services.

The new codes are similar to the inpatient subsequent care codes in that they include an interval history. CPT describes an interval history as the history that "focuses on the period of time since the physician last performed an assessment of the patient" (*CPT Assistant*, January 2000, page 11). Code 99224 requires two of three components, including a problem-focused interval history, problem-focused exam, and medical decision-making that is straightforward or of low complexity. Code 99225 includes an expanded problem-focused interval history, an expanded problem-focused examination, and medical decision-making of moderate complexity. Code 99226 includes a detailed interval history, a detailed exam, and medical decision-making of high complexity.

The description for each of these codes also includes a time element for those billing based on time. For instance, billing code 99224 requires approximately 15 minutes to be spent at the patient's bedside or on the floor/unit dedicated to the patient's care; for 99225, approximately 25 minutes; and for 99226, approximately 35 minutes.

The requirements for the new observation codes match the requirements for the subsequent hospital care codes. The new codes also have times associated with them that match the subsequent hospital care codes. The time for 99224 is 15 minutes, the time for 99225 is 25 minutes, and the time for 99226 is 35 minutes.

Time-based coding requires that more than half of the visit time be spent counseling and coordinating the patient's care. Documentation should reflect the full time of the visit, the time spent counseling and coordinating care, and a detailed description of the counseling given and the coordination of care needed.

PECOS ENROLLMENT UPDATE

In the December 3 column, I detailed the two phases that the Centers for Medicaid and Medicare Services (CMS) is implementing for Part B services requiring an ordering or referring physician. The ordering/referring physician must be enrolled in CMS' Provider Enrollment, Chain, and Ownership System (PECOS), and his or her name and national provider identifier information must be listed on claims (CMS-1500, Line 17, or electronic equivalent) for Part B claims to be paid.

Originally, phase two stipulated that, starting January 3, Medicare would reject Part B claims that fail the ordering/referring provider edits, meaning that your claims will not be paid unless you are enrolled in PECOS. Subsequently, however, CMS announced that phase two of the PECOS implementation would be delayed. *MLN Matters* specifically states that CMS "previously announced that, beginning January 3, 2011, if certain Part B billed items and services require an ordering/referring provider and the ordering/referring provider is not in the claim, is not of a profession that is permitted to order/refer, or does not have an enrollment record in the Medicare... [PECOS], the claim will not be paid. The automated edits will not be turned on effective January 3, 2011. We are working diligently to resolve enrollment backlogs and other system issues and will provide ample advanced notice to the provider and beneficiary communities before we begin any automatic nonpayment actions."

I strongly suggest, however, that all affected providers continue enrolling in PECOS, because the application process takes 45 to 60 days for CMS to complete. You can enroll by using the Internet-based PECOS (cms.gov/MedicareProviderSupEnroll) or download the CMS-855I paper form at cms.gov/cmsforms/cmsforms. If you reassign your Medicare benefits to a group or clinic, you also will need to complete CMS-855R.

POWER POINTS

The 2011 CPT codebook contains three new codes for subsequent outpatient care services: 99224, 99225, and 99226.

CMS has delayed the implementation of PECOS for ordering and referring physicians, but if you are such a doctor, enroll in PECOS now because it can take CMS 45 to 60 days to approve applications.

The author is a medical consultant based in Indianapolis, Indiana. Do you have a primary care-related coding question you would like to have our experts answer in this column? Send it to medec@advanstar.com.

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How to improve your credit score

Q: *I'm just starting out in practice and would like to check on and improve my credit score. How can I do that?*

A: The best way to start is by reading the Fair Credit Reporting Act so you know your rights as you go through the credit process. Then follow as many of these steps as you can:

- Obtain your credit report for free from any of the three credit reporting agencies: Experian (experian.com), Equifax (equifax.com), and TransUnion (Transunion.com).
- Look for errors and write letters disputing them to each credit reporting agency by registered mail with return receipt.
- Pay your bills on time. Some bills require payment in as few as 10 days.
- Pay down your credit cards to an amount not to exceed 50% of your maximum limit.
- Be very careful about not divulging any personal or financial information over the Internet.

Unfortunately, with few exceptions, you can do nothing to remove any accurate, negative information on your credit reports until it cycles off in 7 years from the date of first delinquency. Adding new and positive information to your credit report, however, will count for more each month and any old, negative information will start to count for less.

FIND OUT ABOUT CHARITIES BEFORE YOU DONATE

Q: *My practice is doing well, and now that my children are grown I'd like to start giving back to the community. How can I be certain the charities I donate to are legitimate and that my contributions are tax-deductible and going to people in need rather than the fundraisers?*

A: You can use two sources to check on the legitimacy of a charity and see how much of your donation actually is used to help people. First is the GuideStar Web site at guidestar.org. GuideStar allows you to see for free a charity's public tax return (form 990). It may be more information than you need, but it provides a complete picture.

You also can use the Web site of the National Association of State Charity Officials at nasconet.org/agencies. It shows, on a state-by-state basis, how much of your donation goes to help people and how much goes to fundraising and management expenses. All donations to legitimate charities are tax-deductible.

Other useful Web sites for investigating charities:

- Charity Navigator (charitynavigator.org),
- BBB Wise Giving Alliance (bbb.org/charity),
- American Institute of Philanthropy (charitywatch.org), and
- Military Relief Societies (militaryhomefront.dod.mil).

These organizations will list, and often rate, charities. Small, new, or local charities may not be rated, however. In those cases, nothing beats a personal phone call to the charity.

Don't be shy about asking questions. Ask about whom they use to solicit donations, how donated funds are spent, and what percentage of the dollars raised actually gets to the intended recipients. (You may be surprised to find out how little goes to your intended charity when it hires outside solicitors.) And you'll feel better finding a place where you know your help is going to the people who truly need it.

ModernMedicine NETWORK
NEWS & UPDATES
Learn how charitable donations can reduce your taxes while helping others at MedicalEconmics.com/charitable

We want to hear from you!

Send your money management questions to medec@advanstar.com. Answers to our readers' questions were provided by Dan Nigito, CFP, vice president of Merion Wealth Partners, LLC in Berwyn, Pennsylvania, and Richard J. St. John, president, St. John & Associates, Inc., Roswell, Georgia.

GETTY IMAGES FROM TOP: ARIEL SKELLEY / DAVID GOULD

When to collect deductibles

Q: ***Is the collection of a patient's deductible or co-insurance amount prior to treatment accepted practice? What are the implications on a medical practice in doing so from an overall practice management and patient perspective?***

A: The average patient is now responsible for about 25% of his or her healthcare bill—so if you're not already doing so, you should be asking all patients for amounts due at the time of service. As a general rule, if we know what the patient's financial responsibility is, then yes, it is more than appropriate to ask for the payment at the time of service. Check your payer contracts for specifics. Between eligibility options and online access to payers, it is pretty easy to calculate the patient's portion.

One popular option is to maintain a credit card on file for payment on receipt of the insurance explanation-of-benefits statement. Charge only the allowable amount to prevent a future refund. Payments can be processed on a monthly basis as well.

The key is the educate patients about your policies so they are prepared, not perplexed, by your request for payment. Discuss the patient's specific plan and ultimate responsibility of his or her healthcare bill.

WRONG INSURANCE BILLED

Q: ***What do other practices do regarding billing patients who give you the wrong insurance information and you only find out when it's too late?***

A: This is a problem with accurate registration and insurance verification—or with patient fraud. Everything should be verified at the time of registration. This includes taking a copy of an insurance card and checking a current address and, perhaps, checking eligibility on provider-side Web portals. If the patient is not honest, or personally uninformed, then he or she would be contacted and handled as a "non-insured" patient and billed as such. First of all, make sure that your office has efficient and effective registration processes.

BILLING THE DECEASED

Q: ***What can I do with a large outstanding balance left by a deceased patient?***

A: The only option is to immediately bill the estate and hope that this obligation is settled along with the other outstanding obligations following the demise of the patient. If there is health insurance, of course, then that should be billed, and the billing office also should make an attempt to contact the executor of the estate to determine who might be closing out the deceased party's financial matters.

EXCESSIVE PREPAYMENT REVIEWS

Q: ***I am an out-of-network provider for a large commercial insurer. For months, all my claims with this insurer have been in prepayment review. If I submit a claim after 30 days, I get a letter asking for notes to get paid. The turnover time now is 3 months, and I have submitted more than 200 claims with notes. I have called to inquire when this prepayment review will end, but I never receive any clear answers. Any advice?***

A: We usually see these kinds of letters after a payer audits a provider and claims there are "problems" (for instance, upcoding, unbundling, medically unnecessary tests, etc.) and possibly will demand a refund from the provider. Once the parties resolve the dispute, the payer typically wants to see the records before paying, to ensure that the "problems" identified in the audit are not recurring. At least that's what the payer claims.

This is a form of harassment. If the provider enters into a participating provider agreement with the payer, the agreement usually will include a provision allowing the payer to ask for records as part of a prepayment review. As a nonparticipating provider, you should argue that you never entered into this agreement and that if the payer has not found any issues to date, the prepayment review process should stop because it creates an administrative and economic burden on the provider.

We want to hear from you!

Answers to readers' questions were provided by Susan Childs, Evolution Healthcare Consulting, Rougemont, North Carolina; A. Michael La Penna, The La Penna Group, Grand Rapids, Michigan; and Barry B. Cepelewicz, MD, JD, Meiselman, Denlea, Packman, Carton & Eberz, White Plains, New York. Send your practice management questions to medec@advanstar.com.

GETTY IMAGES; STOCKBYTE

By **STEVEN PODNOS**, *MD, CFP*

Are variable annuities an investment or insurance?

Variable annuities have been sold by insurance companies to physicians and others for many years. These high-commission products were marketed on the basis of capturing gains in the stock market in a tax-deferred envelope.

In the past, investment advisers generally considered variable annuities an expensive way to own mutual funds and did not use them for clients. With the addition of "guaranteed living benefits," however, these vehicles deserve a second look due to their performance in flat or down markets, and as a way of ensuring that doctors and others have enough money to see them through retirement.

These investments involve giving an insurance company a lump sum of after-tax cash. You then may allocate the cash into different mutual funds investing in stocks, bonds, and other common asset classes. At a predetermined point in the future, you are allowed to make certain withdrawals, based on the earnings on the accounts after subtracting expenses.

WITHDRAWAL RIGHTS

In recent years, the insurance companies have added riders that allow guaranteed withdrawal rights of a certain percentage of the account regardless of the actual performance of the underlying investments. These companies also will guarantee a minimal investment return as a "floor," regardless of actual performance. The insurance companies do this by establishing two accounts: a "real" account that invests in securities and is used to pay expenses, and a "phantom" account that grows according to an agreed-on schedule and pays you your distributions. The distributions are usually a fixed percentage of whichever account is higher.

When you die, your family gets the balance of the real account. If that account performs poorly and/or has high expenses, little or nothing may be left for them to inherit. But if your account has good underlying performance and you happen to die early, there may be some assets to leave. Death benefit riders guaranteeing an inheritance also are available.

If the investments do much better than expected, the value of the account from which withdrawal percentages can be drawn increases. For example, one current annuity offers to double your original investment amount if the account is left untouched for 10 years, and then offers a 5% withdrawal rate for life on the doubled investment beginning at age 65. So $100,000 deposited at age 55 would translate into a guaranteed offer of $10,000 a year return for life beginning at age 65.

INSURED INCOME

The addition of guaranteed living benefits enables insurance companies to sell these annuities as an investment and a type of insured income. The underlying expenses, however, usually are too high to realistically allow a decent return on investments. Therefore, these annuities should be evaluated only as sources of guaranteed income, including the assumption that the principal of the investments will not be touched beyond what is mutually agreed to when making the investments. Excess withdrawals of any type usually are penalized severely in terms of guarantee reductions and ultimate benefits. Look for the term "guaranteed withdrawal benefit for life" because this characteristic is vital.

POWER POINTS

- Variable annuities are generally sold through insurance companies.
- Variable annuities provide a guranteed income stream for the duration of retirement.
- Depending on the performance of the underlying investments, they may not leave any assets to inherit.

In sum, variable annuities are now an option to consider as long as you think of them only as a guaranteed lifetime income stream. If a high return is your goal, you're probably better off looking elsewhere.

The author is a financial adviser and the prtincipal of Wealth Care LLC based in Merritt Island, Florida. The ideas expressed in this column are his alone and do not represent the views of *Medical Economics*. If you have a comment or a topic you would like to see covered here, please e-mail medec@advanstar.com.

Latest Research

A summary of current clinical articles from that pile on your desk

HEART DISEASE

Cognitive behavioral therapy may reduce cardiovascular disease

Arch Intern Med. 2011;171:134-140. [January 24, 2011]

Cognitive behavioral therapy (CBT) may decrease the risk of recurrent acute myocardial infarction (AMI) and cardiovascular disease. Researchers from the Uppsala University Hospital in Sweden examined 362 patients aged 75 years or younger who were discharged from the hospital after having a coronary heart disease event. Patients were randomly assigned to receive traditional care alone (170 patients) or in combination with a CBT intervention program (192 patients). Intervention consisted of 20 2-hour sessions during the course of 1 year, focusing on stress management. Patients were followed up for an average of 94 months. The investigators found that patients in the CBT intervention group had a 41% lower rate of fatal and nonfatal first recurrent cardiovascular disease events, as well as 45% fewer recurrent AMIs compared with patients receiving traditional care. Patients who participated in CBT intervention also had a small but insignificant reduction in all-cause mortality compared with patients who received traditional care. There was a strong dose-response effect between attendance at the CBT intervention program and outcome.

Exercise helps patients with heart failure fight depression

Am J Cardiol. 2011;107:64-68. [January 2011]

Researchers at the Ochsner Clinical School–The University of Queensland School of Medicine in New Orleans, Louisiana, studied the effects of structured exercise training (ET) on patients with heart failure due to coronary heart disease, including 151 patients who completed the ET program and 38 who dropped out of rehabilitation without ET. Participants completed questionnaires about their depressive symptoms at baseline and after the structured ET program was completed. The patients' overall rates of depressive symptoms decreased by 40% after ET, from 22% to 13%. Patients who were still depressed after ET had mortality rates that were four times higher than those whose depressive symptoms resolved after exercise. Depressed patients who remained in the ET group had a 59% lower mortality rate than those who dropped out.

Colonoscopy offers strong protection against CRC

Ann Intern Med. 2011;154:22-30. [January 4, 2011]

Colonoscopy may be associated with a strongly reduced risk for colorectal cancer (CRC), with risk reduction observed for both left-sided and right-sided CRC. German researchers collected data on 1,688 patients with CRC and 1,932 controls to assess the association between prior colonoscopy and risk for CRC. Colonoscopy within the last 10 years was related to a 77% reduction in CRC risk. The adjusted odds ratios for right- and left-sided CRC were 0.44 and 0.16, respectively. The reduction in risk was strong for all ages and cancer stages aside from right-sided cancers in people aged 50 to 59 years. Risk reduction in both sides increased over the years.

Air filters may reduce cardiovascular disease risk

Am J Respir Crit Care Med. Online before print. ajrccm.atsjournalsorg/cgi/content/abstract/201010-1572OCv1 [January 21, 2011]

The use of high efficiency particle air (HEPA) filters may help to reduce the risk of cardiovascular disease associated with air pollution exposure. Researchers at Simon Fraser University in Burnaby, Canada, used portable HEPA filters in a randomized crossover intervention study of 45 healthy adult participants from 25 homes in a woodsmoke-impacted community exposed to consecutive 7-day periods of filtered and nonfiltered air to assess the impact on particle exposures and endothelial function. The portable HEPA filters reduced the average concentrations of fine particulates inside homes by 60% and woodsmoke by 75%. These reductions were associated with improved endothelial function, with a 9.4% increase in reactive hyperemia index, as well as decreased inflammation, with a 32.6% decrease in C-reactive protein.

Familial alcoholism risk may be linked to obesity

Arch Gen Psychiatry. 2010;67:1301-1308. [December 2010]

Familial alcoholism risk may be associated with obesity, especially among women. Researchers at the Washington University School of Medicine in St. Louis, Missouri, conducted analyses of the repeated cross-sectional National Longitudinal Alcohol Epidemiologic Survey (1991 to 1992) and National Epidemiologic Survey on Alcohol and Related Conditions (2001 to 2002) to determine whether familial risk of alcohol dependence predicts obesity and whether any such association grew stronger between the early 1990s and early 2000s. Compared with women without a family history of alcoholism in 2001 to 2002, the women with a family history had 49% higher odds of obesity, a highly significant increase from 1991 to 1992. Although the association was significant for men in 2001 to 2002, it was not as strong as for women. The association for women remained robust after adjustment for covariates; however, the association for men did not meet statistical significance criteria after adjustment for covariates.

Prepared jointly by the editors of *Medical Economics* and HealthDay's Physician's Briefing (physiciansbriefing.com).

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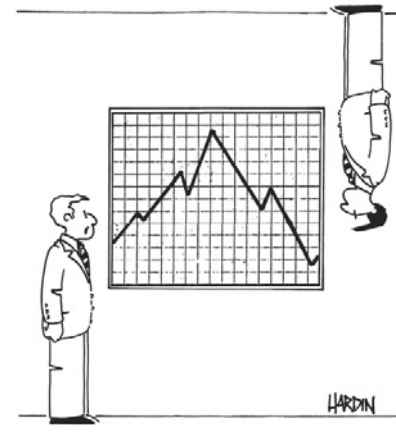

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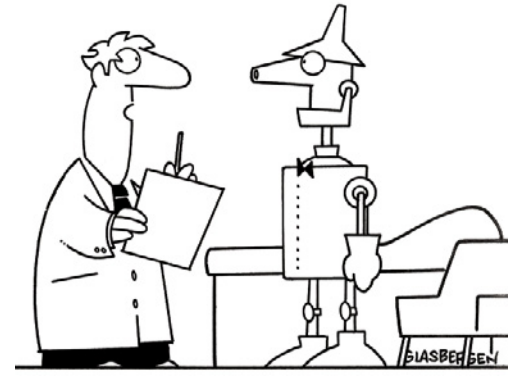

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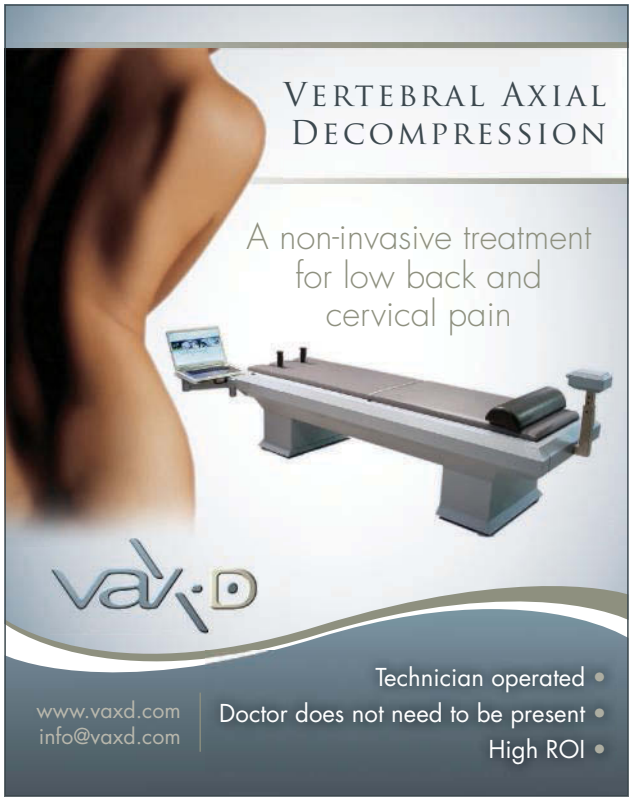

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Reading between the lines

INTERPRETING PATIENTS' BODY LANGUAGE CAN IMPROVE CARE

By **JORDAN GRUMET**, *MD*
Highland Park, Illinois

At varying stages in my medical career I have learned to acquire information in different ways. As a beginning medical student, I concentrated on case studies. As I became a resident, my focus changed to taking histories and physical exams. Now as an attending physician, I have learned to use both body language and my own emotional reactions to enhance patient care.

The ability to interpret body language can be like a sixth sense to physicians. I usually can tell whether patients are depressed by the way they walk into my office. I notice how their heads hang down as they walk or whether they answer when I call out to them in the waiting room.

A lot of information can be found in the subtleties of gestures and mannerisms.

"THE ABILITY TO INTERPRET BODY LANGUAGE CAN BE LIKE A SIXTH SENSE TO PHYSICIANS."

A DIFFERENTIAL DIAGNOSIS

When Mrs. W walked into my office, I knew that she was depressed. Her eyes were focused on the ground, and her gait was slow and deliberate. As I took her history I learned that she had been losing weight at an alarming rate. She was having abdominal pain and couldn't eat. Her examination showed a thin woman who was otherwise normal. I described the workup for her weight loss and prescribed an antidepressant.

The results of her lab tests were normal. There were no thyroid problems, diabetes, or anemia. She was up to date on cancer screening. The only abnormality was a CT scan of the abdomen that showed a small nodule on the liver. Although I had doubts about the importance of this finding, there was no other explanation for her weight loss and abdominal pain. So I ordered a biopsy and waited. In the meantime, her depression was starting to break, and she was feeling better. But her weight was still dropping. She was now below 100 pounds.

When the liver biopsy results were normal, she came to my office for a follow-up visit. I had no magical diagnosis to explain her condition after 3 months of searching. She still wasn't eating. She appeared frail, as if the slightest breeze would knock her over. I reviewed her symptoms again, and we discussed her home situation. There was nothing new to help guide treatment. Feeling uncomfortable with my own inability to make a diagnosis, I asked her to follow up in 2 weeks.

I found myself deep in thought one morning as my next patient walked in. He was a large man. For the first time I felt threatened in my exam room. I cautiously took a history and examined him. As he strode out to the reception area, he abruptly turned toward me. "By the way, thank you for caring for my wife," he said.

I quickly looked at the demographic page on my computer and realized that although they had different last names, this was Mrs. W's husband. I quickly called Mrs. W. I asked immediately, "So how long has he been abusing you?"

There was a long pause, and then she spoke softly, "Dr. G. I..." And then she hung up.

THE ART OF MEDICINE

I barely recognized the woman approaching from across the street. She was confident with her head held high. As Mrs. W shook my hand, I remembered our last conversation. I had neither seen nor heard from her in 3 years.

I was relieved to see that not only was she okay, but she had gained 30 pounds. She apologized for the abrupt discontinuation of our relationship. After hanging up the phone, she quickly packed up her daughter and moved to another city. She had filed for a divorce and recently moved back.

Mrs. W is again my patient. Over the years of her absence I continued to study and hone my skills. What once was solely a science has now also become an art—the art of medicine. And we owe it to our patients to become experts.

The author is an assistant professor at the University of Chicago School of Medicine. Send your feedback to medec@advanstar.com.

We want to hear from you!

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Brief Summary of full Prescribing Information

The following is a brief summary only. Please see full Prescribing Information for complete product information.

INDICATIONS AND USAGE

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

Prophylaxis of Gout Flares: COLCRYS is indicated for prophylaxis of gout flares.

Treatment of Gout Flares: COLCRYS is indicated for treatment of acute gout flares when taken at the first sign of a flare.

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Fatal Overdose: Fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine. COLCRYS should be kept out of the reach of children.

Blood Dyscrasias: Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia have been reported with colchicine used in therapeutic doses.

Drug Interactions: Colchicine is a P-gp and CYP3A4 substrate. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine given with P-gp and strong CYP3A4 inhibitors.

If treatment with a P-gp or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, the patient's dose of colchicine may need to be reduced or interrupted [*see DRUG INTERACTIONS*]. Use of COLCRYS in conjunction with P-gp or strong CYP3A4 inhibitors (this includes all protease inhibitors, except Fosamprenavir) is contraindicated in patients with renal or hepatic impairment [*see CONTRAINDICATIONS*].

Monitor for toxicity and if present consider temporary interruption or discontinuation of COLCRYS.

Neuromuscular Toxicity: Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, or benzafibrate (themselves associated with myotoxicity) or cyclosporine with COLCRYS may potentiate the development of myopathy [*see DRUG INTERACTIONS*]. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

ADVERSE REACTIONS

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

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1.800.FDA.1088.

You may also report negative side effects to the manufacturer of COLCRYS by calling 1.888.351.3786.

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

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