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for Primary Care Physicians

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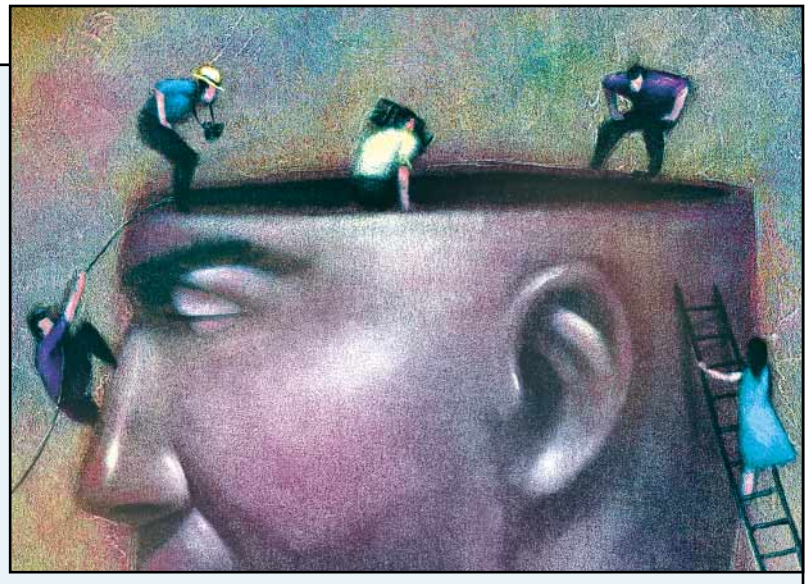

Special Populations in Depression
Practical Approaches to Depression in Seniors

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Advances in Assessing and Managing Insomnia

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A Multidisciplinary Approach to the Management of Chronic Pain

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Case File

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*Rozerem™ (ramelteon) is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Rozerem can be prescribed for long-term use.

Important safety information

Rozerem should not be used in patients with hypersensitivity to any components of the formulation, severe hepatic impairment, or in combination with fluvoxamine. Failure of insomnia to remit after a reasonable period of time should be medically evaluated, as this may be the result of an unrecognized underlying medical disorder. Hypnotics should be administered with caution to patients exhibiting signs and symptoms of depression. Rozerem has not been studied in patients with severe sleep apnea, severe COPD, or in children or adolescents. The effects in these populations are unknown. Avoid taking Rozerem with alcohol. Rozerem has been associated with decreased testosterone levels and increased prolactin levels. Health professionals should be mindful of any unexplained symptoms possibly associated with such changes in these hormone levels. Rozerem should not be taken with or immediately after a high-fat meal. Rozerem should be taken within 30 minutes before going to bed and activities confined to preparing for bed. The most common adverse events seen with Rozerem that had at least a 2% incidence difference from placebo were somnolence, dizziness, and fatigue.

Please see adjacent Brief Summary of Prescribing Information.

You can prescribe Rozerem for as long as you need to*

Clinical studies show no evidence of potential abuse, dependence, or withdrawal†

- **First and only**—nonscheduled prescription insomnia medication... not a controlled substance and can be prescribed for long-term use[1]
- **First and only**—prescription insomnia medication that targets the normal sleep-wake cycle[1]
- **First and only**—prescription insomnia medication with no evidence of abuse potential in clinical studies[1]
- **First and only**—prescription insomnia medication that does not promote sleep by CNS depression[1]
- **One simple 8-mg dose**[1]

†Rozerem is not a controlled substance. A clinical abuse liability study showed no differences indicative of abuse potential between Rozerem and placebo at doses up to 20 times the recommended dose (N=14). Three 35-day insomnia studies showed no evidence of rebound insomnia or withdrawal symptoms with Rozerem compared to placebo (N=2082).[1,2]

Please visit www.rozerem.com

Rozerem™
ramelteon 8-mg tablets

Proven for sleep.
Nonscheduled for added safety.

Rozerem™ ramelteon 8-mg tablets

Takeda

Brief Summary of Prescribing Information

ROZEREM™
(ramelteon) Tablets

INDICATIONS AND USAGE
ROZEREM is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

CONTRAINDICATIONS
ROZEREM is contraindicated in patients with a hypersensitivity to ramelteon or any components of the ROZEREM formulation.

WARNINGS
Since 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 a reasonable period 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 cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with ROZEREM during the clinical development program.

ROZEREM should not be used by patients with severe hepatic impairment.

ROZEREM should not be used in combination with fluvoxamine (see **PRECAUTIONS: Drug Interactions**).

A variety of cognitive and behavior changes have been reported to occur in association with the use of hypnotics. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotics.

Patients should avoid engaging in hazardous activities that require concentration (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

After taking ROZEREM, patients should confine their activities to those necessary to prepare for bed.

PRECAUTIONS
General
ROZEREM has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations.

Patients should be advised to exercise caution if they consume alcohol in combination with ROZEREM.

Use in Adolescents and Children
ROZEREM has been associated with an effect on reproductive hormones in adults, e.g., decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ROZEREM may have on the reproductive axis in developing humans (see **Pediatric Use**).

Information for Patients
Patients should be advised to take ROZEREM within 30 minutes prior to going to bed and should confine their activities to those necessary to prepare for bed.

Patients should be advised to avoid engaging in hazardous activities (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

Patients should be advised that they should not take ROZEREM with or immediately after a high-fat meal.

Patients should be advised to consult their health care provider if they experience worsening of insomnia or any new behavioral signs or symptoms of concern.

Patients should consult their health care provider if they experience one of the following: cessation of menses or galactorrhea in females, decreased libido, or problems with fertility.

Laboratory Tests
No standard monitoring is required.

For patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels and testosterone levels should be considered as appropriate.

Drug Interactions
ROZEREM has a highly variable intersubject pharmacokinetic profile (approximately 100% coefficient of variation in C_{max} and AUC). As noted above, CYP1A2 is the major isozyme involved in the metabolism of ROZEREM; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree.

Effects of Other Drugs on ROZEREM Metabolism
Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ROZEREM 16 mg and fluvoxamine, the $AUC_{0\text{-}inf}$ for ramelteon increased approximately 190-fold, and the C_{max} increased approximately 70-fold, compared to ROZEREM administered alone. ROZEREM should not be used in combination with fluvoxamine (see **WARNINGS**). Other less potent CYP1A2 inhibitors have not been adequately studied. ROZEREM should be administered with caution to patients taking less strong CYP1A2 inhibitors.

Rifampin (strong CYP enzyme inducer): Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease of approximately 80% (40% to 90%) in total exposure to ramelteon and metabolite M-II, (both $AUC_{0\text{-}inf}$ and C_{max}) after a single 32 mg dose of ROZEREM. Efficacy may be reduced when ROZEREM is used in combination with strong CYP enzyme inducers such as rifampin.

Ketoconazole (strong CYP3A4 inhibitor): The $AUC_{0\text{-}inf}$ and C_{max} of ramelteon increased by approximately 84% and 36%, respectively, when a single 16 mg dose of ROZEREM was administered on the fourth day of ketoconazole 200 mg twice daily administration, compared to administration of ROZEREM alone. Similar increases were seen in M-II pharmacokinetic variables. ROZEREM should be administered with caution in subjects taking strong CYP3A4 inhibitors such as ketoconazole.

Fluconazole (strong CYP2C9 inhibitor): The total and peak systemic exposure ($AUC_{0\text{-}inf}$ and C_{max}) of ramelteon after a single 16 mg dose of ROZEREM was increased by approximately 150% when administered with fluconazole. Similar increases were also seen in M-II exposure. ROZEREM should be administered with caution in subjects taking strong CYP2C9 inhibitors such as fluconazole.

Interaction studies of concomitant administration of ROZEREM with fluoxetine (CYP2D6 inhibitor), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon or the M-II metabolite.

Effects of ROZEREM on Metabolism of Other Drugs
Concomitant administration of ROZEREM with omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), and warfarin (CYP2C9 [S]/CYP1A2 [R] substrate) did not produce clinically meaningful changes in peak and total exposures to these drugs.

Effect of Alcohol on Rozerem
Alcohol: With single-dose, daytime co-administration of ROZEREM 32 mg and alcohol (0.6 g/kg), there were no clinically meaningful or statistically significant effects on peak or total exposure to ROZEREM. However, an additive effect was seen on some measures of psychomotor performance (i.e., the Digit Symbol Substitution Test, the Psychomotor Vigilance Task Test, and a Visual Analog Scale of Sedation) at some post-dose time points. No additive effect was seen on the Delayed Word Recognition Test. Because alcohol by itself impairs performance, and the intended effect of ROZEREM is to promote sleep, patients should be cautioned not to consume alcohol when using ROZEREM.

Drug/Laboratory Test Interactions
ROZEREM is not known to interfere with commonly used clinical laboratory tests. In addition, *in vitro* data indicate that ramelteon does not cause false-positive results for benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screening methods *in vitro*.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenesis
In a two-year carcinogenicity study, $B6C3F_1$ mice were administered ramelteon at doses of 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage. Male mice exhibited a dose-related increase in the incidence of hepatic tumors at dose levels ≥ 100 mg/kg/day including hepatic adenoma, hepatic carcinoma, and hepatoblastoma. Female mice developed a dose-related increase in the incidence of hepatic adenomas at dose levels ≥ 300 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors in male mice was 30 mg/kg/day (103-times and 3-times the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the maximum recommended human dose [MRHD] based on an area under the concentration-time curve [AUC] comparison). The no-effect level for hepatic tumors in female mice was 100 mg/kg/day (827-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male and female rats were administered ramelteon at doses of 0, 15, 60, 250 or 1000 mg/kg/day by oral gavage. Male rats exhibited a dose-related increase in the incidence of hepatic adenoma and benign Leydig cell tumors of the testis at dose levels ≥ 250 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. Female rats exhibited a dose-related increase in the incidence of hepatic adenoma at dose levels ≥ 60 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors and benign Leydig cell tumors in male rats was 60 mg/kg/day (1,429-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC). The no-effect level for hepatic tumors in female rats was 15 mg/kg/day (472-times and 16-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The development of hepatic tumors in rodents following chronic treatment with non-genotoxic compounds may be secondary to microsomal enzyme induction, a mechanism for tumor generation not thought to occur in humans. Leydig cell tumor development following treatment with non-genotoxic compounds in rodents has been linked to reductions in circulating testosterone levels with compensatory increases in luteinizing hormone release, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of luteinizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily ramelteon administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma testosterone levels. In the same study, luteinizing hormone levels were elevated over a 24-hour period after the last ramelteon treatment; however, the durability of this luteinizing hormone finding and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following ramelteon treatment occurred at plasma levels of ramelteon and M-II in excess of mean clinical plasma concentrations at the MRHD, the relevance of both rodent hepatic tumors and benign rat Leydig cell tumors to humans is not known.

Mutagenesis
Ramelteon was not genotoxic in the following: *in vitro* bacterial reverse mutation (Ames) assay; *in vitro* mammalian cell gene mutation assay using the mouse lymphoma $TK^{+/-}$ cell line; *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes; and in *in vivo* micronucleus assays conducted in mouse and rat. Ramelteon was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of S9 metabolic activation.

Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver S9 fraction used in the *in vitro* genetic toxicology studies described above, exceeded the concentration of ramelteon; therefore, the genotoxic potential of the M-II metabolite was also assessed in these studies.

Impairment of Fertility
Ramelteon was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 6, 60, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a ramelteon dose up to 600 mg/kg/day (786-times higher than the MRHD on a mg/m^2 basis). Irregular estrus cycles, reduction in the number of implants, and reduction in the number of live embryos were noted with dosing females at ≥ 60 mg/kg/day (79-times higher than the MRHD on a mg/m^2 basis). A reduction in the number of corpora lutea occurred at the 600 mg/kg/day dose level. Administration of ramelteon up to 600 mg/kg/day to male rats for 7 weeks had no effect on sperm quality and when the treated male rats were mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of ramelteon at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with doses ≥ 60 mg/kg/day, but no effects were seen on implantation or embryo viability. The no-effect dose for fertility endpoints was 20 mg/kg/day in females (26-times the MRHD on a mg/m^2 basis) and 600 mg/kg/day in males (786-times higher than the MRHD on a mg/m^2 basis) when considering all studies.

Pregnancy: Pregnancy Category C
Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 times higher than the maximum recommended human dose [MRHD] on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Ramelteon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of ramelteon on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered ramelteon by oral gavage at doses of 0, 10, 40, 150, or 600 mg/kg/day during gestation days 6 -17, which is the period of organogenesis in this species. Evidence of maternal toxicity and fetal teratogenicity was observed at doses greater than or equal to 150 mg/kg/day. Maternal toxicity was chiefly characterized by decreased body weight and, at 600 mg/kg/day, ataxia and decreased spontaneous movement. At maternally toxic doses (150 mg/kg/day or greater), the fetuses demonstrated visceral malformations consisting of diaphragmatic hernia and minor anatomical variations of the skeleton (irregularly shaped scapula). At 600 mg/kg/day, reductions in fetal body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 40 mg/kg/day (1,892-times and 45-times higher than the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the MRHD based on an area under the concentration-time curve [AUC] comparison). Pregnant rabbits were administered ramelteon by oral gavage at doses of 0, 12, 60, or 300 mg/kg/day during gestation days 6-18, which is the period of organogenesis in this species. Although maternal toxicity was apparent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was associated with any dose level. The no-effect level for teratogenicity was, therefore, 300 mg/kg/day (11,862-times and 99-times higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The effects of ramelteon on pre- and post-natal development in the rat were studied by administration of ramelteon to the pregnant rat by oral gavage at doses of 0, 30,100, or 300 mg/kg/day from day 6 of gestation through parturition to postnatal (lactation) day 21, at which time offspring were weaned. Maternal toxicity was noted at doses of 100 mg/kg/day or greater and consisted of reduced body weight gain and increased adrenal gland weight. Reduced body weight during the post-weaning period was also noticed in the offspring of the groups given 100 mg/kg/day and higher. Offspring in the 300 mg/kg/day group demonstrated physical and developmental delays including delayed eruption of the lower incisors, a delayed acquisition of the righting reflex, and an alteration of emotional response. These delays are often observed in the presence of reduced offspring body weight but may still be indicative of developmental delay. An apparent decrease in the viability of offspring in the 300 mg/kg/day group was likely due to altered maternal behavior and function observed at this dose level. Offspring of the 300 mg/kg/day group also showed evidence of diaphragmatic hernia, a finding observed in the embryo-fetal development study previously described. There were no effects on the reproductive capacity of offspring and the resulting progeny were not different from those of vehicle-treated offspring. The no-effect level for pre- and post-natal development in this study was 30 mg/kg/day (39-times higher than the MRHD on a mg/m^2 basis).

Labor and Delivery
The potential effects of ROZEREM on the duration of labor and/or delivery, for either the mother or the fetus, have not been studied. ROZEREM has no established use in labor and delivery.

Nursing Mothers
Ramelteon is secreted into the milk of lactating rats. It is not known whether this drug is excreted in human milk. No clinical studies in nursing mothers have been performed. The use of ROZEREM in nursing mothers is not recommended.

Pediatric Use
Safety and effectiveness of ROZEREM in pediatric patients have not been established. Further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent patients.

Geriatric Use
A total of 654 subjects in double-blind, placebo-controlled, efficacy trials who received ROZEREM were at least 65 years of age; of these, 199 were 75 years of age or older. No overall differences in safety or efficacy were observed between elderly and younger adult subjects.

ADVERSE REACTIONS
Overview
The data described in this section reflect exposure to ROZEREM in 4251 subjects, including 346 exposed for 6 months or longer, and 473 subjects for one year.

Adverse Reactions Resulting in Discontinuation of Treatment
Six percent of the 3594 individual subjects exposed to ROZEREM in clinical studies discontinued treatment owing to an adverse event, compared with 2% of the 1370 subjects receiving placebo. The most frequent adverse events leading to discontinuation in subjects receiving ROZEREM were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%).

ROZEREM Most Commonly Observed Adverse Events in Phase 1-3 trials
The incidence of adverse events during the Phase 1 through 3 trials (% placebo, n=1370; % ramelteon [8 mg], n=1250) were: headache NOS (7%, 7%), somnolence (3%, 5%), fatigue (2%, 4%), dizziness (3%, 5%), nausea (2%, 3%), insomnia exacerbated (2%, 3%), upper respiratory tract infection NOS (2%, 3%), diarrhea NOS (2%, 2%), myalgia (1%, 2%), depression (1%, 2%), dysgeusia (1%, 2%), arthralgia (1%, 2%), influenza (0, 1%), blood cortisol decreased (0, 1%).

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 clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

DRUG ABUSE AND DEPENDENCE
ROZEREM is not a controlled substance.

Human Data: **See the CLINICAL TRIALS section, Studies Pertinent to Safety Concerns for Sleep-Promoting Agents, in the Complete Prescribing Information.**

Animal Data: Ramelteon did not produce any signals from animal behavioral studies indicating that the drug produces rewarding effects. Monkeys did not self-administer ramelteon and the drug did not induce a conditioned place preference in rats. There was no generalization between ramelteon and midazolam. Ramelteon did not affect rotorod performance, an indicator of disruption of motor function, and it did not potentiate the ability of diazepam to interfere with rotorod performance.

Discontinuation of ramelteon in animals or in humans after chronic administration did not produce withdrawal signs. Ramelteon does not appear to produce physical dependence.

OVERDOSAGE
Signs and Symptoms
No cases of ROZEREM overdose have been reported during clinical development.

ROZEREM was administered in single doses up to 160 mg in an abuse liability trial. No safety or tolerability concerns were seen.

Recommended Treatment
General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate vital signs should be monitored, and general supportive measures employed.

Hemodialysis does not effectively reduce exposure to ROZEREM. Therefore, the use of dialysis in the treatment of overdosage is not appropriate.

Poison Control Center
As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may contact a poison control center for current information on the management of overdosage.

Rx only

Manufactured by:
Takeda Pharmaceutical Company Limited
540-8645 Osaka, JAPAN

Manufactured in:
Takeda Ireland Ltd.
Kilruddery, County Wicklow, Republic of Ireland

Marketed by:
Takeda Pharmaceuticals America, Inc.
One Takeda Parkway
Deerfield, IL 60015

05-1124 Revised: Apr., 2006

L-RAM-00029

References: 1. Rozerem package insert, Takeda Pharmaceuticals America, Inc. **2.** Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative adverse effects. *Arch Gen Psychiatry.* 2006;63:1149-1157.

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Director of Pain Management, Department of Anesthesiology
Philadelphia VA Medical Center
Clinical Professor of Psychiatry and Anesthesiology
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Practical Neuroscience for Primary Care Physicians is a publication series brought to you by FAMILY PRACTICE NEWS and INTERNAL MEDICINE NEWS, the leading independent medical newspapers for primary care physicians. Each issue provides primary care physicians with timely and relevant clinical updates in neuroscience on depression and anxiety, headache, insomnia, pain management, and other topics that are immediately useful in day-to-day patient care. Featured are in-depth articles, case studies, and columns presented by thought leaders.

This publication was produced by the customized publication department of Elsevier/International Medical News Group. The ideas and opinions expressed in this supplement are those of the faculty and do not necessarily reflect the views of the Publisher.

INTERNATIONAL MEDICAL NEWS GROUP

From the Desk of...

Welcome to the second issue of *Practical Neuroscience for Primary Care Physicians*, a supplement series created as a practical resource for primary care physicians. I, along with Elsevier/IMNG, hope you enjoyed the inaugural issue as much as we enjoyed publishing the supplement.

In this issue, **William Clay Jackson, MD, DipTh**, a practicing physician in family and palliative medicine in Memphis, Tennessee, authors the 'Special Populations in Depression' series by discussing depression in seniors. **Ellen H. Miller, MD**, Clinical Associate Professor of Medicine, Albert Einstein College of Medicine, New York, New York, examines advances in the management of insomnia. **Rollin M. Gallagher, MD, MPH, DABPM**, Director of Pain Management, Department of Anesthesiology, Philadelphia VA Medical Center; and Clinical Professor of Psychiatry and Anesthesiology and Director, Center for Pain Medicine, Research and Policy at the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, addresses the management of chronic pain. In our 'Case File' section, **Joseph A. Lieberman III, MD, MPH**, Associate Editor, *Delaware Medical Journal*, Professor of Family Medicine, Jefferson Medical College, Hockessin, Delaware, shares a case study of depression in an elderly patient.

Look for the next two supplements in the September and December issues of *Family Practice News* and *Internal Medicine News*. Also, be sure to visit the publication's web site at www.practicalneuroscience.com for additional editorial. Through our web site, we also welcome submissions of case studies or point of view columns. We look forward to hearing from our loyal readers.

Cordially,

Larry Culpepper, MD, MPH
Guest Editor
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William Clay Jackson, MD, DipTh

Practical Approaches to Depression in Seniors

Clinical depression is often underdiagnosed and undertreated in seniors (defined as individuals who are 65 years of age or older) in the primary care setting.[1-5] In the context of multiple medical concerns that occur in elder patients, the symptoms of depression can be unrecognized.

When a patient has a number of medical comorbidities, psychiatric comorbidities tend to be deemphasized by both the patient and the practitioner. This article identifies some of the challenges that clinicians face in recognizing depressive symptomatology in seniors and describes practical approaches to help address the needs of these patients.

Prevalence of Depression

Estimates of the prevalence of depression in older Americans vary widely, depending on the definition of depression and the study population. Some studies have found that the prevalence of major depressive disorder (MDD) is 10% to 15% of all primary care patients,[6] with significant symptomatology of clinical depression experienced by up to 25% of medical outpatients[7]— a rate similar to the prevalence of hypertension.[8] While the prevalence of MDD declines with age, overall depressive symptoms increase; one study found that up to 37% of older Americans in primary care settings suffer from depressive symptoms.[9,10] Generalists should be aware of the overall high incidence of MDD in their practices, but also screen for subtler depressive symptoms, which are more common.

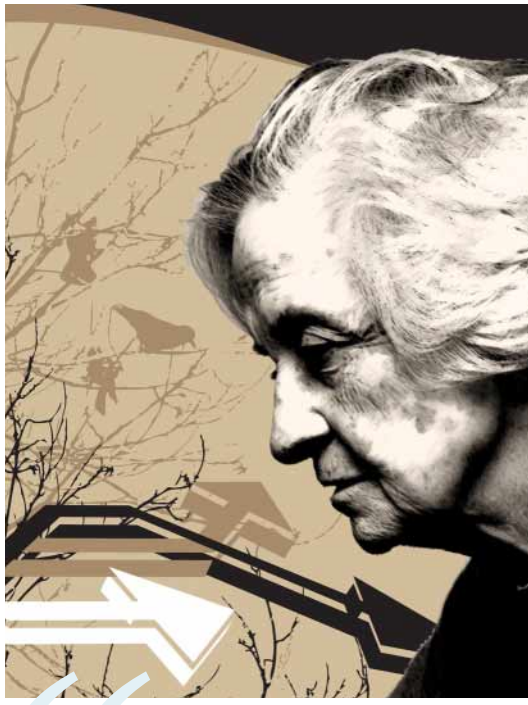
The Role of Primary Care Clinicians

Primary care clinicians can serve a key role in helping seniors who experience symptoms of clinical depression. Recognition of clinical depression in seniors can be hampered by an inability or reluctance by these patients to report symptoms of depression (**Figure** on page 8). Many seniors tend to minimize psychiatric complaints, believing, for instance, that their blood pressure is more important than whether they cry or sleep well at night. Within the context of an ongoing therapeutic relationship where a robust level of comfort and trust has been established, clinicians can proactively screen for depression at regular intervals to detect symptoms and intervene before a mental health problem worsens.

Looking for Symptoms

Symptoms of clinical depression may include persistent sad, anxious, or "empty" mood; feelings of hopelessness and pessimism; feelings of guilt, worthlessness, and helplessness; loss of interest or pleasure; decreased energy and fatigue; difficulty concentrating, remembering, and making decisions; insomnia, early-morning awakening, or oversleeping; appetite and/or weight loss or overeating or weight gain; thoughts of death or suicide, or suicide attempts; restlessness and irritability; and persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain.[11] Whereas the severity of any of these symptoms may vary with individuals and change over time, these variations in presentation of clinical depression are particularly evident in elder patients. For example, elders with clinical depression typically do not report depressed moods; rather, they routinely present with nonspecific physical complaints such as insomnia, anorexia, and fatigue.[12]

In primary care, clinicians often observe a wider spectrum in seniors, as compared with patients under 65 years of age, between depressive symptomatology versus a strict diagnosis of MDD when applying the criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).[13] It is instructive to remember that the DSM-IV criteria were based on consensus recommendations from clinicians who typically saw midlife adults in subspecialty settings. Furthermore, we continue to see a paucity of research in studies that include elders; only a small number of patients over 75 years of age have been included in any trials of antidepressants.[14,15]



Primary care clinicians can serve a key role in helping seniors who experience symptoms of clinical depression.

With respect to diagnostic specificity, clinicians must ask themselves: Should we treat elder patients with depressive symptoms who don't meet strict DSM-IV criteria for MDD? In my experience, I take a careful look at patients with depressive symptoms to determine if these symptoms are driving dysfunction in their lives. In cases where the symptoms are dysfunctional but not diagnostic, my usual practice is to discuss treatment options (both pharmacologic and nonpharmacologic), with close follow-up of the patient's progress over time.

Challenging Assumptions

An additional challenge in recognizing depressive symptomatology in seniors is a tendency among some primary care clinicians to regard advanced age as a time of multiple losses and, therefore, a time of sadness in general. Clinicians may expect elder patients to be sad because their bodies are not as robust as they once were, or perhaps they have experienced the loss of loved ones. However, this assumption is false; although loss is universal, depression is not a normal part of aging.[16] A tendency to recoil from lifelong pursuits and joys should be read as abnormal behavior and investigated, rather than dismissed.

Making Assessments

Differentiating cognitive dysfunction versus affective dysfunction can be difficult in some seniors. Many symptoms of clinical depression overlap with manifestations of various medical and neurologic diseases. Certainly it is important for clinicians to screen for Alzheimer's and other dementias when evaluating depressed patients. The converse is also true—when evaluating patients with cognitive changes, clinical depression must be considered as an etiology.

As a general rule, if a patient with cognitive dysfunction shows insight about their cognitive dysfunction with such statements as "My memory is going...I just can't remember" or "I think I have Alzheimer's disease," that patient is likely to be depressed. When a patient has dementia, this sort of insight typically disappears with the memory loss. Conversely, when a family member brings in the patient and says, "Grandma can't remember...," and Grandma says, "No, I don't have any problems," this paucity of insight tends to be associated with dementia.

Generalists may feel uncertain as to how to weigh the severity of depressive mood in seniors following the death of a loved one. The findings of the Yale Bereavement Study—a longitudinal cohort study of bereaved individuals (N=233 adults with mean age of 62.9 years)—provides data about what clinicians should expect regarding the role of five grief indicators (disbelief, yearning, anger, depression, and acceptance of the death) as normal patterns of grief.[17] Based on these findings, individuals who experience any of the indicators beyond 6 months post-loss may reflect a more difficult than average adjustment, suggesting the need for further evaluation of complicated or prolonged grief disorder.[17] Psychosocial distress that persists beyond 6 months should prompt clinicians to address the needs of these patients, utilizing spiritual, psychosocial, and/or pharmacologic interventions.

Figure. Direct-to-Patient Message From the National Institute of Mental Health

Older Adults ...

Before you say — "I'm fine" — ask yourself if you feel:

- nervous or "empty"
- guilty or worthless
- very tired and slowed down
- you don't enjoy things the way you used to
- restless and irritable
- like no one loves you
- like life is not worth living

Or if you are:

- sleeping more or less than usual
- eating more or less than usual
- having persistent headaches, stomach aches, or chronic pain

These may be symptoms of depression, a treatable medical illness.

But your doctor can only treat you if you say how you are really feeling.

Depression is not a normal part of aging.

Talk to your doctor.

Can be displayed in the primary care setting (including patient reception area and exam rooms).

Source: National Institute of Mental Health. *Older Adults: Depression And Suicide Facts.* Bethesda, Md: National Institute of Mental Health; 2001. NIH publication 03-4593. Available at: http://www.nimh.nih.gov/publicat/elderlydepsuicide.cfm. Accessed March 9, 2007.

Using Screening Tools

The use of epidemiologically researched, evidence-based screening tools can be helpful in discovering clinical depression in seniors. Such tools include the two-question initial screening instrument developed by Pignone and colleagues (namely, asking "Over the past 2 weeks have you felt down or hopeless?" and "Over the past 2 weeks have you felt little interest in doing things?"),[18] the BATHE technique of psychosocial interviewing,[19] the Patient Health Questionnaire 9 (a nine-item, self-administered evaluation),[20] and the 15-item version of the Geriatric Depression Scale.[21] The Clinical Global Impression scale can be used to help clinicians assess treatment response over time in patients with depressive symptomatology.[22] Across the full spectrum of ages, the simple question "Are you depressed?" can lead to a clarifying response. In primary care, we should not underemphasize the value of asking this direct question and the responses that patients provide.

If left untreated, clinical depression impairs one's enjoyment of life and can lead to disability, increased caregiver burden, poor adherence with one's medical treatment plan, and the ultimate adverse outcome of depression—suicide. Older men are at the greatest risk of suicide, with 31.8 completed suicides per year per 100,000 men who are 65 years of age or older, compared with 4.1 suicides per year per 100,000 women who are 65 years of age or older.[23] The majority of seniors who have committed suicide were seen by their primary care physician within the month prior to their suicide, and 77% had seen a physician within a year.[24]

Clinicians need to be on guard for any signs of suicidality, asking elder patients indirect questions such as "Do you think death is coming soon?" and "Why do you think that?" as well as direct questions such as "Do you feel that your depression is bad enough that you may hurt yourself?" Some clinicians may fear that seniors are suggestible, leading them to shy away from such discussions. However, if patients are thinking about suicide, openly addressing the issue doesn't make things worse. On the contrary, it can make things better, because patients can actively approach their mental health challenges directly.

Determining Treatment Options

Many effective therapies are available for the treatment of clinical depression in seniors. Antidepressant medications, as well as short-term psychotherapy, are effective treatments for late-life depression.[7] Newer classes of antidepressants, such as selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors, are generally preferred over older medications, such as tricyclic antidepressants and monoamine

oxidase inhibitors, because they have fewer and less severe potential adverse events.[25] In elder patients, the axiom of "start low and go slow" is a good guideline in terms of dosing. Because of the slower rate of response in elder patients, clinicians may need to delay dose increases slightly (as compared to younger patients).

In some cases, medical comorbidities in seniors can complicate treatment, including patients who have cardiac, gastrointestinal, renal, or hepatic dysfunction. Electroconvulsive therapy is another effective nonpharmacologic treatment for depression in elders, with particular utility when depression is not responsive to medications, when antidepressants are not tolerated due to adverse effects, or when a rapid response is necessary due to accompanying life-threatening complications.[26]

Various types of psychotherapy are effective in treating seniors with clinical depression, including interpersonal psychotherapy (focusing on grief, interpersonal deficits, role disputes, and transitions) and cognitive-behavioral therapy (designed to address pathological ideas and behaviors associated with depression). Reminiscence therapy, which focuses on improving both self-esteem and social intimacy through the recounting of past experiences,[27] can be meaningful for the elder patient and helps to give a sense of coherence or purpose to the story of an individual's life. Befriending programs can be useful to elder patients, as well as pet therapy and other nonpharmacologic interventions.[28] Whenever a lack of family and community support exists in the lives of elder patients, clinicians should take an active role in trying to mediate the establishment of appropriate psychosocial support for their patients.

Providing Ongoing Care

Vigilance is the key in monitoring the treatment of seniors with clinical depression. In my clinical practice, I make it a priority to see any patient within 2 weeks of the time of a new pharmacologic intervention for affective or cognitive disorders. The follow-up visit is important to make sure the recommended intervention has had some positive effects. If so, it's critical to underline the importance of adherence; studies have found that more than one third of older adults in the primary care setting stop taking newly prescribed antidepressants within 4 to 6 weeks.[29] It's also an opportunity to evaluate any unexpected outcomes, either from misdiagnosis or any adverse events relating to the pharmacology of the medication itself. Given the decreased hepatic and renal clearance of medications, decreased volume of distribution, and decreased albumin in the bloodstream of elder patients, I recommend frequent follow-up (with visit frequency no less than on a monthly basis) until remission is achieved.

Conclusion

Clinical depression requires as much concern and awareness in primary care as diabetes, heart disease, and pneumonia. Understanding that the majority of patients with clinical depression are treated in the primary care setting, generalists can serve a key role in recognizing depressive symptomatology and implementing treatment interventions in seniors. Primary care clinicians can address both emotional problems and physical problems with an appreciation of the relationship between mental health and medical conditions in their patients. When administering pharmacologic therapy, clinicians should use caution, applying the "start low and go slow" approach to the use of antidepressants. In some cases, as compared with younger patients, it may be prudent to apply a lower threshold for looking at psychosocial augmentation for elder patients as stand-alone interventions or in combination with pharmacologic augmentation. Careful follow-up in ongoing care is a vital component in the treatment of clinical depression in seniors and can facilitate a robust recovery in the patient, as well as great professional satisfaction for the treating clinician.

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Advances in Assessing and Managing Insomnia

> **Studies have found that insomnia is associated with an increased prevalence of chronic medical conditions, as well as an increased incidence of mental disorders and substance abuse.[5,6]**

Today more Americans than ever are going through the day half awake. According to recent studies, an estimated 40 to 70 million Americans are affected by intermittent or chronic sleep problems,[1] and 30% to 35% of Americans experience nightly insomnia.[2] Individuals with insomnia have impaired next-day functioning, which impacts their quality of life and places them at increased risk of motor vehicle accidents.[3,4] Studies have found that insomnia is associated with an increased prevalence of chronic medical conditions, as well as an increased incidence of mental disorders and substance abuse.[5,6] Yet, despite the widespread occurrence of insomnia and the potential for serious consequences when insomnia is ignored or left untreated, many people do not mention their sleep problems to their health care professionals. This article discusses practical approaches for clinicians in the primary care setting to assess and manage the care of people with insomnia.

Characteristics of Insomnia

According to the World Health Organization, insomnia is defined as repeated difficulty with sleep initiation (difficulty falling asleep), maintenance (difficulty staying asleep), duration (waking too early in the morning), and/or quality of sleep; this difficulty persists despite adequate opportunity and time for sleep and, most importantly, results in next-day impairment.[7] Insomnia should not be confused with sleep deprivation, which often occurs among people who work outside daytime hours (such as night shift workers, including truck drivers and health care professionals) and individuals (particularly teenagers) who choose to stay up all night.

Insomnia is described in different ways. Acute insomnia (a transient condition measured in nights to ≤4 weeks) may occur in otherwise normal sleepers during times of emotional or physical discomfort (eg, due to jet lag, sleeping in an unusual sleep environment, having an acute medical illness, or experiencing a life change such as marriage, divorce, or loss of a loved one). Symptoms of acute insomnia often resolve as soon as the underlying cause has been addressed. However, chronic insomnia (a condition lasting at least one month) may require a more in-depth assessment when its effects lead to impairment in next-day functioning.

Another way to describe insomnia is in terms of primary insomnia or comorbid insomnia. Primary insomnia is characterized as a sleep disturbance that cannot be explained by any underlying medical, psychiatric, or environmental problem. This type of insomnia is usually associated with a state of hyperarousal,[8] involving mechanisms of the nervous system as well as excess activation of the hypothalamic, pituitary, and adrenal systems, resulting in a prolonged sleep latency (taking a long time from going to bed until actually falling asleep). People with primary insomnia often experience exhaustion.

Comorbid insomnia is associated with underlying medical or psychiatric conditions, such as chronic pain, anxiety, or depression. Because this type of insomnia occurs in the context of another medical condition, treatment of both the underlying medical or psychiatric condition and the insomnia directly is needed. For example, people with fibromyalgia, chronic fatigue syndrome, or arthritis may experience more pain at night than during the day, which keeps them awake. People with gastric reflux disease or thyroid imbalance, as well as people (particularly the elderly) taking various medications for other chronic illnesses, may experience comorbid insomnia. In addition, people who take decongestant medications (either over-the-counter or prescription medications), smoke cigarettes, or consume caffeine (especially during the evening) may find that these behaviors keep them awake.

Obstructive sleep apnea (a problem that involves an obstruction of the pharynx) is another cause of comorbid insomnia, which is most frequently reported in middle-aged, overweight men. Other comorbid conditions include the underlying sleep disorders, restless legs syndrome (typically identified with difficulty in sleep onset), and periodic limb movement disorder (typically identified with disruptions in sleep maintenance).

Studies have found a greater prevalence of insomnia among older people, women (more than men), and adults who are divorced, separated, or widowed (more than married adults), as well as individuals with lower education and lower incomes.[9] These groups may be regarded as at-risk populations for insomnia.

Ellen H. Miller, MD

Detecting Symptoms of Insomnia

More research is needed to develop a better understanding of why many people do not tell their health care providers about their sleep problems. Perhaps they think sleep problems are a normal part of life; maybe they have low expectations of what clinicians can do to help relieve somatic distress, or it simply does not occur to them to seek help with sleep problems. One study published in 2005 found that 52% of adults (namely, 326 of the 632 study participants who underwent initial screening for insomnia) who made an office visit for nonurgent primary care reported discussing their insomnia with a physician.[10] Further analysis of study data found that discussing insomnia with a physician was independently associated with having a greater number of medical conditions, being more highly educated, reporting less total sleep per night, and perceiving greater daytime impairment due to insomnia.[10] In addition to making insomnia resolution a priority among patients with chronic illnesses, these researchers advised primary care clinicians to extend their focus beyond sleep quality and tracking the number of hours patients sleep to identify patients' concerns about the impact of poor sleep on their daytime functioning.[10]

Ask Patients Specific Questions

Clinicians can take the first step by simply asking the key question—"Are you having any trouble with your sleep?"—as part of the routine assessment of each patient's health. If the patient's response is affirmative, ask more questions.[11] If next-day impairment does not occur, the patient may not need treatment. However, if next-day effects are present, further evaluation to determine an underlying cause is warranted, as well as consideration of effective behavioral and pharmacologic therapies for managing insomnia.

Identify Medications Associated With Insomnia

Clinicians will find it useful to consider the potential of different medications that can impact sleep (**Table**).[12,13] Medications associated with insomnia include the use of certain antidepressants, antihypertensives, antineoplastics, anticholinergics, sympathomimetic amines, neurologics, hormone therapy, and other agents. When permissible, adjustments in timing of certain medications may help relieve any interference with a patient's sleep cycle.

Look for Clues

A detailed physical examination of patients may reveal clues of comorbid insomnia. First, look in the patient's mouth to assess for a crowded pharynx, which can be a sign of obstructive sleep apnea. Next, look at the neck and feel the thyroid, noting the size of the gland and any signs of hyperthyroidism. Assess the heart for any signs of congestive heart failure, which may be associated with paroxysmal nocturnal dyspnea. Ask patients about any pain in their joints, suggestive of arthritis. Assess the abdomen for any masses and conduct a neurologic examination, noting any signs of neuropathy or symptoms of multiple sclerosis. The focus of these patient examinations is to adopt a symptom-driven and diagnosis-driven approach.

Managing Insomnia

Promote Sleep Hygiene

In addition to conducting a comprehensive assessment to identify the presence of comorbid insomnia, clinicians can educate their patients with insomnia on adopting good sleep habits.

A sleep diary can be a useful self-awareness tool for patients to gain insights on their sleep habits and sleep hygiene, as well as an aid to help evaluate such factors as their evening routine (with respect to activity level and intake of food, alcohol, coffee, and/or nicotine), sleep environment (alone or with a bed partner), and exposure to bright light during the day (versus making the room very dark at night to promote restful sleep). Various sleep hygiene techniques can make a difference as interventions to promote improvements in sleep.[11,12,14]

Implement Behavioral Changes

Behavioral strategies for managing insomnia have been found effective in achieving specific goals relating to improvements in sleep.[15] These strategies include cognitive therapy, which challenges any dysfunctional beliefs and misconceptions about sleep and insomnia of individual patients;

Table. Some Medications Associated With Insomnia[12,13]

Antidepressants	Antihypertensives	Antineoplastics	Anticholinergics
SSRIs	Clonidine	Medroxyprogesterone	Ipratropium bromide
Bupropion	ß-blockers	Leuprolide acetate	
MAOIs	Propranolol, Atenolol	Goserelin acetate	
Venlafaxine	Pindolol	Pentostatin	
	Methyldopa	Daunorubicin	
	Reserpine	Interferon α	
Sympathomimetic Amines	**Hormones**	**Neurologic**	**Miscellaneous**
Bronchodilators	Oral Contraceptives	Phenytoin	Quinidine
Terbutaline	Thyroid Preparations	Topiramate	Opiates
Albuterol	Cortisone	Methylphenidate	Nicotine
Salmeterol	Progesterone	Lamotrigine	Caffeine
Metaproterenol		Levodopa	Aspirin, Caffeine
Xanthine Derivatives			Acetaminophen, Aspirin, Caffeine
Theophylline			
Decongestants			Aspirin, Codeine Phosphate
Phenylpropanolamine			Cough, Cold Preparations
Pseudoephedrine			

MAOIs = monamine oxidase inhibitors, SSRIs = selective serotonin reuptake inhibitors

relaxation training, which uses such techniques as progressive muscular relaxation, meditation, yoga, and biofeedback to reduce physiologic and cognitive arousal at bedtime; sleep restriction, which can improve sleep continuity by limiting time spent in bed; and stimulus control, which encourages individuals to relate the bed/bedroom solely as a place for sleep or sexual activity.[15]

Use of Pharmacologic Agents

Pharmacotherapy is one of the most common treatments for insomnia management.[9,16] Several classes of medications are used for the treatment of insomnia. Sedating antidepressants (eg, amitriptyline, doxepin, trazodone) prescribed at low doses have been found to improve subjective and objective measures of insomnia in patients with major depression.[11] However, potential problems relating to their use include anticholinergic effects (eg, dry mouth, blurred vision, constipation, urinary retention, memory impairment, confusion, delirium), residual effects in terms of sedation and cognitive impairment, and drug-drug interactions.[17]

Benzodiazepines (eg, flurazepam, temazepam, triazolam) have been shown to reduce sleep latency, decrease the number of awakenings, increase total sleep time, and result in a subjective improvement in sleep quality. However, they may alter the normal sleep architecture; adverse events include daytime sedation, psychomotor and cognitive impairment, and rebound insomnia, as well as respiratory depression and psychological dependence in vulnerable populations.[17]

Benzodiazepine receptor agonists (eg, zaleplon, zolpidem, eszopiclone, zolpidem controlled release [CR]) have been found to maintain normal sleep architecture and improve sleep latency.[3] Prescribing considerations include potential adverse events such as headache, drowsiness/somnolence, dizziness, nausea, myalgia, and amnesia; the advisability of dosage reduction in the elderly or hepatically compromised patients; the potential for dependence in vulnerable populations; and respiratory effects in certain individuals.[11,12]

Melatonin receptor agonists (eg, ramelteon) have been found to effectively reduce sleep latency. Studies of its use in adults over 65 years of age have shown that it can be used in patients with mild to moderate chronic obstructive pulmonary disease, as well as patients with sleep apnea.[18] Ramelteon can be prescribed for long-term use, as can the other new agents eszopiclone and zolpidem CR.

Looking ahead, clinicians can expect to see the findings of new studies that investigate the safety and efficacy of long-term use of pharmacologic agents in managing insomnia. In addition to therapeutic endpoints for measuring sleep latency, more attention will be directed to a better understanding of the waking function, metabolic parameters, and effective ways to determine underlying disease processes relating to insomnia. The emergence of mechanism-specific therapy would enable clinicians to make corrections in a specific defect affecting individual patients.

Combining Interventions

Behavioral and pharmacologic therapies, alone or in combination, are effective in improving sleep continuity and efficiency in people with insomnia.[16] A randomized, placebo-controlled, 8-week clinical study of 78 older adults (mean 65 years of age) with insomnia compared the effects of cognitive-behavioral therapy (including stimulus control, sleep restriction, sleep hygiene, and cognitive therapy) with the effects of pharmacologic therapy using temazepam, as well as the effects of using both interventions.[16] These researchers found that pharmacologic therapy had a more immediate effect (with sleep improvements within a few nights), whereas the cognitive-behavioral therapy had a more long-lasting effect (based on follow-up data at 12-month and 24-month intervals). Additional research is needed to evaluate to what extent the integration of behavioral and pharmacologic approaches can yield optimal outcomes for people with insomnia.

Conclusion

Insomnia can have an unfavorable impact on an individual's general and psychological health. Clinicians can begin their assessment of patients with insomnia by determining if their condition can be characterized as primary insomnia (without any underlying medical, psychiatric, or environmental problem) or comorbid insomnia (occurring in the context of another medical condition). Although women, older adults, people receiving care in the primary care setting, and people with a history of psychiatric disorders may be at higher risk for insomnia, all patients with insomnia can benefit from a discussion on sleep hygiene techniques. Cognitive-behavioral and pharmacologic therapy, alone or in combination, can be used to effectively manage insomnia, with ongoing follow-up care on an individualized basis to track outcomes and make adjustments as needed to achieve optimal improvements in sleep patterns without impaired next-day functioning.

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CASE FILE

Joseph A. Lieberman III, MD, MPH

Clinical Case: Elderly Man With Insomnia and Depression

Presentation

B.H. is a 68-year-old retiree who presents to the office for his routine 3-month checkup. He has been seen for the past 5 years and is being treated for mild hypertension, BPH, and mild osteoarthritis of the knees. His current medications include: atenolol, acetylsalicylic acid (81mg/d), hydrochlorothiazide, terazosin and acetylsalicylic acid/acetaminophen prn "knee pain." He claims that he is taking his medications as prescribed but only rarely needs to take the acetylsalicylic acid/acetaminophen for his knees. His vital signs are within normal limits (WNL), his height and weight are also WNL (and essentially unchanged over the past 5 years), and his "pain index" was reported as "one" on a scale of "zero to ten." He has been retired for 6 months and complains that he is not sleeping well. He denies any other symptoms with the exception of occasional joint aches and pains. When asked about his sleep, he states that he frequently has trouble getting to sleep as well as staying asleep, and he often wakes early in the morning and cannot get back to sleep. When this happens, he's a "mess the next day" ("no energy, no stamina, doesn't feel like doing anything"). He claims that this happens more nights than not, and he dated its onset to "about the time he retired." According to his wife, he snores "softly" on occasion, but she has noted no breathing lapses or unusual movements of his extremities proximate to, or during, his sleep.

Initial Evaluation

B.H. has normal vital signs, height and weight, and minimal pain (using a visual analog scale). His physical examination reveals a well-developed, well-nourished white male in no acute distress and appearing his stated age. A review of systems conducted during the physical examination was non-contributory. His positive physical findings were limited to his knees, where very mild crepitations were detected on passive range of motion assessment.

Psychosocial Assessment

Because of B.H.'s symptoms of insomnia and his recent change of status to "retired" put him at risk for other comorbid conditions, a focused psychosocial assessment using the BATHE technique was conducted.

Background: "What else is going on in your life?"

Patient response: "I've recently retired and now I've got nothing to do. I can go to bed when I want, get up when I want, eat when I want, and do what I want to do."

Affect: "How do you feel about that?"

Patient response: "At first it was great, but after a while it got boring."

Trouble: "What's troubling you the most?"

Patient response: "I feel so useless. I used to take pride in my work. I did a good job and people respected me for who I was. Now, nobody even notices me. It's all very depressing."

Handling: "How are you handling this?"

Patient response: "I'm not dealing with this well at all. It all looks so hopeless. I don't even enjoy the things that I used to like to do. My wife calls me a grouch, and I think that it's responsible for my lousy sleep."

Empathy: You share with the patient that this must be difficult, but you are glad that he came in because there are a number of things that can be done to help with his problem, but first you need some additional information.

Because B.H. has screened positively for depression using the United States Preventive Task Force's Screener (positive for depressed mode and anhedonia), his symptoms were further evaluated using the SIG-E CAPS mnemonic. Using this assessment tool, if a patient has five or more positive symptoms (at least one of which must be depressed mood or anhedonia) for at least 2 weeks, and this represents a change from previous behavior, he meets DSM-IV criteria for the diagnosis of major depressive disorder.

S: Increased or decreased sleep and decreased sexual desire
(Patient acknowledged sleep problems and stated "what's a sex life?" in response to that question.)

I: Decreased interest or pleasure in almost all activities
(Patient acknowledged this on previous questioning.)

G: Inappropriate guilt or feeling of worthlessness/hopelessness
(Patient acknowledged this on previous questioning.)

E: Decreased energy or fatigue
(Patient acknowledged this on previous questioning.)

C: Decreased concentration
(Patient claims that this has indeed happened, although fortunately, over the past 6 months, he has not had much to concentrate on.)

A: Increased or decreased appetite with weight gain or loss
(Patient claims no change in appetite and, on physical exam, there has been no change in his weight.)

P: Psychomotor agitation or retardation
(Patient denies any psychomotor symptoms.)

S: Suicidal ideation, plan, or attempt
(Patient denies any thoughts of suicide.)

The patient answered positively to five of the SIG-E CAPS questions and therefore satisfies the DSM-IV criteria for the diagnosis of major depressive disorder. He also satisfies criteria for the diagnosis of comorbid insomnia. Because these conditions are truly "comorbid," to optimize outcome, it is necessary to treat both conditions as just treating one of them will not guarantee resolution of the other.

Management Plan

B.H. starts on a vigorous approach to his problems including cognitive behavioral therapy, instruction in good sleep hygiene, and an exercise program. He and his wife were given the "homework assignment" of identifying opportunities for him to participate in gainful activities that will "exercise his mind" and, at the same time, restore some of his self-esteem. In addition, he begins taking an antidepressant as well as a hypnotic medication. He was seen on a regular basis and made slow, but steady, progress to the point where after 8 weeks, he was essentially symptom free, a contributing member of society, and looking forward to the time when his therapy could be discontinued.

To submit a case study for possible inclusion in an upcoming issue and for guidelines on submitting a case file, please visit www.practicalneuroscience.com.

A Multidisciplinary Approach to the Management of Chronic Pain

More than 75 million Americans (about 25% of the entire population) have chronic or recurrent pain,[1] and 40% of them report that the pain has a moderate or severe impact on their lives. Along with physical and emotional suffering, chronic pain confers a large economic impact. For example, lost productivity attributable to pain in workers is estimated to cost employers more than $60 billion yearly alone.[2]

Personal consequences also result from poorly controlled chronic pain which adversely affects quality of life, including social activities, occupational functioning, and psychological welfare. Medical comorbidities and iatrogenic consequences often accompany chronic pain, and the severity of pain associated with a medical condition can affect the outcome of clinical treatment. The burdens imposed by chronic pain can be minimized by judicious and selective integration of one or several treatments, depending on diagnosis, mechanisms, and complexity.[3] However, designing an effective treatment plan requires both an understanding of the biopsychosocial phenomenology of pain disorders and how to individualize clinical management strategies that address this multifaceted phenomenology.[4]

Understanding Chronic Pain

Nociceptive vs Neuropathic Pain

For purposes of conceptualizing mechanism-based pharmacotherapy of chronic pain, it is useful to consider two broad categories of pain, nociceptive and neuropathic. Nociceptive pain results from neural pathway activation in response to stimuli from tissue damage or threatened tissue damage, such as in acute pain from a simple stimulus such as a needle prick, an injury such as sunburn or sprain, or a disease such as arthritis. Neuropathic pain arises from a primary lesion or dysfunction of the nervous system—such as in nerve compression or trauma from radiculopathy due to herniated disc or from carpal tunnel syndrome—or diseases such as post-herpetic neuralgia, multiple sclerosis, and diabetic neuropathy. Some conditions lead to a combination of nociceptive and neuropathic pain, known as mixed pain states. Examples include osteoarthritis of the spine with spinal stenosis and radiculopathy and cancer invading both tissue and nerve plexuses and chronic pelvic pain with muscle spasm and vulvodynia. Mixed pain states are mediated by complex input from inflammatory, immunologic, and neuropathological processes.

Neurobiology of Chronic Pain

Persistent, uncontrolled pain has multiple biological and psychological effects which account for its clinical presentation. For example, nerve damage caused by injury such as a crush or amputation injury or a disease such as diabetes (diabetic neuropathy), herpes zoster (shingles and post-herpetic neuralgia), or a toxin such as taxol chemotherapy (neuropathy) results in damaged pain nerves firing ectopically causing neuropathic pain.[5,6] Stress, in both animal models and humans, activates the noradrenergic system and sympathetic excitation which causes increased ectopic nerve firing of damaged pain fibers. Thus, patients affected by these conditions invariably have pain that is sensitive to psychological stress or heightened emotions.

Persistent pain can also directly change the physiology and anatomy of the central nervous system (CNS). Prolonged nociception has been associated with overactivation of pain pathways in the CNS through pathophysiologic processes such as neural sensitization, neuroplasticity, and kindling.[7] The process of sensitization arises from both peripheral and central processes. Following neural trauma, affected nerves can initiate ectopic discharges (action potentials in the absence of normal stimuli) leading to phenotypic changes in the dorsal root ganglion and lowering the threshold for a potentially painful stimulus to initiate action potentials in nociceptive neurons. A persistent barrage of pain signals accompanied by axonal degeneration of injured nerves initiates a process of central sensitization and neuroplasticity in the spinal cord, such that stimulation of polymodal sensory fibers, which normally would not initiate a pain signal to the CNS, now activate spin thalamic pain pathways so that non-painful stimuli, including touch, pressure and movement, cause pain. Additionally, reduced activity in descending neurotransmitter systems that modulate pain transmission, such as norepinephrine and serotonin, also results in faulty communication of pain impulses. The end result is a lowered threshold for activation in damaged nerves, increased nociceptive response to inflammation, and higher levels of pain.[5,6,7]

Thus, effective treatment of chronic pain employs a variety of methods to prevent this neural activation. For example, gabapentin and pregabalin block calcium channel activation, lidocaine and tricylic antidepressants (TCAs) block sodium channel activation to reduce neuronal firing, and TCAs, duloxetine, and venlafaxine act to enhance norepinephrine and serotonin reuptake, enhancing pain modulation.[3,8,9]

Pain and Emotion

Pain is conditioned such that prior experience determines future responses to painful stimuli. Laboratory studies demonstrate that when warm and nociceptive stimuli are applied together, and then warmth is applied alone, brain imaging shows that the expectation of pain acti-

vates the anterior cingulate gyrus, where pain suffering is experienced.[10]

Thus the pairing of the hospital environment and painful procedures for a child with cancer may activate the neural networks causing pain. Brain pathways involved in the regulation of mood may also influence an individual's response to painful stimuli. The prefrontal cortex and the anterior cingulate cortex attach emotional valence to the experience of pain, which may modulate descending and ascending circuits that regulate pain transmission. As mentioned above, serotonin and norepinephrine are the primary neurotransmitters involved in this system, which helps explain why some antidepressants are useful for treating pain as well as depression.[11,12]

Pain and Depression

Chronic pain and depression are interconnected in multiple ways.[11-15] Chronic pain can cause depression in people who have no history of depressed mood. Patients who have a history of depression, but are currently in remission, can be driven into relapse by chronic pain. Some patients lapse into a repeating cycle of remission, relapse, and recovery. Since depression is an important factor influencing functional ability, quality of life, and other key outcomes in the management of chronic pain, physicians must remain clinically vigilant to identify signs and symptoms of depression that can complicate pain management. Evidence for onset or relapse of a major depressive episode is often subtle, and can easily be confused with nonadherence, personality disorders, or requests for more narcotics. Missed appointments, poor adherence to physical therapy, and lack of interest in activities that would help relieve pain are potential signs of depression in a patient affected by chronic pain.

Goal-Oriented Pain Management

Practitioners of pain medicine often find themselves in a difficult practice environment characterized by a financing system that allows for procedures such as nerve blocks and spinal injections and brief visits for medication management over longitudinal management that selectively integrates medical, physical, and psychological therapies to address the biopsychosocial factors causing and perpetuating chronic pain and dysfunction.[3,4,16-18] In certain circumstances, limited self-management is most cost-effective—for example, evidence suggests that cost-effective care for acute low back pain without so-called "red flags" (indicating need for immediate medical intervention) is a combination of a brief period of restricted activity, ice packs, and nonprescription pain relievers, a strategy that leads to return to work at the lowest cost.[19]

The managed care approach to pain treatment emphasizes pharmacotherapy after limited evaluation, and little or no opportunity for integrated biopsychosocial treatment or consultation with a pain medicine specialist. Pharmacotherapy alone, choosing medications based on mechanism, and emphasizing functional recovery with self-management, can be effective in cases of limited biopsychosocial complexity. But often, limited third-party support for appropriate evaluation and integrated biopsychosocial treatment leads to treatment failure, continued pain, inability to work, job loss, depression, and loss of health insurance.[20] Family systems and society as a whole suffer from these outcomes.

For several years, health planners have been considering more effective models for providing pain treatment in a community.[20] The pain medicine and primary care community rehabilitation model emphasizes training primary care providers in using evidence-based clinical algorithms to manage different chronic pain conditions.[20] Ideally, a multidisciplinary pain medicine practice group is readily accessible to support primary care providers when use of algorithms fails to control pain and its consequences in a timely fashion. Thus, a network of community providers (physicians, nurses, physical therapists, psychologists, and pharmacists) can be dedicated to this mission with facilitated access to telephone consultations, and timely pain medicine clinic consultation for greater complexity. Using information technology, such as the electronic medical record, PDAs, and electronic libraries may enable providers in a health system to have immediate access to information critical to real-time clinical decision-making. Programs in the Department of Veterans Affairs (VA) Health System have demonstrated the promise of dedicated pain management programs based on the premise of primary care management supported by a team of pain medicine specialists.[21,22] In such systems, VA specialty pain teams work closely with primary care clinics using the computerized medical record to create a virtually integrated team approach to care at the level needed for each patient.

Biopsychosocial Model of Care

Self-management

Self-management is a cornerstone of biopsychosocial approach to pain management. Providers can empower patients to be partners in their care through public information web sites, such as http://www.nationalpainfoundation.org, which can educate patients about the multiple options available to help gain better mastery and control over fear, anxiety, stress reactions, and environmental pain triggers. These techniques include a pain diary, relaxation skills, cognitive training, sleep hygiene, self-hypnosis, distraction, and physical exercise.

Elimination of Pain Triggers

Options for directly eliminating triggers for pain include surgery, exercise, nerve ablation, and chemotherapy. If triggers cannot be eliminated, reducing the frequency and severity of trigger activation often can be addressed in multiple ways. Medications such as nonsteroidal anti-inflammatory drugs can reduce activation of nociceptors and the inflammatory response. Behavioral strategies to reduce activation include positioning and ergonomics, weight loss, braces and orthotics, pacing and avoidance, strengthening and stretching, and stress management.

Interruption of Pain Signals

Patients have numerous options for interrupting the pain signal. Icing painful areas is a simple and effective, but often overlooked intervention that closes the pain signaling gateway in the dorsal horn. Other useful therapies include transcutaneous electrical nerve stimulation, nerve blocks, stretching, acupuncture and acupressure,

and neurostimulation. Other useful options are designed to reduce CNS reactivity to the pain signal. These include relaxation and biofeedback, hypnosis, cognitive therapy aimed at eliminating the tendency to imagine pain having catastrophic effects, and medications that help control anxiety, such as serotonin and norepinephrine reuptake inhibitors (SNRIs), eg, duloxetine.

Restoration of Motivation

Demonstrating empathy and understanding can go a long way toward minimizing the demoralization that often results from chronic pain conditions. Other ways to restore a patient's spirit include prayer or meditation, self-reflection, meaningful rituals, meaningful goals, spiritual healing, and support groups.

Restoration of Healthy Social Interactions

Unfortunately, patients with chronic pain often seek help from individuals who are negative, critical, or otherwise unsupportive. A good clinician will encourage patients to seek healthy social interactions that will provide safe pleasure and help them recover. The first step often involves improving communication skills and helping the patient learn to utilize their family and community for support. Helpful interventions can include family therapy, interpersonal problem solving, vocational training, volunteer work, religious activity, and support groups.

Objective Results

A biopsychosocial approach to pain management sounds good in theory, but the model's value remains open to debate without objective data to support the approach. Meta-analyses of "packaged" treatment programs for chronic pain have shown that integration of medical, psychotherapeutic, and physical therapies benefits patients in several ways.[13,14] including improved pain and mood, reduce impairment, improved rates of return to work, and more effective use of health care resources. These benefits tend to remain stable over time, and treatment was shown to have a causal relationship with outcome. Investigations of integrated treatment for chronic pain have yet to identify which specific interventions were most efficacious. In addition, selective packaging of interventions is needed to meet specific needs of a variety of patient groups and individuals.

Figure. Choosing Medication Based on Many Factors

Ease of Use
- Dosing simplicity
- Titration simplicity
- Patient competence and convenience

Pain's Psychosocial Context and the Doctor/Patient Relationship
- Stigma
- Cost
- Illness behavior
- Risk of treatment non-adherence
- Risk of medication misuse

Use of Medications

The choice of medications for treating chronic pain is based on numerous factors, including the patient's diagnosis, mechanisms of pain, ability to adhere to medical advice, drug efficacy, medical and psychiatric comorbidities, response to prior treatment, and the risk of adverse effects such as side effects, toxicity, and drug-drug interactions.[8,23,24] Psychosocial factors (such as the stigma sometimes associated with use of opiates) and issues involving the doctor-patient relationship (cost, illness behavior, nonadherence, and medication misuse) also figure into medication selection (**Figure**).

Several medications have demonstrated efficacy in randomized controlled trials of neuropathic pain, including agents with and without US Food and Drug Administration approval for treatment of neuropathic pain. Approved agents include the lidocaine patch 5%, gabapentin, pregabalin, and the SNRI duloxetine. Therapies to treat neuropathic pain that demonstrate efficacy, but do not have FDA approval, include carbamazepine, tricyclic antidepressants, the SNRI venlafaxine, the opioids oxycodone and tramadol, and the gamma-aminobutyric acid B agonist baclofen.

Summary

Tens of millions of Americans have intermittent or chronic pain, which is often inadequately treated. A multidisciplinary approach that addresses a patient's physical and psychological needs offers the most effective form of treatment. Multiple medications have demonstrated efficacy in chronic pain, but the effectiveness of specific medications varies according to the pathophysiology of the painful condition and other factors such as adherence and comorbidities. Knowing which agent is most effective for a given diagnosis can improve treatment.

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Resources in the SPOTLIGHT

INSOMNIA RESOURCES

American Academy of Sleep Medicine (AASM)

The goals of the AASM are to set the clinical standards for the field of sleep medicine, serve as an advocate for recognizing, diagnosing, and treating sleep disorders, educate professionals dedicated to providing optimal sleep health care, and foster the development and application of scientific knowledge.

www.aasmnet.org

American Sleep Association (ASA)

The ASA acts as a complete source for sleep information and communication to people interested in sleep and sleep disorders. The mission of the ASA is to improve sleep health by increasing public awareness about sleep health and sleep disorders. The organization also serves to educate health care providers on the diagnosis and treatment of sleep disorders.

www.americansleepassociation.org

World Sleep Foundation (WSF)

WSF is an educational resource for patients, medical professionals, and the general public, informing them of the latest clinical advances in the management and treatment of sleep disorders. The mission of the WSF includes fostering professional standards among sleep disorder professionals and industry, providing communication among all of those affected by sleep disorders, and stimulating continued research on sleep disorders.

www.worldsleepfoundation.com

CHRONIC PAIN RESOURCES

American Chronic Pain Association (ACPA)

The mission of the ACPA is to raise awareness among the health care community, policy makers, and the public about what it is like living with chronic pain. The resources available on the ACPA web site seek to help improve the quality of lives of individuals suffering from chronic pain as well as the professionals who help them.

www.theacpa.org

The American Academy of Pain Medicine (AAPM)

This medical specialty society is involved in education, training, advocacy, and research in the specialty of pain medicine. The Academy promotes quality care of patients with pain as a symptom of disease and primary pain disease. This academy represents the diverse scope of the pain field through membership from a variety of origins, including such specialties as anesthesiology, internal medicine, neurology, and psychiatry.

www.painmed.org

American Academy of Pain Management (AAPM)

The largest pain organization in the United States, the American Academy of Pain Management provides credentialing, accreditation of facilities, quality publications, and more. The goal of the American Academy of Pain Management is to bring together the professionals who work with individuals in pain and to assist in the creation of quality services for those individuals.

www.aapainmanage.org

PRACTICAL BITS

Quick and Practical Diagnostic Tools from Dr Lieberman

SIG-E CAPS

If a patient has screened positively for depression through the United States Preventive Task Force's Screener, he or she should be further evaluated using the SIG-E CAPS mnemonic. If the physician determines the patient has 5 or more of the symptoms in SIG-E CAPS as well as depressed mood and/or anhedonia, he or she meets the criteria for major depressive disorder.

S: Increased or decreased Sleep or decreased Sexual desire
I: Decreased Interest or pleasure in favorite activities
G: Inappropriate Guilt or feelings of hopelessness or worthlessness
E: Decreased Energy or increased fatigue
C: Decreased Concentration
A: Change in Appetite with weight gain or loss
P: Psychomotor agitation or retardation
S: Suicidal ideation or suicide attempt

Source: Lieberman JA III. The differential diagnosis of fatigue and executive dysfunction in primary care. *J Clin Psychiatry*. 2004;64:40-43.

CYMBALTA®

(duloxetine hydrochloride) Delayed-release Capsules

Brief Summary: Consult the package insert for complete prescribing information.

WARNING

Suicidality in Children and Adolescents—Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be 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. Cymbalta is not approved for use in pediatric patients. (*See* WARNINGS *and* PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

INDICATIONS AND USAGE: Cymbalta is indicated for the: treatment of major depressive disorder (MDD); the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN); treatment of generalized anxiety disorder (GAD).

CONTRAINDICATIONS: ***Hypersensitivity***—Known hypersensitivity to duloxetine or any of the inactive ingredients. ***Monoamine Oxidase Inhibitors (MAOIs)***—Concomitant use with Cymbalta is contraindicated (*see* WARNINGS). ***Uncontrolled Narrow-Angle Glaucoma***—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use is not recommended in patients with uncontrolled narrow-angle glaucoma.

WARNINGS: Clinical Worsening and Suicide Risk—Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, ie, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be 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. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (*see* PRECAUTIONS, Discontinuation of Treatment with Cymbalta).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder—A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta is not approved for use in treating bipolar depression.

MAOIs—In patients receiving a serotonin reuptake inhibitor (SSRI) in combination with an 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 SSRIs and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Cymbalta and MAOIs have not been evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

Serotonin Syndrome—The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea).

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated (*see* CONTRAINDICATIONS *and* WARNINGS, Potential for Interaction with MAOIs).

If concomitant treatment of Cymbalta 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* PRECAUTIONS, Drug Interactions).

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended (*see* PRECAUTIONS, Drug Interactions).

PRECAUTIONS: ***General***—Hepatotoxicity—Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) of placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, elevation of ALT > 3 times the upper limit of normal occurred in 1% (39/3732) of Cymbalta-treated patients compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively. Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease. Orthostatic Hypotension and Syncope—Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors (*see* CLINICAL PHARMACOLOGY, Drug-Drug Interactions, *and* PRECAUTIONS, Drug Interactions) and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy. Effect on Blood Pressure—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg BID. At the highest 200 mg BID dose, the increase in mean pulse rate was 5.0-6.8 bpm and increases in mean blood pressure were 4.7-6.8 mm Hg (systolic) and 4.5-7 mm Hg (diastolic) up to 12 hours after dosing. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes). Activation of Mania/Hypomania—In placebo-controlled trials in patients with MDD, activation of mania or hypomania was reported in 0.1% (2/2327) of duloxetine-treated patients and 0.1% (1/1460) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP or GAD placebo-controlled trials. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of MDD. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania. Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.04% (3/8504) of patients treated with duloxetine and 0.02% (1/6123) of placebo-treated patients. Cymbalta should be prescribed with care in patients with a history of a seizure disorder. Hyponatremia—Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported and appeared to be reversible when Cymbalta was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted. Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma (*see* CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma). Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in placebo-controlled clinical trials of up to 10 weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in either the MDD or GAD Cymbalta-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, 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 Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics). Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta and by 0.2% in the routine care groups. Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis). For this reason, Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients.

Laboratory Tests—No specific laboratory tests are recommended.

Drug Interactions—*Potential for Other Drugs to Affect Cymbalta*—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism. Inhibitors of CYP1A2—Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided. Inhibitors of CYP2D6—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (eg, fluoxetine, quinidine). *Potential for Duloxetine to Affect Other Drugs*—Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates. Drugs Metabolized by CYP2D6—Cymbalta is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (eg, propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered. Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity.

Cymbalta May Have a Clinically Important Interaction with the Following Other Drugs—Alcohol—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol. In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen (*see* PRECAUTIONS, Hepatotoxicity). CNS-Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action. Serotonergic Drugs—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta and the potential for serotonin syndrome, caution is advised when Cymbalta is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (*see* WARNINGS, Serotonin Syndrome). The concomitant use of Cymbalta with other SSRIs, SNRIs, or tryptophan is not recommended (*see* PRECAUTIONS, Drug Interactions). Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* WARNINGS, Serotonin Syndrome). Potential for Interaction with Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution

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is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Monoamine Oxidase Inhibitors—*See* CONTRAINDICATIONS *and* WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis). In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors. Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*. Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at daily doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

Pregnancy—Pregnancy Category C—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development. When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rats; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and =1 times the human dose of 120 mg/day on a mg/m^2 basis in rats; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits). When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

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

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (*see* WARNINGS, Monoamine Oxidase Inhibitors). When treating a pregnant woman with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended.

Pediatric Use—Safety and effectiveness in the pediatric population have not been established (*see* BOX WARNING *and* WARNINGS, Clinical Worsening *and* Suicide Risk). Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN premarketing studies, 33% (357) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPN studies, 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. As with other antidepressants, Cymbalta has been associated with cases of clinically significant hyponatremia (*see* Hyponatremia, *under* PRECAUTIONS).

ADVERSE REACTIONS: Cymbalta has been evaluated for safety in 2418 patients diagnosed with MDD who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 Cymbalta-treated patients, 1139 patients participated in eight 8 or 9 week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated patients were exposed for at least 180 days and 445 Cymbalta-treated patients were exposed for at least 1 year. Cymbalta has also been evaluated for safety in 1074 patients with diabetic peripheral neuropathy representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated patients, 568 patients participated in two 12 to 13 week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with placebo, were exposed to Cymbalta for up to 12 months at 60 mg twice daily in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had 12 months of exposure.

Cymbalta has also been evaluated for safety in 668 patients with GAD representing 95 patient-years of exposure. These 668 patients participated in 9- or 10-week placebo-controlled trials at doses ranging from 60 to 120 mg once daily. Of these 668 patients, 449 were exposed for at least 2 months to Cymbalta.

In the full cohort of placebo-controlled clinical trials for any indication, safety has been evaluated in 8504 patients treated with duloxetine and 6123 patients treated with placebo. In clinical trials, a total of 23,983 patients have been exposed to duloxetine. In duloxetine clinical trials, adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping similar types of events into a smaller number of standardized event categories is necessary. MedDRA terminology was 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 receiving therapy following baseline evaluation. Events reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 10% of the 1139 patients who received Cymbalta in the MDD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (Cymbalta 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo). Diabetic Peripheral Neuropathic Pain—Approximately 14% of the 568 patients who received Cymbalta in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients receiving placebo. Nausea (Cymbalta 3.5%, placebo 0.4%), dizziness (Cymbalta 1.6%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0%) and fatigue (Cymbalta 1.1%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo). Generalized Anxiety Disorder—Approximately 16% of the 668 patients who received Cymbalta in the GAD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 495 patients receiving placebo. Nausea (Cymbalta 3.7%, placebo 0.2%), vomiting (Cymbalta 1.4%, placebo 0%), and dizziness (Cymbalta 1.2%, placebo 0.2%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials—Major Depressive Disorder—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of MDD placebo-controlled trials (N=1139 Cymbalta; N=777 placebo) with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, vomiting; Metabolism and Nutrition Disorders—appetite decreased (includes anorexia); Investigations—weight decreased; General Disorders and Administration Site Conditions—fatigue; Nervous System Disorders—dizziness, somnolence, tremors; Skin and Subcutaneous Tissue Disorders—sweating increased; Vascular Disorders—hot flushes; Eye Disorders—vision blurred; Psychiatric Disorders—insomnia (includes middle insomnia), anxiety, libido decreased, orgasm abnormal (includes anorgasmia); Reproductive System and Breast Disorders—males only: erectile dysfunction, ejaculation delayed, ejaculatory dysfunction (includes ejaculation disorder and ejaculation failure).

The following events were reported by at least 2% of patients treated with Cymbalta for MDD and had an incidence Òplacebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.

The most commonly observed adverse events in Cymbalta-treated MDD patients (incidence Õ5% and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating.

Diabetic Peripheral Neuropathic Pain—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPN placebo-controlled trials (N=225 Cymbalta 60 mg BID; N=228 Cymbalta 60 mg QD; N=115 Cymbalta 20 mg QD; N=223 placebo) with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, constipation, diarrhea, dry mouth, vomiting, dyspepsia, loose stools; General Disorders and Administration Site Conditions—fatigue, asthenia, pyrexia; Infections and Infestations—nasopharyngitis; Metabolism and Nutrition Disorders—decreased appetite, anorexia; Musculoskeletal and Connective Tissue Disorders—muscle cramp, myalgia; Nervous System Disorders—somnolence, headache, dizziness, tremor; Psychiatric Disorders—insomnia; Renal and Urinary Disorders—pollakiuria; Reproductive System and Breast Disorders—erectile dysfunction; Respiratory, Thoracic and Mediastinal Disorders—cough, pharyngolaryngeal pain; Skin and Subcutaneous Tissue Disorders—hyperhidrosis.

The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence Òplacebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence Õ5% and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia.

Generalized Anxiety Disorder—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of GAD placebo-controlled trials (doses of 60-120 mg once daily) (N=668 Cymbalta; N=495 placebo) and with an incidence greater than placebo were: Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, vomiting, abdominal pain, dyspepsia; General Disorders and Administration Site Conditions—fatigue; Metabolism and Nutrition Disorders—appetite decreased; Nervous System Disorders—dizziness, somnolence, tremor, paraesthesia; Psychiatric Disorders—insomnia, libido decreased, agitation, orgasm abnormal; Reproductive System and Breast Disorders—ejaculation delayed, erectile dysfunction; Respiratory, Thoracic and Mediastinal Disorders—yawning; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—hot flushes.

The following events were reported by at least 2% of patients treated with Cymbalta for GAD and had an incidence Òplacebo: nasopharyngitis, upper respiratory tract infection, headache, pollakiuria, and musculoskeletal pain (includes myalgia, neck pain).

The most commonly observed adverse events in Cymbalta-treated GAD patients (incidence Õ5% and at least twice the incidence in placebo patients) were: nausea; fatigue; dry mouth; somnolence; constipation; insomnia; appetite decreased; hyperhidrosis; libido decreased; vomiting; ejaculation delayed; and erectile dysfunction.

Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of Cymbalta did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from Caucasian patients.

Effects on Male and Female Sexual Function—Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Sexual side effects spontaneously reported by at least 2% of either male or female patients taking Cymbalta in MDD placebo-controlled trials were: Males (N=378 Cymbalta; N=247 placebo): orgasm abnormal (includes anorgasmia), ejaculatory dysfunction (includes ejaculation disorder and ejaculation failure), libido decreased, erectile dysfunction, ejaculation delayed. Females (N=761 Cymbalta; N=530 placebo): orgasm abnormal, libido decreased.

Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that there is no evidence that its effects differ from other antidepressants. Physicians should routinely inquire about possible sexual side effects. See Table 5 in full PI for specific ASEX results.

Urinary Hesitation—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related. ***Laboratory Changes***—Cymbalta treatment, for up to 9 weeks in MDD, 9-10 weeks in GAD, or 13 weeks in DPN placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients (*see* PRECAUTIONS). ***Vital Sign Changes***—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure, averaging up to 2 mm Hg. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure (*see* PRECAUTIONS). Duloxetine treatment, for up to 13 weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3 beats per minute. ***Weight Changes***—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13 weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. ***Electrocardiogram Changes***—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13 weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg BID, no prolongation of the corrected QT interval was observed.

Postmarketing Spontaneous Reports—Adverse events reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, hallucinations, hypersensitivity, hypertensive crisis, rash, Stevens-Johnson Syndrome, supraventricular arrhythmia, trismus, and urticaria.

DRUG ABUSE AND DEPENDENCE: ***Controlled Substance Class***—Duloxetine is not a controlled substance. ***Physical and Psychological Dependence***—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE: There is limited clinical experience with Cymbalta overdose in humans. In premarketing clinical trials, cases of acute ingestions up to 1400 mg, alone or in combination with other drugs, were reported with none being fatal. Postmarketing experience includes reports of overdoses, alone or in combination with other drugs, with duloxetine doses of almost 2000 mg. Fatalities have been very rarely reported, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed drugs) included serotonin syndrome, somnolence, vomiting, and seizures. ***Management of Overdose***—There is no specific antidote to Cymbalta, 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.

Literature revised March 1, 2007

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Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules PV 5901 AMP

Treat the symptoms of depression your patients talk about, and those they don't. Many times, patients don't mention some of their symptoms because they don't realize they are related. That's where Cymbalta can help. Cymbalta treats the emotional, anxious, and painful somatic symptoms of depression.[1a-c,2*] To learn more about treating beyond the obvious, visit www.insidecymbalta.com

*Cymbalta 60 mg/day vs placebo ($P \leq .05$) by MMRM for major depressive disorder on mean change in HAM-D_{17} Total Score, Maier Subscale, Psychic Anxiety, and Visual Analog Scale. Full antidepressant response may take 4-6 weeks.
MMRM=Mixed-effects Models Repeated Measures analysis

References: 1. Data on file, Lilly Research Laboratories:
a: CYM20060101A; b: CYM20060101B; c: CYM20050315S.
2. Fava M, et al. *J Clin Psychiatry*. 2004;65(4):521-530.

treat beyond the obvious

Cymbalta® duloxetine HCl DELAYED RELEASE CAPSULES

Important Safety Information

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.**
- **Patients started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.**
- **Cymbalta is not approved for use in pediatric patients.**

Cymbalta should not be used concomitantly with monoamine oxidase inhibitors (MAOIs) or thioridazine and not in patients with a known hypersensitivity or with uncontrolled narrow-angle glaucoma.

Clinical worsening and suicide risk: All adult and pediatric patients being treated with an antidepressant for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially when initiating drug therapy and when increasing or decreasing the dose. A health professional should be immediately notified if the depression is persistently worse or there are symptoms that are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication.

Development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs, including triptans. Concomitant use is not recommended.

Cymbalta should not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (CrCl <30 mL/min).

Postmarketing, severe elevations of liver enzymes or liver injury with a hepatocellular, cholestatic, or mixed pattern have been reported.

Cymbalta should generally not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Cases of orthostatic hypotension and/or syncope as well as cases of hyponatremia have been reported.

As observed in DPNP clinical trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases up to 52 weeks, an increase in HbA_{1c} in both the Cymbalta (0.5%) and routine care groups (0.2%) was noted.

Most common adverse events (≥5% and at least twice placebo) in premarketing clinical trials were:

MDD: nausea, dry mouth, constipation, fatigue, decreased appetite, somnolence, and increased sweating. **DPNP:** nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia. **GAD:** nausea, fatigue, dry mouth, somnolence, constipation, insomnia, appetite decreased, increased sweating, libido decreased, vomiting, ejaculation delayed, and erectile dysfunction.

See Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent page.

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