Effects on the Cost of Practicing Medicine

The promise of EBM—improved patient care and higher standards of care—comes at a cost. While many argue that the savings far outweigh the expenses, physicians will no doubt see some effect on the cost of practicing medicine.

Fast Facts

- *EBM—including guidelines and protocols— has the potential to bolster treatment decisions and improve the likelihood of reimbursement. But there may be a downside to this. Page 46*
- *As new evidence-based systems are created to improve patient care, new ways to bill for services must be developed. For example, the evidence for health care teams may pave the way for expanded reimbursement for ancillary care providers. Page 51*
- *Evidence-based guidelines may have legal implications for physicians, too. Page 54*

Beyond potential benefits to patient care, EBM may also lead to one solution for rising healthcare costs. "Evidence-based Medicine can be applied—and should be applied—as it relates to cost savings in medicine, if done prudently," says Greg Brown, M.D., Director of Clinical Informatics of TeamHealth a physician-staffing company headquartered in Knoxville, Tenn. "A lot of shotgun approaches can be virtually eliminated if we can tighten the probabilities and put them into algorithmic pathways."

Dennis Schmuland, M.D., director, Microsoft U.S. Healthcare and Life Sciences Health Plan Industry Management, and a

Master the Fine Art of Sleep

Prescribe LUNESTA first-line—for a full 7 to 8 hours of sleep

LUNESTA has been studied in large, well-controlled clinical trials in **all** of the following patient types:

- Patients With Insomnia Comorbid With Major Depressive Disorder
- Patients With Insomnia Comorbid With Generalized Anxiety Disorder
- Patients With Insomnia Comorbid With Rheumatoid Arthritis
- Patients With Insomnia Comorbid With Menopause

The failure of insomnia to remit after 7 to 10 days of treatment should be medically evaluated.

Any night or every night

Leave the rest to...

Lunesta® (eszopiclone)c
1, 2 AND 3 MG TABLETS

LUNESTA is indicated for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, LUNESTA administered at bedtime decreased sleep latency and improved sleep maintenance. LUNESTA is not indicated for the treatment of depression, generalized anxiety disorder, rheumatoid arthritis, or menopause.

Important Safety Information

LUNESTA, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, LUNESTA should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients should not take LUNESTA unless they are prepared to get a full night's sleep. As with other hypnotics, patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (eg, operating machinery or driving a motor vehicle) after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of LUNESTA. In clinical trials, the most common adverse events associated with LUNESTA were unpleasant taste, headache, somnolence, dizziness, dry mouth, infection, and pain.

LUNESTA has been classified as a Schedule IV controlled substance. Sedative hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. These patients should be under careful surveillance when receiving LUNESTA or any other hypnotic. Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

LUNESTA, like other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression. LUNESTA should not be taken with alcohol. Dosage adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents because of the potentially additive effects.

Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. See dosage and administration in complete prescribing information.

Please see brief summary of complete prescribing information.

6SRZO412

Lunesta®
(eszopiclone)c
1, 2 AND 3 MG TABLETS

BRIEF SUMMARY

INDICATIONS AND USAGE

LUNESTA is indicated for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, LUNESTA administered at bedtime decreased sleep latency and improved sleep maintenance.

CONTRAINDICATIONS

None known.

WARNINGS

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including LUNESTA. Because some of the important adverse effects of LUNESTA appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly (see **DOSAGE AND ADMINISTRATION in the Full Prescribing Information**).

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seem out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following rapid dose decrease or abrupt discontinuation of the use of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see **DRUG ABUSE AND DEPENDENCE**).

LUNESTA, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, LUNESTA should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (e.g., operating machinery or driving a motor vehicle) after ingesting the drug, and be cautioned about potential impairment of the performance of such activities on the day following ingestion of LUNESTA. LUNESTA, like other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression. LUNESTA should not be taken with alcohol. Dose adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents, because of the potentially additive effects.

PRECAUTIONS

General

Timing Of Drug Administration: LUNESTA should be taken immediately before bedtime. Taking a sedative/hypnotic while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.

Use In The Elderly And/Or Debilitated Patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. The recommended starting dose of LUNESTA for these patients is 1 mg (see **DOSAGE AND ADMINISTRATION in the Full Prescribing Information**).

Use In Patients With Concomitant Illness: Clinical experience with eszopiclone in patients with concomitant illness is limited. Eszopiclone should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

A study in healthy volunteers did not reveal respiratory-depressant effects at doses 2.5-fold higher (7 mg) than the recommended dose of eszopiclone. Caution is advised, however, if LUNESTA is prescribed to patients with compromised respiratory function.

The dose of LUNESTA should be reduced to 1 mg in patients with severe hepatic impairment, because systemic exposure is doubled in such subjects. No dose adjustment appears necessary for subjects with mild or moderate hepatic impairment. No dose adjustment appears necessary in subjects with any degree of renal impairment, since less than 10% of eszopiclone is excreted unchanged in the urine.

The dose of LUNESTA should be reduced in patients who are administered potent inhibitors of CYP3A4, such as ketoconazole, while taking LUNESTA. Downward dose adjustment is also recommended when LUNESTA is administered with agents having known CNS-depressant effects.

Use In Patients With Depression: Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Information For Patients: Patient information is printed in the complete prescribing information.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions

CNS-Active Drugs

Ethanol: An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol 0.70 g/kg for up to 4 hours after ethanol administration.

Paroxetine: Coadministration of single doses of eszopiclone 3 mg and paroxetine 20 mg daily for 7 days produced no pharmacokinetic or pharmacodynamic interaction.

Lorazepam: Coadministration of single doses of eszopiclone 3 mg and lorazepam 2 mg did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of either drug.

Olanzapine: Coadministration of eszopiclone 3 mg and olanzapine 10 mg produced a decrease in DSST scores. The interaction was pharmacodynamic; there was no alteration in the pharmacokinetics of either drug.

Drugs That Inhibit CYP3A4 (Ketoconazole): CYP3A4 is a major metabolic pathway for elimination of eszopiclone. The AUC of eszopiclone was increased 2.2-fold by coadministration of ketoconazole, a potent inhibitor of CYP3A4, 400 mg daily for 5 days. C_{max} and $t_{1/2}$ were increased 1.4-fold and 1.3-fold, respectively. Other strong inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, nefazodone, troleandomycin, ritonavir, nelfinavir) would be expected to behave similarly.

Drugs That Induce CYP3A4 (Rifampicin): Racemic zopiclone exposure was decreased 80% by concomitant use of rifampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone.

Drugs Highly Bound To Plasma Protein: Eszopiclone is not highly bound to plasma proteins (52-59% bound); therefore, the disposition of eszopiclone is not expected to be sensitive to alterations in protein binding. Administration of eszopiclone 3 mg to a patient taking another drug that is highly protein-bound would not be expected to cause an alteration in the free concentration of either drug.

Drugs With A Narrow Therapeutic Index

Digoxin: A single dose of eszopiclone 3 mg did not affect the pharmacokinetics of digoxin measured at steady state following dosing of 0.5 mg twice daily for one day and 0.25 mg daily for the next 6 days.

Warfarin: Eszopiclone 3 mg administered daily for 5 days did not affect the pharmacokinetics of (R)- or (S)-warfarin, nor were there any changes in the pharmacodynamic profile (prothrombin time) following a single 25-mg oral dose of warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In a carcinogenicity study in Sprague-Dawley rats in which eszopiclone was given by oral gavage, no increases in tumors were seen; plasma levels (AUC) of eszopiclone at the highest dose used in this study (16 mg/kg/day) are estimated to be 80 (females) and 20 (males) times those in humans receiving the maximum recommended human dose (MRHD). However, in a carcinogenicity study in Sprague-Dawley rats in which racemic zopiclone was given in the diet, and in which plasma levels of eszopiclone were reached that were greater than those reached in the above study of eszopiclone, an increase in mammary gland adenocarcinomas in females and an increase in thyroid gland follicular cell adenomas and carcinomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 150 (females) and 70 (males) times those in humans receiving the MRHD. The mechanism for the increase in mammary adenocarcinomas is unknown. The increase in thyroid tumors is thought to be due to increased levels of TSH secondary to increased metabolism of circulating thyroid hormones, a mechanism that is not considered to be relevant to humans.

In a carcinogenicity study in B6C3F1 mice in which racemic zopiclone was given in the diet, an increase in pulmonary carcinomas and carcinomas plus adenomas in females and an increase in skin fibromas and sarcomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 8 (females) and 20 (males) times those in humans receiving the MRHD. The skin tumors were due to skin lesions induced by aggressive behavior, a mechanism that is not relevant to humans. A carcinogenicity study was also performed in which CD-1 mice were given eszopiclone at doses up to 100 mg/kg/day by oral gavage; although this study did not reach a maximum tolerated dose, and was thus inadequate for overall assessment of carcinogenic potential, no increases in either pulmonary or skin tumors were seen at doses producing plasma levels of eszopiclone estimated to be 90 times those in humans receiving the MRHD—i.e., 12 times the exposure in the racemate study.

Eszopiclone did not increase tumors in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

Mutagenesis: Eszopiclone was positive in the mouse lymphoma chromosomal aberration assay and produced an equivocal response in the Chinese hamster ovary cell chromosomal aberration assay. It was not mutagenic or clastogenic in the bacterial Ames gene mutation assay, in an unscheduled DNA synthesis assay, or in an *in vivo* mouse bone marrow micronucleus assay.

(S)-N-desmethyl zopiclone, a metabolite of eszopiclone, was positive in the Chinese hamster ovary cell and human lymphocyte chromosomal aberration assays. It was negative in the bacterial Ames mutation assay, in an *in vitro* ^{32}P-postlabeling DNA adduct assay, and in an *in vivo* mouse bone marrow chromosomal aberration and micronucleus assay.

Impairment Of Fertility: Eszopiclone was given by oral gavage to male rats at doses up to 45 mg/kg/day from 4 weeks premating through mating and to female rats at doses up to 180 mg/kg/day from 2 weeks premating through day 7 of pregnancy. An additional study was performed in which only females were treated, up to 180 mg/kg/day. Eszopiclone decreased fertility, probably because of effects in both males and females, with no females becoming pregnant when both males and females were treated with the highest dose; the no-effect dose in both sexes was 5 mg/kg (16 times the MRHD on a mg/m^2 basis). Other effects included increased preimplantation loss (no-effect dose 25 mg/kg), abnormal estrus cycles (no-effect dose 25 mg/kg), and decreases in sperm number and motility and increases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

Pregnancy

Pregnancy Category C: Eszopiclone administered by oral gavage to pregnant rats and rabbits during the period of organogenesis showed no evidence of teratogenicity up to the highest doses tested (250 and 16 mg/kg/day in rats and rabbits, respectively; these doses are 800 and 100 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). In the rat, slight reductions in fetal weight and evidence of developmental delay were seen at maternally toxic doses of 125 and 150 mg/kg/day, but not at 62.5 mg/kg/day (200 times the MRHD on a mg/m^2 basis).

Eszopiclone was also administered by oral gavage to pregnant rats throughout the pregnancy and lactation periods at doses of up to 180 mg/kg/day. Increased postimplantation loss, decreased postnatal pup weights and survival, and increased pup startle response were seen at all doses; the lowest dose tested, 60 mg/kg/day, is 200 times the MRHD on a mg/m^2 basis. These doses did not produce significant maternal toxicity. Eszopiclone had no effects on other behavioral measures or reproductive function in the offspring.

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

Labor And Delivery: LUNESTA has no established use in labor and delivery.

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

Pediatric Use: Safety and effectiveness of eszopiclone in children below the age of 18 have not been established.

Geriatric Use: A total of 287 subjects in double-blind, parallel-group, placebo-controlled clinical trials who received eszopiclone were 65 to 86 years of age. The overall pattern of adverse events for elderly subjects (median age = 71 years) in 2-week studies with nighttime dosing of 2 mg eszopiclone was not different from that seen in younger adults. LUNESTA 2 mg exhibited significant reduction in sleep latency and improvement in sleep maintenance in the elderly population.

ADVERSE REACTIONS

The premarketing development program for LUNESTA included eszopiclone exposures in patients and/or normal subjects from two different groups of studies: approximately 400 normal subjects in clinical pharmacology/pharmacokinetic studies, and approximately 1550 patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 263 patient-exposure years. The conditions and duration of treatment with LUNESTA varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term and longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tabulations that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while the patient was receiving therapy following baseline evaluation.

Adverse Findings Observed in Placebo-Controlled Trials

Adverse Events Resulting in Discontinuation of Treatment: In placebo-controlled, parallel-group clinical trials in the elderly, 3.8% of 208 patients who received placebo, 2.3% of 215 patients who received 2 mg LUNESTA, and 1.4% of 72 patients who received 1 mg LUNESTA discontinued treatment due to an adverse event. In the 6-week parallel-group study in adults, no patients in the 3 mg arm discontinued because of an adverse event. In the long-term 6-month study in adult insomnia patients, 7.2% of 195 patients who received placebo and 12.8% of 593 patients who received 3 mg LUNESTA discontinued due to an adverse event. No event that resulted in discontinuation occurred at a rate of greater than 2%.

Adverse Events Observed at an Incidence of ≥2% in Controlled Trials. The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from a Phase 3 placebo-controlled study of LUNESTA at doses of 2 or 3 mg in non-elderly adults. Treatment duration in this trial was 44 days. Data are limited to adverse events that occurred in 2% or more of patients treated with LUNESTA 2 mg (n=104) or 3 mg (n=105) in which the incidence in patients treated with LUNESTA was greater than the incidence in placebo-treated patients (n=99).[1]

Body as a whole: headache (13%, 21%, 17%), viral infection (1%, 3%, 3%). Digestive system: dry mouth (3%, 5%, 7%), dyspepsia (4%, 4%, 5%), nausea (4%, 5%, 4%), vomiting (1%, 3%, 0%). Nervous system: anxiety (0%, 3%, 1%), confusion (0%, 0%, 3%), depression (0%, 4%, 1%), dizziness (4%, 5%, 7%), hallucinations (0%, 1%, 3%), libido decreased (0%, 0%, 3%), nervousness (3%, 5%, 0%), somnolence (3%, 10%, 8%). Respiratory system: infection (3%, 5%, 10%). Skin and appendages: rash (1%, 3%, 4%). Special senses: unpleasant taste (3%, 17%, 34%). Urogenital system: dysmenorrhea* (0%, 3%, 0%), gynecomastia** (0%, 3%, 0%).

*Gender-specific adverse event in females

**Gender-specific adverse event in males

[1]Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abnormal dreams, accidental injury, back pain, diarrhea, flu syndrome, myalgia, pain, pharyngitis, and rhinitis.

Adverse events that suggest a dose-response relationship in adults include viral infection, dry mouth, dizziness, hallucinations, infection, rash, and unpleasant taste, with this relationship clearest for unpleasant taste.

The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from combined Phase 3 placebo-controlled studies of LUNESTA at doses of 1 or 2 mg in elderly adults (ages 65-86). Treatment duration in these trials was 14 days. Data are limited to events that occurred in 2% or more of patients treated with LUNESTA 1 mg (n=72) or 2 mg (n=215) in which the incidence in patients treated with LUNESTA was greater than the incidence in placebo-treated patients.[1]

Body as a whole: accidental injury (1%, 0%, 3%), headache (14%, 15%, 13%), pain (2%, 4%, 5%). Digestive system: diarrhea (2%, 4%, 2%), dry mouth (2%, 3%, 7%), dyspepsia (2%, 6%, 2%). Nervous system: abnormal dreams (0%, 3%, 1%), dizziness (2%, 1%, 6%), nervousness (1%, 0%, 2%), neuralgia (0%, 3%, 0%). Skin and appendages: pruritus: (1%, 4%, 1%). Special senses: unpleasant taste (0%, 8%, 12%). Urogenital system: urinary tract infection (0%, 3%, 0%).

[1]Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abdominal pain, asthenia, nausea, rash, and somnolence.

Adverse events that suggest a dose-response relationship in elderly adults include pain, dry mouth, and unpleasant taste, with this relationship again clearest for unpleasant taste. These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice because patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contributions of drug and non-drug factors to the adverse event incidence rate in the population studied.

Other Events Observed During The Premarketing Evaluation Of LUNESTA. Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section and reported by approximately 1550 subjects treated with LUNESTA at doses in the range of 1 to 3.5 mg/day during Phase 2 and 3 clinical trials throughout the United States and Canada. All reported events are included except those already listed here or listed elsewhere in labeling, minor events common in the general population, and events unlikely to be drug-related. Although the events reported occurred during treatment with LUNESTA, they were not necessarily caused by it.

Events are listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those that occurred on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those that occurred in fewer than 1/100 patients but in at least 1/1,000 patients; **rare** adverse events are those that occurred in fewer than 1/1,000 patients. Gender-specific events are categorized based on their incidence for the appropriate gender.

Frequent: chest pain, migraine, peripheral edema.

Infrequent: acne, agitation, allergic reaction, alopecia, amenorrhea, anemia, anorexia, apathy, arthritis, asthma, ataxia, breast engorgement, breast enlargement, breast neoplasm, breast pain, bronchitis, bursitis, cellulitis, cholelithiasis, conjunctivitis, contact dermatitis, cystitis, dry eyes, dry skin, dyspnea, dysuria, eczema, ear pain, emotional lability, epistaxis, face edema, female lactation, fever, halitosis, heat stroke, hematuria, hernia, hiccup, hostility, hypercholesteremia, hypertension, hypertonia, hypesthesia, incoordination, increased appetite, insomnia, joint disorder (mainly swelling, stiffness, and pain), kidney calculus, kidney pain, laryngitis, leg cramps, lymphadenopathy, malaise, mastitis, melena, memory impairment, menorrhagia, metrorrhagia, mouth ulceration, myasthenia, neck rigidity, neurosis, nystagmus, otitis externa, otitis media, paresthesia, photosensitivity, reflexes decreased, skin discoloration, sweating, thinking abnormal (mainly difficulty concentrating), thirst, tinnitus, twitching, ulcerative stomatitis, urinary frequency, urinary incontinence, urticaria, uterine hemorrhage, vaginal hemorrhage, vaginitis, vertigo, vestibular disorder, weight gain, weight loss.

Rare: abnormal gait, arthrosis, colitis, dehydration, dysphagia, erythema multiforme, euphoria, furunculosis, gastritis, gout, hepatitis, hepatomegaly, herpes zoster, hirsutism, hyperacusis, hyperesthesia, hyperlipemia, hypokalemia, hypokinesia, iritis, liver damage, maculopapular rash, mydriasis, myopathy, neuritis, neuropathy, oliguria, photophobia, ptosis, pyelonephritis, rectal hemorrhage, stomach ulcer, stomatitis, stupor, thrombophlebitis, tongue edema, tremor, urethritis, vesiculobullous rash.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: LUNESTA is a Schedule IV controlled substance under the Controlled Substances Act. Other substances under the same classification are benzodiazepines and the nonbenzodiazepine hypnotics zaleplon and zolpidem. While eszopiclone is a hypnotic agent with a chemical structure unrelated to benzodiazepines, it shares some of the pharmacologic properties of the benzodiazepines.

Abuse, Dependence, and Tolerance

Abuse and Dependence: In a study of abuse liability conducted in individuals with known histories of benzodiazepine abuse, eszopiclone at doses of 6 and 12 mg produced euphoric effects similar to those of diazepam 20 mg. In this study, at doses 2-fold or greater than the maximum recommended doses, a dose-related increase in reports of amnesia and hallucinations was observed for both LUNESTA and diazepam.

The clinical trial experience with LUNESTA revealed no evidence of a serious withdrawal syndrome. Nevertheless, the following adverse events included in DSM-IV criteria for uncomplicated sedative/hypnotic withdrawal were reported during clinical trials following placebo substitution occurring within 48 hours following the last LUNESTA treatment: anxiety, abnormal dreams, nausea, and upset stomach. These reported adverse events occurred at an incidence of 2% or less. Use of benzodiazepines and similar agents may lead to physical and psychological dependence. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. These patients should be under careful surveillance when receiving LUNESTA or any other hypnotic.

Tolerance: Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use of these drugs for a few weeks.

No development of tolerance to any parameter of sleep measurement was observed over six months. Tolerance to the efficacy of LUNESTA 3 mg was assessed by 4-week objective and 6-week subjective measurements of time to sleep onset and sleep maintenance for LUNESTA in a placebo-controlled 44-day study, and by subjective assessments of time to sleep onset and WASO in a placebo-controlled study for 6 months.

OVERDOSAGE

There is limited premarketing clinical experience with the effects of an overdosage of LUNESTA. In clinical trials with eszopiclone, one case of overdose with up to 36 mg of eszopiclone was reported in which the subject fully recovered. Individuals have fully recovered from racemic zopiclone overdoses up to 340 mg (56 times the maximum recommended dose of eszopiclone).

Signs And Symptoms: Signs and symptoms of overdose effects of CNS depressants can be expected to present as exaggerations of the pharmacological effects noted in preclinical testing. Impairment of consciousness ranging from somnolence to coma has been described. Rare individual instances of fatal outcomes following overdose with racemic zopiclone have been reported in European postmarketing reports, most often associated with overdose with other CNS-depressant agents.

Recommended Treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. The value of dialysis in the treatment of overdosage has not been determined.

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

Rx only.

SEPRACOR 12/06

board-certified family physician, says that payers—such as health plans and self-insured employers—will lead the way to EBM. "With consumers at the reins and the support of stakeholders across the healthcare system, EBM real-time benefits are well within reach."

But while payers may lead the way, practicing physicians may find that the changes affect their bottom line as well—in both positive and negative ways. Data collection may save money, but it also *costs* money, which can be a burden on small practices. Many practices have balked at the cost of fully implementing electronic medical records. Now they may not have a choice.

EBM has the potential to streamline aspects of patient care, which can save physicians and their staff time. EBM is also part and parcel of the pay-for-performance trend and other reimbursement changes, and it has implications for medical malpractice litigation and contract negotiations with payers.

"A lot of people are doing lots of research producing and advancing the state of knowledge," says R. Lawrence Van Horn, Ph.D., M.P.H., M.B.A., at The Owen Graduate School of Business, Vanderbilt University. "We're learning more and more about what works and what doesn't work; and, very simply, we should do less of what doesn't work and do more of what works. We should reward or support those who are doing more of what works and encourage those who don't, to revisit the way they are treating patients and change accordingly."

Time-Saving Guidelines

According to a study published in the *American Journal of Public Health* in April 2003, performing all the recommended preventive care for an average patient population would take a family physician 7.4 hours of each day—leaving little time to address any acute complaints that arose. This leaves physicians with a major time-management conundrum.

Physicians are being asked to manage their patients in a way that is difficult to accommodate within the amount of time they have, explains William Caplan, M.D., Director of Clinical Strategy at Kaiser Permanente Care Management Institute. "All of their time would be spent on maintenance and prevention activities without being able to deal with the acute symptomatic

issues that the patient was presenting with," yet all of these things are necessary.

Developing guidelines for single conditions such as diabetes, hypertension, asthma, or chronic obstructive pulmonary disease "is somewhat disconnected from the reality of our patients, who are now presenting with more and more multiple chronic conditions," Dr. Caplan says. EBM may be able to help physicians manage these more complicated situations. "What we need is an integrated system of decision supports that tells the physician what issues are the most significant and present the highest risk of morbidity for that patient. Those two things should have the highest priority, and "all of those issues need to be tracked over time in a system of care," Dr. Caplan says.

The goal is to provide a tool for the physician that takes a very complicated circumstance and simplifies it to some degree. Physicians would use the tool to find the preferred treatment protocol or appropriate selection of drugs for a patient who has two or three of these chronic conditions.

For example, blood-pressure control parameters differ greatly in the patient with hypertension, diabetes, *and* heart disease compared with the patient who has isolated hypertension, Dr. Caplan says. Kaiser's Prevent Heart Attacks and Strokes Everyday (PHASE) program in northern California is designed to help physicians manage patients with hypertension, diabetes, previous documented heart disease, chronic renal insufficiency, or combinations of conditions. The goal is to provide a tool for the physician that takes a very complicated circumstance and simplifies it to some degree. Physicians would use the tool to find the preferred treatment protocol or appropriate selection of drugs for a patient who has two or three of these chronic conditions.

Many organizations are using "active guidelines" within electronic medical records to save physicians time and to focus the patient encounter. For example, a physician treating a diabetes patient for hypertension can use the EMR to link back into the section of the guideline that refers to that patient, Dr. Caplan explains. "It pulls the appropriate recommendations and reference materials in a way that is concise, and then it is linked into an order set. You can actually order the drugs within the elec-

tronic system that are both evidence-based and mapped to that patient's set of conditions, and you can do it in a way that minimizes inefficiency."

Vendors who produce electronic systems or knowledge bases are working toward a seamless transition that will allow physicians to use reference and guideline materials and order sets without navigating through a complicated electronic environment, Dr. Caplan says.

Insurance, Reimbursements, and Challenges

EBM—including guidelines and protocols— has the potential to bolster treatment decisions and improve the likelihood of reimbursement. But there may be a real downside if payers or malpractice prosecutors misuse the information. If a physician strays from evidence-based guidelines or misinterprets data, he or she may run the risk of forfeiting reimbursement—and perhaps even facing legal consequences.

The meaning of "evidence" is to a degree in the eye of the beholder. "The concept of what is good evidence is actually quite a fluid one," says Sara Rosenbaum, J.D., professor of law and policy at George Washington University School of Public Health Services in Washington, D.C. "Depending on who gets to define what is evidence that would be relevant to the decision about care and coverage, the results can be very different."

For example, a physician who bases a patient's treatment on past experience or even a clinical study that he or she believes is sufficient evidence may run into trouble if the payer contends that the evidence is not relevant or strong enough because there have been no randomized, double-blind, controlled studies. On that basis, the payer could deny coverage.

TennCare, Tennessee's Medicaid demonstration program, has on the books a definition of medical necessity that has the potential to cause trouble, says Professor Rosenbaum. (TennCare was created in 1994 to replace Tennessee's original Medicaid program.) "In its definition, TennCare basically puts the burden on the patient and the patient's provider to have to affirmatively show safety and efficacy of medical care—essentially the FDA standard, which has never been used in medical care—and classifies as irrelevant clinical inferences drawn from similar cases."

She notes it is not clear that this definition has ever been put into effect, but its provisions are stringent.

The burden is more than arduous, she explains, adding that it would be virtually impossible to rebut. "Nobody could meet that burden of proof because most medical care has not been subject to randomized control trials for safety and efficacy," Professor Rosenbaum states. "It would exclude virtually all of medical care. It literally allows the payer to exclude from payment anything the payer doesn't want."

Professor Rosenbaum points out that in the Medicare Part D drug benefit program, the burden of proof is on the patient and the provider to demonstrate the need for an exception from the

Evidence-based Oncology Protocols

As with most conditions, there's a lot of variability in how patients with cancer are treated. Variations may be due to the patients' overall health, the physician's approach to care, the availability of services in a certain area, or a multitude of other factors. At Kaiser Permanente, management is using EBM to determine which variations are most effective. The goal is "to standardize around a common set of protocols that are supported by evidence and experience," says William Caplan, M.D., Director of Clinical Strategy at Kaiser Permanente Care Management Institute. "We are trying to create a set of standardized treatment protocols for many of our major cancer diagnoses."

Kaiser has collected the cancer treatment variations supported by a review of the evidence through clinical trial programs and literature that the health plan's oncologists and oncology groups are using. Those variations are being reviewed by a panel of inter-regional oncology chiefs.

Kaiser has already developed guidelines on the use of antiemetics and management of neutropenic fever caused by use of chemotherapeutic agents, and the use of Epogen and similar agents in maintaining hemoglobin in blood counts, according to Dr. Caplan. The pharmacy service's analytic unit uses evidence-based processes to evaluate new therapeutic agents for oncology, as well as other conditions, for potential inclusion in the formulary. "We have our own internal capacity to evaluate these agents through the Pharmacy and Audit Services that gather the relevant and current evidence in support of these drugs and do an assessment and evaluation."

formulary. If the insurer denies the exception, only the physician's most arduous efforts on behalf of a patient will get that patient covered, she says.

Once a provision is already on the books, it can be difficult to make changes. That's why Professor Rosenbaum says, "The time to deal with this is as legislation is being developed. It is a whole different approach to thinking through involvement in the policy-making process."

Most people simply do not understand the significance of this issue, and most physicians are not active enough in health policy issues to get involved when decisions like this are being made, Professor Rosenbaum says.

Drug Costs

EBM may also lead to a more comprehensive cost-benefit analysis of therapeutic agents. An EBM approach allows a larger range of data to be considered.

The two key factors used in deciding which drugs to add to a formulary or recommend to a patient are disease-related outcomes and patient-related outcomes, says pharmacist Paul Chrisp, Ph.D., Editor-in-chief of *Core Evidence,* a new evidence-based journal for medical decision-making. The editors describe the publication as the first international, peer-reviewed journal to assess new drugs by critically evaluating evidence on clinical effectiveness and outcomes. The assessments in *Core Evidence* speculate on the potential economic impact of a new drug or its impact on resource use within a particular healthcare setting. Value for money and evidence-based clinical effectiveness are the two big drivers in health care today, says Dr. Chrisp. "Any decision on whether to use a particular new drug in any healthcare setting is dependent on its cost effectiveness."

Disease-related study outcomes are easy to measure, Dr. Chrisp says. They answer questions that are important to healthcare providers, such as how much one drug lowers cholesterol or how much another drug reduces blood pressure.

Patient-related outcomes, on the other hand, provide answers to the questions that matter to the patient, such as these: Will taking this drug prevent me from having a heart attack? Will it stop my symptoms? Will I be able to walk to the bus stop or

make my own meals? This information is harder to come by.

Dr. Chrisp says *Core Evidence* ties these two together by presenting evidence of a drug's clinical effectiveness and economic arguments about its likely impact in practice. "What we try to do is take the widest context of what doctors are actually facing and what formulary groups are actually facing when making these decisions and present the evidence in a coherent way," he says.

"We focus on the things that matter to doctors and patients, and we evaluate the strength and reliability of the evidence against those key outcomes and say whether the evidence actually supports the drug or is equivocal or is weak," Dr. Chrisp explains. Where patient-related outcomes are mentioned in clinical studies, "we try to emphasize that," and he adds, "where they're lacking, we say that there is no patient-related outcome evidence for this drug, only disease-related outcomes, and that in itself is an important observation."

Value for money and evidence-based clinical effectiveness are the two big drivers in health care today, says Dr. Chrisp. "Any decision on whether to use a particular new drug in any healthcare setting is dependent on its cost effectiveness."

For example, in a recent review of a drug used in Alzheimer's disease, the journal's analysis indicated the drug was cost effective if *all* aspects of care are considered, such as the time spent by family members caring for elderly relatives with Alzheimer's disease. Without the patient-related data, however, the same drug did not appear cost effective.

According to Dr. Chrisp, readers are finding this type of information helpful. Feedback from managed-care groups and health services indicates the information is very useful, and in some instances the reviews become the cornerstone of formulary work. For the average physician, a journal like *Core Evidence* can help with planning and budgeting to accommodate promising new drugs. Physicians need to keep up with the latest developments, and not to waste money on less effective treatments. Physicians also need to make sure they are able to engage in discussions with patients who ask about new drugs they see advertised on television or in the press, he adds.

"It's about effective use of resources," says Dr. Chrisp, "that's

the bottom line."

Incentive Costs

Insurance companies are also using EBM to establish coverage and reimbursement schedules. According to Thomas Simmer, M.D., Senior Vice President and Chief Medical Officer at Blue Cross Blue Shield Michigan, EBM concepts fall into three categories at his organization:

- New technology assessments, which determine what is investigational and what is considered established therapy.
- Clinical practice guidelines endorsed by the health plan. (These are evidence-based guidelines rather than consensus guidelines, and the level of evidence behind them is communicated to the practitioner. Those endorsements go through an organization called the Michigan Quality Improvement Consortium.)
- Pay-for-performance programs, which BCBSM calls "value partnerships." "These are programs where we work with physicians through physician organizations," Dr. Simmer says. These include more than 50 physician organizations and 1.2 million members. The metric that governs that program links to EBM particularly on the quality side, he explains.

"It's a little bit different on the cost side," which Dr. Simmer says "has primarily focused on generic use; and you could argue that's evidence based because there's a slew of evidence that generics are equivalent to branded substances with the same chemical composition, and that it's just more cost effective to prescribe a generic," he explains.

The metrics for quality center around five conditions, says Dr. Simmer: diabetes mellitus, persistent asthma, congestive heart failure, coronary heart disease, and appropriate use of antibiotics. Blue Cross Blue Shield Michigan uses 17 standard measures (not original to BCBSM) in these categories. Each of their groups is measured by these standards, and an overall report for the health plan is created. The goal is to improve health plan performance for all the practice groups.

"In our company we have an incentive payment process" that rewards physicians who meet or exceed baseline goals, with extra rewards for those who go beyond the stated goal, he

explains. Using a flexible approach allows physicians to have more latitude to focus on the areas they want to focus on, based on the realities they face in their individual groups. "We reward the groups based on the level of their contribution to our health plan achieving its overall goals for this quality improvement program," Dr. Simmer says. He estimates that the reward pool to be divided among the three categories for 2007 will amount to some $25 million.

"We want to engender a collaborative spirit of sharing best practices" and sharing rewards, Dr. Simmer explains. By stimulating individual groups' creativity, not only do individual groups improve, but the entire plan improves by adopting successful programs the members have created.

New Ways to Bill for Services

As new evidence-based systems are created to improve patient care, new ways to bill for services must be developed. This has been especially true for services for patients with chronic conditions, says Dr. Simmer.

In the old model, the physician-patient encounter was based on a chief complaint; and the encounter was documented in the physician's medical record, which was also problem oriented and focused on the chief complaint. But the effectiveness of that model has been challenged. The new "Chronic Care Model recognizes that the physician's care has to be organized around the condition the patients have, not around the problem [with which] they present," Dr. Simmer explains. "We have had to change some of our reimbursement policies to be able to pay for the care components" which were previously non-payable services, says Dr. Simmer. Instead of having a physician-patient encounter, the goal is "a productive interaction between an informed, activated patient and a prepared, proactive practice team." That opens the door for payment for services provided by a nurse or other staff member.

To implement this model, a practice may set up a system of "planned visits." First the practice sends a letter to the patient with a chronic illness telling of the upcoming visit and what to expect. When the patient arrives at the office, the medical assistant who greets the patient has a printed list of all the services

that person needs. In the case of a diabetic patient, Dr. Simmer says the medical assistant would be trained to do a rigorous foot exam and, if needed, retinal photography. The physician reviews test results graphically displayed in a binder so the patient can compare progress relative to the goals set with the physician. Often patients may also have group visits during which people with similar conditions bring their binders and talk about such things as what was difficult about managing their weight, Dr. Simmer explains.

The result is "an activated patient," and that is important, Dr. Simmer says, "because 99.99 percent of the time, the patient is not at the doctor's office, and the real key is what they do outside of the doctor's office. The old model of just telling people what to do doesn't work. It frustrates everybody."

Even though there has been literature to prove this model's effectiveness, it has been difficult to implement because care provided by non-physician members of the practice team was not billable. Physicians were not able to practice the way they thought they should because of reimbursement issues.

To change that, Dr. Simmer says, "We have had to work with the doctors to figure out a way to make these services— that we all consider to be valid – payable." It isn't easy, he adds, but "this is part of redesigning care so that the business case for that care is solidly based on what's billable as a legitimate fee for service."

To make it work, BCBSM had to use Medicaid codes because the CPT codes produced by the American Medical Association were largely physician centric. "They don't have too many codes for billing non-physician services coming out of the AMA," Dr. Simmer says. BCBSM found the valid HIPAA-compliant codes they needed were only used by Medicaid. It turned out, he explains, "Medicaid had to cross this bridge a while back to pay for social workers and other things because the patient population was needier when it came to structuring the care."

The two codes BCBSM uses to cover non-physician services provided by other members of the care team are T1015 and T1019. These codes allow for services to be billed when they are "incident to the physician visit," Dr. Simmer explains.

The way it works is simple. After seeing the patient, the physi-

cian says the rest of the care team has to provide the remaining services, which can then be billed using the Medicaid codes at $60 for every 30 minutes that non-physician care providers (nurses, social workers, pharmacists, diabetes educators, nutritionists, and others) on the care team spend with the patient.

"They can now bill us" for those services, Dr. Simmer says. "We've allowed these groups to bill these codes as 'incident to the doctor's visit' so that the patient's co-pay only applies to the doctor's visit. There's no additional co-pay for the rest of these services."

Is it working? Dr. Simmer says their groups are now telling BCBSM that this has made it possible for them to create a healthcare team—the model supported by the evidence for treating chronic conditions. However, he notes not all practices have been able to set up the model. He points out that in a practice with only two or three physicians, there may not be the patient numbers to justify the creation of a whole care team.

Some physicians may also be unwilling to give up their role as sole provider. However, Dr. Simmer points out, paraphrasing a favorite quote: "When you're talking with patients, remember

HMO EBM Advantage x 2: Rx Analysis

When Cox-2 Inhibitor drugs came on the market, Kaiser Permanente's pharmacy analytic services and medical groups did their own evaluation of the drugs' risks and benefits. They collected data internally and made a judgment that Cox-2 inhibitors were to be used only in selective instances based upon their risk. "Because of that," says William Caplan, M.D., Director of Clinical Strategy, Kaiser Permanente Care Management Institute, "the prescribing patterns of those drugs by our clinicians were quite different from what we saw nationally. And as it turned out, those drugs were indeed associated with levels of risk that were really, I think, unwarranted, given their benefit."

Kaiser's reviews also changed the pattern of prescribing for upper respiratory illnesses, which are overwhelmingly viral in origin, Dr. Caplan notes, based on existing evidence and external guidelines that clearly pointed to overuse of medications that lack efficacy. As a result, Kaiser physicians' use of antibiotics for these conditions has greatly diminished.

it's not the information that *you* impart, it's the information that *they* need and retain. Your role as educator is not to be the sage on the stage, but to be the guide on the side."

There is belief that patients want to see the doctor, not ancillary care providers. While that may be true at first, the evidence suggests that when patients actually interact with multiple members of the team on a consistent basis, they begin to have trust in that team and its members, says Risa Lavizzo-Mourey, M.D., M.B.A., and CEO of the Robert Wood Johnson Foundation. Then, if they see the nurse practitioner instead of the physician, "they don't feel as though they're being slighted because they are getting what they need, when they need it." However, when patients do not know all the members of the team and are not able to develop the ongoing, trusting relationships with ancillary providers, that's when people are at risk of feeling they're not getting the care they expected, she adds.

Liability Cost Savings

Liability is the most important legal issue involving EBM, says Professor Rosenbaum, both in terms of patient care and the physician's legal liability. On the plus side, EBM helps practitioners and providers develop systems that incorporate the best available research that can help reduce liability risks.

For example, when the professional liability market hardened, TeamHealth went to a self-insurance model for their providers. In order to decrease the cost of this undertaking, the organization decided to look at its large database of actuarial experience to determine where its greatest ongoing exposure was and to see whether changing patient behaviors could induce better outcomes.

TeamHealth looked at two major areas that Gar LaSalle, M.D., Chief Medical Officer of TeamHealth, says "seemed to have a high number of high-dollar cost claims." One was acute coronary syndrome, which he notes is still a leading cause of malpractice claims in this country. However, TeamHealth has been able to dramatically reduce that claim in its organization. Its solution was to analyze available research on the topic and develop a curriculum to educate physicians about the prudent approach to acute coronary syndrome, using high-risk clinical scenarios and essential information from current literature on the

subject. Physicians must pass a test to prove their competency in the area before the organization's insurance will cover them, Dr. LaSalle explains.

TeamHealth took a similar path to review how physicians handled transient ischemic attacks (TIAs). The company reviewed billing data, actuarial experience, and the evolving standard of care for managing TIAs in the subset of patients who go on to have a stroke within a short time period. Dr. LaSalle says, creating a standarized system "was not turn-key" (instantly ready to implement). To make it work, TeamHealth used a two-pronged approach that first exposed their physicians to what the current literature said and then gave the physicians "their own statistics and profiles" showing what the physicians were actually doing.

Physicians should remember, however, that guidelines and protocols do not provide legal protection. Practice guidelines tell physicians what they can do for a patient; but, notes Professor Rosenbaum, "If you rely unquestionably on practice guidelines and do not protest if you don't think that they are appropriate for your patient, you will be liable for malpractice."

Insurance companies may use EBM as the basis for encouraging practitioners to prescribe generic rather than brand drugs. Managed-care companies may develop treatment protocols for chronic conditions based on EBM. Practice guidelines may be established as a result of EBM research.

Physicians should remember, however, that guidelines and protocols do not provide legal protection. Practice guidelines tell physicians what they can do for a patient; but, notes Professor Rosenbaum, "If you rely unquestionably on practice guidelines and do not protest if you don't think that they are appropriate for your patient, you will be liable for malpractice. The insurer probably will not be."

Although the protest may result in a denial, physicians are expected to fight for their patients, adds Professor Rosenbaum. "When a practice guideline is ill suited for one of your patients, you really have to go the extra mile to try to get the insurer to do the right thing."

In some cases the physician may succeed in persuading the insurer to change a decision. But even if that outcome seems

unlikely, the physician must make an effort for the patient's sake as well as for the physician's legal protection. Physicians should not simply accept the verdict of an insurer; they must question and evaluate based on evidence and, if the evidence warrants, challenge the verdict.

"What we know about medicine is constantly changing," says Dr. Kramer. "Sometimes our intuition or notions of what is true turn out to be wrong; so we all need to be prepared for surprises, and we all need to be prepared to keep rethinking our assumptions."

"You have to tell your patient, 'Look, this is what your insurer will cover. I am advising you that you need X and Y, and your insurer will only pay for Z. I will help you fight with the insurer to help you get that coverage. I want you to understand that if you only want what the insurer covers and we can't budge the insurer, then it is against my medical advice [to proceed with the insurer's recommendation]," Professor Rosenbaum says. "I would not only fight for the patient, but I would write the patient a letter; I would note in the medical record that you counseled the patient. This is where communicating with patients is absolutely critical," she adds.

"In other words, you have got to do an informed consent with your patient. You can't just blindly follow because the insurer says that is what you are supposed to do," Professor Rosenbaum says.

This type of clear communication with the patient is not only the proper thing to do in terms of patient care, Professor Rosenbaum adds, but it is also the best way to limit your own liability exposure.

Regardless of the physician's medical setting—managed care, HMO, PPO, or other—"If you comply without protest and go along with a practice standard that you know is simply not appropriate—but that is what the payer will pay for – then you actually could face liability."

When BCBSM talks to physicians, "We tell them that people who practice according to Evidence-based Medicine are obviously better protected than those who don't; and unless they change how they practice medicine, there's a gap," says Dr. Simmer. "That gap is a dangerous thing for them, but we haven't gotten very far with doctors feeling in any way consoled by Evi-

dence-based Medicine as a means of addressing the liability questions. That's what we say to them, but it doesn't carry much water for us."

EBM in Action

Medical oncologist Barnett Kramer, M.D., M.P.H., Associate Director for Disease Prevention at the National Institutes of Health and Director of the Office of Medical Applications Research, walks physicians through the process of making medical decisions using EBM.

"What we know about medicine is constantly changing," says Dr. Kramer. "Sometimes our intuition or notions of what is true turn out to be wrong; so we all need to be prepared for surprises, and we all need to be prepared to keep rethinking our assumptions."

There are different ways to test our assumptions, he says, but the randomized trial is probably the strongest and most efficient test.

Dr. Kramer explains the process of evidence-based decision making as looking for the strongest evidence that is out there, which is sometimes—but not always—a randomized, controlled trial or trials, and seeing how well it applies to the clinical decision you have to make and how it applies to your patient.

He lists the formal steps involved in making an evidence-based decision:

1. Frame the question at hand. What are the salient questions that I have to sort through for this patient?

2. Look at the literature or look at the summaries of the literature to see what the best evidence is that addresses that question.

3. Decide how closely the strongest evidence or the aggregate of evidence fits the patient that you're dealing with.

4. Make the decision, and then help the patient to make the decision.

5. Evaluate the outcome of your decision, creating a feedback loop to see whether the main question was formulated in the right way; then you can go back to evaluate whether the outcome was as you anticipated or whether you need to reformulate the question or keep it open.

People who have suspicions about evidence-based decision making may not be aware that it is patient based and patient oriented, Dr. Kramer says. The physician trying to make an impor-

tant clinical decision does not accept the literature without interpretation. And, there is a certain art in interpreting and evaluating the consequences of your decisions, he adds.

Obviously no physician can make a complete, systematic search of the literature for every decision that he or she will make. All physicians need to look for ways to streamline decisions. Fortunately, there are a number of databases that a physician can consult with formal rating systems or at least formal assessments of the strength of the evidence.

All physicians need to look for ways to streamline decisions. Fortunately, there are a number of databases that a physician can consult with formal rating systems or at least formal assessments of the strength of the evidence.

Dr. Kramer gives an example of formulating the question: "Let's say I already know that my patient has a rising PSA. What do I do about it?" He says one could go to the existing databases that summarize the literature. Three databases he likes are the National Cancer Institute Physician Data Query (*www.cancer.gov/cancertopics/pdq*), UpToDate (*www.uptodate.com*), and the American College of Physicians' PIER (*www.pier.acponline.org*).

These databases allow for quick assessments of important clinical questions, Dr. Kramer says. "You can search on the questions or keyword or topic. They try to tell you to whom the evidence applies and how strong the evidence is and, usually, what the potential harms are, not just the benefits, and what is the strength of the evidence or the strength of the recommendation." An added benefit is that the reviews are usually systematic so they do not rely on one author's recollection of the literature, which Dr. Kramer notes can be selective.

The search results can be read pretty quickly, he says. "Even when I attend in the clinic, I have these databases on the computer; and it doesn't take more than perhaps 10 or 20 minutes to read through" the results of a search, he says.

The next step is to ask how closely the literature applies to the patient in question. Is the age right? Obviously, Dr. Kramer notes, if the physician is trying to make a decision on a very ill 85-year-old and finds that all the studies were done on healthy

60-year-olds, the physician has to apply clinical judgment about whether the benefits will be of the same magnitude as in the literature and likewise will the harms be of the same magnitude.

Then the physician can sit down with the patient and tell the patient what is known from the literature and how it applies to the patient. Of course, Dr. Kramer says, if the patient wants the physician's opinion about which way he or she would go, then obviously the physician can give his or her opinion, provided it is based on the totality of the evidence.

Ideally, Dr. Kramer says, physician and patient make the treatment decision together. However, he notes, often the benefits so greatly outweigh the harms of an intervention that it is easy to say the standard practice would be to give a specific therapy or specific advice. But "there are many cases in medicine where it's a much closer call," Dr. Kramer adds. The decision may be driven by personal factors that only the patient can know. In those circumstances, he says, it is most useful to explain everything to the patient, including the salient important benefits and everything that is known about the important harms, and to see if the patient feels comfortable making the decision or has further questions.

"Every patient has his or her different style," Dr. Kramer says. Some may listen to the pros and cons and say, "I came here to get your opinion. What would you say?" In that case, if the physician knows the patient's values and concerns and is comfortable doing so, he or she can make a recommendation.

Similarly, knowing the patient's fears gives the physician an opportunity to provide information that will ease them. For example, a patient who is afraid of surgery because someone close to him died on the operating table may be reassured by learning that the risk of dying from this surgery is relatively low. An elderly patient may decline surgery that the evidence says would add five to seven years to his life because he has other medical problems and is less concerned about the additional life span than about the up-front harms, Dr. Kramer says.