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for Primary Care Physicians

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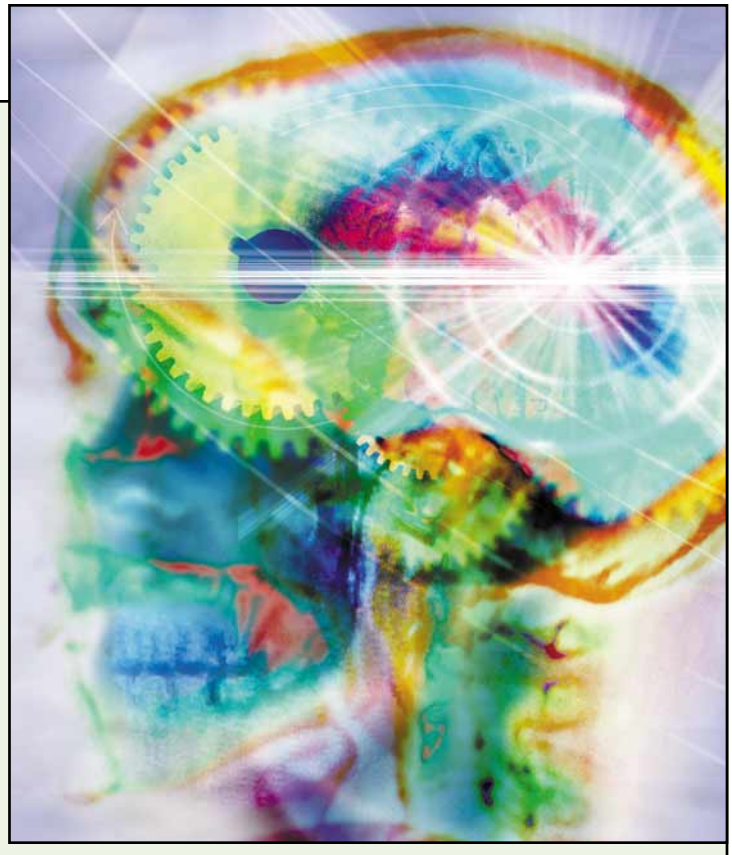

Special Populations in Depression
Recognizing and Managing Depression in Women

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Management of Disabling Migraine Episodes

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Point of View
Challenges in Primary Care Persist Over Time

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Case Files

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

Start and stay with nonscheduled Rozerem—ZERO evidence of abuse or dependence

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

- **First and only**—nonscheduled prescription insomnia medication... not a controlled substance and approved 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]
- **Promote sleep with Rozerem**—patients who took Rozerem fell asleep faster than those who took placebo[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
05-1114

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 inter-subject 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-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-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 postnatal 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
Five 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

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

Marketed by:
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Lincolnshire, IL 60069

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 PI02-0002-1

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 side effects. *Arch Gen Psychiatry.* In press.

Practical Neuroscience
for Primary Care Physicians

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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 Publisher

Welcome to the inaugural issue of *Practical Neuroscience for Primary Care Physicians*, a supplement series created as a practical resource for primary care physicians. The publishers of *Family Practice News* and *Internal Medicine News* have developed this special quarterly series to address neuropsychosocial disorders. We hope that Elsevier's proven success in providing high-quality news and information in primary care medicine and psychiatry will make this new quarterly series for 2007 an immediately useful tool.

Each issue will feature in-depth articles, case studies, and columns presented by thought leaders in the field covering topics such as depression and anxiety, headache, insomnia, and pain management.

In this issue, **Larry Culpepper, MD, MPH**, Professor and Chairman of Family Medicine, Boston University School of Medicine; Chief of Family Medicine, Boston Medical Center, Boston, Massachusetts; and guest editor of the series, will kick off the "Special Populations in Depression" series by focusing on depression in women. **Carolyn Bernstein, MD**, Assistant Professor of Neurology, Cambridge Hospital, Harvard Medical School, Boston, Massachusetts, will offer her experience with treating disabling migraine. **William Clay Jackson, MD, DipTh**, a practicing physician in family medicine and palliative medicine in Memphis, Tennessee, comments on the challenges in primary care. In our "Case Files" section, **Joseph A. Lieberman III, MD, MPH**, Associate Editor, *Delaware Medical Journal*, Professor of Family Medicine, Jefferson Medical College, Hockessin, Delaware, shares case studies of depression/insomnia and chronic pain/anxiety/insomnia.

Look for future supplements in the June, September, and December issues of *Family Practice News* and *Internal Medicine News*. Each will include an installment of our "Special Populations in Depression" series and will focus on seniors, men, and minority populations, respectively. Upcoming topics also will include chronic pain and physical activity, addiction, managing anxiety disorders, smoking cessation, bipolar illness, and much more. You can also access the supplement series online at www.familypracticenews.com, www.internalmedicinenews.com, or www.practicalneuroscience.com. Our online presence gives you the opportunity to offer feedback or even submit a case study of your own.

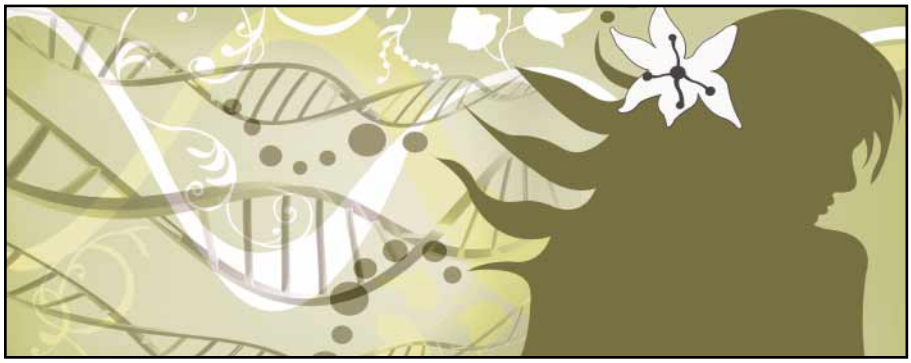
We hope you will join us as our readers and participants in this new series.

Cordially,

Alan J. Imhoff
Publisher and President
Elsevier/IMNG

Larry Culpepper, MD, MPH, Guest Editor

Recognizing and Managing Depression in Women



At any given time in the United States, about 19 million adults have clinical depression.[1] Many, if not most, of these patients initially present to primary care physicians. An estimated 10% of patients who are seen by primary care physicians have depression. However, 65% to 70% of those cases go unrecognized, an average of about six cases per week in the typical primary care practice.[2] Appropriate treatment can alleviate depression in 80% to 90% of patients, but because the condition often goes unrecognized, depression adversely affects the lives of millions of people. According to the World Health Organization, depression currently ranks as the fourth most disabling disease and is expected to rise to second by 2020.[3] Depression disproportionately affects women; the incidence and prevalence of depression among women are about double those of men.[4] A combination of artifactual factors (increased symptom reporting by women and a possible diagnostic bias), biological factors, and psychosocial factors probably contributes to the gender disparity in the epidemiology of depression.[5] Busy primary care physicians can easily incorporate a simple screen for depression into the routine care of female patients and identify those patients that require a more detailed workup for depression. Once recognized, patients with clinical depression can begin appropriate treatment, which has a high likelihood of success.

Diagnosing Depression

Assessment Tools

Primary care physicians can incorporate screening for depression into every patient's periodic health assessment. An affirmative response to either of two questions can identify with a high degree of confidence those patients who require a more thorough evaluation for depression:[6]

1. Over the past 2 weeks have you felt down or hopeless?
2. Over the past 2 weeks have you felt little interest in doing things?

Several diagnostic instruments are available to evaluate patients identified by the initial screening assessment. In my own practice, I use the Patient Health Questionnaire 9, a nine-item, self-administered evaluation that poses one additional question to explore the impact of depression if a patient checks any of the nine items.[7]

Gender Differences

Men and women differ in several respects with regard to the presentation of depression.

Kornstein et al[8] found that women are more likely to have reverse vegetative symptoms (weight gain, hypersomnia), comorbid anxiety or eating disorders, association with interpersonal stressors, seasonal effect on mood, and possibly a greater risk of chronicity and recurrence.

Women are less likely than men to have comorbid substance abuse problems and associations with work stressors. Additionally, more women attempt suicide but are less likely than men to be successful.[8,9]

Women may have hormonal triggers to depressive episodes related to reproductive events. During the menstrual cycle, some women have premenstrual depressive symptoms, which comprise premenstrual syndrome (PMS); premenstrual dysphoric disorder (PMDD, a severe form of PMS); and premenstrual exacerbation of depression.[10-12] Women affected by premenstrual emotional symptoms may have underlying depression. For example, one study showed that almost 40% of women complaining of premenstrual emotional symptoms had evidence of depression, anxiety, and comorbid depression and anxiety.[12]

Some women also have premenstrual exacerbation of underlying depression.[13-15] The exacerbation differs from PMS and PMDD in that symptoms persist during the follicular phase of the menstrual cycle, whereas PMS and PMDD symptoms are present only during the luteal phase. A host of psychiatric and medical symptoms can worsen during the premenstrual

Depression disproportionately affects women; the incidence and prevalence of depression among women are about double those of men.

HORMONAL TRIGGERS OF DEPRESSION

Depression in women may be related to the various reproductive events in their lives.

- Menstrual cycle
  - Premenstrual syndrome
  - Premenstrual dysphoric disorder
  - Premenstrual exacerbation of depression
- Pregnancy
- Postpartum
- Perimenopausal
- Transition between perimenopause and menopause

period, including anxiety, eating disorders, substance abuse, seizures, migraine, pain disorders, and asthma. One study of chronically depressed premenopausal women showed that 60% had worsening of mood depression at some point in the menstrual cycle.[16] Specific symptoms affected by the menstrual cycle included depressive symptoms, anxiety, irritability, and mood lability.

Pregnant and postpartum women represent a special population with an increased risk for depression. About 5% of middle class women and as many as 25% of low income women experience postpartum depression.[17] In about half the cases, the onset of depressive symptoms occurs before delivery.[18] Women with a history of postpartum depression are at especially high risk for developing the condition again, as are those with a history of PMDD or depression unrelated to pregnancy.

The perimenopausal period offers another time when women have an increased risk for new-onset depression or relapse. In a study of 231 perimenopausal women followed for 8 years, 59 (25.5%) women developed major depression during follow-up, and half of those presented with significant depressive symptoms.[19] Laboratory data showed that estradiol levels did not predict depression, but the degree of fluctuation in the hormone did. The authors concluded that women in the transition period between perimenopause and menopause have a fivefold increased risk of depression.

Treatment of Major Depression

Goals

Depression is a chronic condition requiring chronic treatment, analogous to other chronic conditions, such as diabetes and arthritis, commonly seen in primary care practices. Treatment goals and strategies can be separated into acute, continuation, and maintenance phases.[20] During the first 6 to 12 weeks of treatment (acute phase), the goals are to achieve a response and then a remission. From 4 to 9 months, the goal is to prevent relapse (continuation phase). Maintenance therapy (which continues for at least a year) focuses on preventing recurrence. Guidelines developed by the Agency for Health Care Policy and Research and by the American Psychiatric Association specify remission as the principal treatment goal for clinically depressed patients.[21,22]

Four principal outcomes characterize the possible results of treatment for depression: response, remission, relapse, and recurrence.[21,23]

Strategy

Acute management of major depression in the primary care setting comprises patient education, shared decision making, supportive counseling, and treatment-specific counseling.[24] Education helps patients understand and accept the diagnosis, reduces any stigmas that they might associate with the condition, and helps increase patient compliance with treatment. Many patients benefit from counseling related to sleep, exercise, and substance abuse. For some patients, counseling by a primary care physician or by referral may be a useful treatment adjunct. Depressed patients often have deficient coping mechanisms and need assistance in resolving issues in their lives. Shared decision making with regard to treatment will improve patient adherence.[25]

Psychotherapy

Cognitive behavioral therapy is possibly the best evaluated psychotherapeutic technique in the treatment of depression. Psychotherapy is effective by itself or as an adjunct or augmentation to pharmacotherapy. Psychotherapy is as effective as pharmacotherapy, but the response to psychotherapy usually lags behind that of drug treatment by a month or 6 weeks.[26] Primary care practitioners should be aware of the psychotherapy resources available for referral of patients. Clinicians who frequently treat depression might consider developing referral relationships with one or more counselors.

Pharmacotherapy

For most clinically depressed patients, pharmacotherapy is the treatment of choice because of its more rapid onset of action than that of other forms of treatment. In the primary care setting, first-line pharmacotherapy for depression almost always centers on the selective serotonin reuptake inhibitors (SSRIs) and the selective norepinephrine reuptake inhibitors (SNRIs).

Drugs in the SSRI and SNRI classes have similar efficacy but differ to some extent in their side-effect profiles. An individual patient may respond better to one drug than another or find one drug more tolerable than another in the same class. Lack of response with one drug in a class should not discourage a trial of a similar drug. In choosing a specific antidepressant agent, a primary care physician should be guided by his or her professional experience with individual drugs. Additionally, a patient with prior exposure to antidepressant therapy might have a preference for a specific drug.

About 25% of patients discontinue antidepressant therapy because of side effects,[27] so the issue is not inconsequential. Potential adverse effects with SSRIs and SNRIs include gastrointestinal effects (particularly nausea) and central nervous system effects, including anxiety, agitation, sleep disturbance, and tremor. When these effects occur, they usually disappear within 1 to 3 weeks. The effects sometimes can be minimized by changing the time of administration or temporarily decreasing the dose.[24]

Long-term side-effect issues with SSRIs and SNRIs consist primarily of weight gain and sexual dysfunction. The effects differ among various agents. For example, paroxetine appears more likely to be associated with significant weight gain than other SSRIs.[28] Sexual side effects (which include delayed orgasm) might be minimized by delaying the dosage of long-acting agents, such as escitalopram, citalopram, and sertraline.[29] Another option would be to switch a patient to an atypical agent such as bupropion, which has been reported to cause fewer sexual side effects than SSRIs.[30]

PHASES OF TREATMENT GOALS AND STRATEGIES[20]

Goals and strategies for treating depression can be separated into three phases: acute, continuation, and maintenance.

PHASE	TIME PERIOD	GOAL
Acute	First 6 to 12 weeks of treatment	Achieve a response and then remission
Continuation	4 to 9 months	Prevent relapse
Maintenance	Continues for at least 1 year	Prevent recurrence

Treatment Duration

As previously stated, depression is a chronic condition that requires chronic treatment. For a first lifetime episode of depression, treatment should continue for 6 to 9 months.[31] Longer duration of therapy might be required for patients with complicating issues: comorbid anxiety, severe initial symptoms, difficulty attaining a response, deficient social support, or comorbid substance abuse. Patients with a history of three or more episodes of depression should receive long-term maintenance therapy.[31]

Unfortunately, the goal of treatment remission often is complicated by poor patient adherence. As many as 33% of patients in primary care discontinue antidepressant therapy within 1 month of starting, and more than 40% discontinue within 3 months. More than 60% of the patients who stop therapy do not inform their physicians of the decision.[32]

Several practice management strategies have demonstrated potential for improving medication adherence in patients being treated for depression. Most of the strategies share the common approach of active management (such as regular follow-up by telephone) to promote adherence.[24]

Referral

Primary care physicians should not hesitate to refer patients to a mental health specialist whenever the need arises. The need for referral may arise in a variety of ways: uncertainty about the diagnosis, patients with complicating circumstances such as comorbid substance abuse, concern that a patient might have bipolar disorder instead of unipolar depression, or reluctance on the patient's part to accept the diagnosis or enter into treatment. Additionally, a consult with a psychotherapist might be considered before referring a patient for cognitive-behavioral therapy or another form of psychotherapy.

Summary

Depression is a common condition in the primary care setting. Primary care practitioners should incorporate a brief screening for clinical depression into each patient's periodic health assessment. Women present special considerations in the diagnosis and management of depression, including different clinical presentations compared to men and hormonal issues that can affect the frequency, nature, and severity of symptoms associated with depression. Effective treatment is available for management of depression in primary care. Primary care practitioners should strive to form a partnership with the patient to achieve the treatment goal of remission, which is possible in a high percentage of patients.

Dr Culpepper has disclosed that he is a consultant to Eli Lilly and Company, Forest Laboratories, Inc, Pfizer Inc, and Wyeth.

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CASE FILES

Joseph A. Lieberman III, MD, MPH

Clinical Case: Man With Insomnia and Depression

Presentation

J.M. is a 39-year-old firefighter who came to the office at the insistence of his wife. His principal complaint was worsening sleep problems over the past year. He often has difficulty falling asleep, and then he wakes up repeatedly. As a result, he feels chronically fatigued at work and fears that he is no longer a useful member of his firefighting crew. The patient also worries about his lack of motivation for doing things with his family. When he is not working, he would rather watch television than do anything else. He denies any history of a psychiatric disorder.

Initial Evaluation

J.M. is 5'10" tall and weighs 180 lb. His vital signs include a pulse of 70 bpm, respiration of 20, temperature of 98.6°F, and blood pressure of 132/84 mm Hg. A pain assessment reveals a rating of 0 on a scale of 0 to 10. His physical examination reveals a well-developed, well-nourished white man in no acute distress, appearing his stated age, and with no significant physical findings.

Psychosocial Assessment

The patient's history and physical examination lead to a preliminary diagnosis of major depressive disorder/dysthymia with comorbid insomnia. A psychosocial assessment is performed, using the BATHE technique:

Background: "What else is going on in your life?"
Patient response: "Nothing else."

Affect: "How do you feel about that?"
Patient response: "Lousy. I don't like feeling this way. I'd like a good night's sleep and some energy."

Trouble: "What's troubling you the most?"
Patient response: "My wife, kids, and coworkers are all unhappy with me."

Handling: "How are you handling this?"
Patient response: "Not well. I'm short-tempered, irritable, and not nice to be around."

Empathy: Tell the patient that this must be difficult, and you want to work with him to resolve the problem.

A reliable, two-question screen for major depressive disorder complements the information gained with the BATHE technique.

1. During the past 2 weeks, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past 2 weeks, have you often been bothered by having little interest or pleasure in doing things?

The patient has a positive screen for depression. His symptoms are further evaluated by means of the SIG-E CAPS mnemonic for major depressive disorder.

S: Increased or decreased sleep and decreased sexual desire
(Patient acknowledges decreased sleep.)

I: Decreased interest or pleasure in almost all activities
(Patient acknowledges decreased interest and pleasure.)

G: Inappropriate guilt or feeling of worthlessness/hopelessness
(Patient acknowledges feelings of worthlessness/hopelessness.)

E: Decreased energy or fatigue
(Patient acknowledges decreased energy and fatigue.)

C: Decreased concentration
(Patient acknowledges decreased concentration.)

A: Increased or decreased appetite with weight gain or loss
(Patient denies any change in appetite or weight.)

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

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

By this assessment, the criteria for major depression are five or more positive symptoms (at least one of which must be depressed mood or anhedonia) for at least 2 weeks, which represent a change from previous behavior. This patient meets the criteria. The psychosocial evaluation continues with inquiry about his alcohol intake and history of drug use. He admits to drinking an occasional beer (his CAGE questionnaire – a screening test for alcohol dependence – was negative), and he denies use of any other drugs. He also denies any other psychiatric symptoms, such as excessive worrying, mania, or hypomania.

On the basis of the information elicited, the patient's diagnosis is major depressive disorder with comorbid insomnia.

Management Plan

The patient starts a graduated exercise program, receives instruction in the principles of good sleep hygiene, and initiates drug therapy with a selective serotonin reuptake inhibitor and a hypnotic medication. Concomitant treatment of the depression and sleep disturbance is essential because treating one condition does not guarantee improvement in the other. These conditions are truly comorbid, and, therefore, optimal management mandates addressing both of these problems simultaneously. He was seen in clinic or contacted weekly and his progress monitored. His sleep improved immediately, but his symptoms of depression took 6 weeks to totally resolve. Because this was his first episode of major depressive disorder, he should continue antidepressant therapy for at least a year. His hypnotic medication can be discontinued sooner, as long as he remains asymptomatic.

Clinical Case: Woman With Chronic Pain, Anxiety, and Insomnia

Presentation

S.M., a 40-year-old housewife, was seen in the office following her husband's work-related relocation. She has two young children and claims, "Everything would be fine if I were free of my severe, chronic pain and could get some sleep." The pain and associated debility have gotten progressively worse since a relatively innocuous onset approximately 2 years ago.

The patient has been diagnosed as having fibromyalgia and treated with a variety of agents for the past year with mixed results. Her treatment began with nonsteroidal anti-inflammatory agents, an exercise program, and a tricyclic antidepressant. The antidepressant provided some symptom relief but caused nightmares, so the patient discontinued it.

The patient's major symptoms are persistent fatigue, pain "all over" (7 on a 0 to 10 scale), and insomnia. She says "I'm jittery as a cat on a hot tin roof." She denies headaches, facial pain, changes in bowel habits, dysmenorrhea, irritable bladder, and heightened sensitivity to odors, bright lights, or noise, although she does get "car sick" very easily.

Initial Evaluation

The patient is 5'6" tall and weighs 138 lb. Her vital signs include a pulse of 64 bpm, respiration of 18, temperature of 98.4°F, and blood pressure of 110/70 mm Hg. Physical examination reveals a well-developed, well-nourished woman, appearing her stated age, and in no acute distress, but claiming moderate to severe pain in response to even light touch on most areas of her body. She is particularly sensitive to pressure to the back of her head, upper back and neck, upper chest, elbows, hips, and knees. She also demonstrates a mild nonexudative pharyngitis and some cervical/axillary adenopathy. The remainder of her examination is unremarkable.

Initial Assessment

The preliminary diagnosis is fibromyalgia, insomnia, and possible anxiety/depressive disorder. To better clarify her psychosocial status, the BATHE technique was employed.

Background: "What is going on in your life?"
Patient response: "A lot of chaos, with the move, my husband's new job, finding a school for the kids. These have been made worse by my chronic pain, poor sleep, and bad nerves."

Affect: "How do you feel about that?"
Patient response: "Terrible! I'm in pain all of the time, can't sleep, and just stressed out by everything."

Trouble: "What's troubling you the most?"
Patient response: "My lack of sleep. If I could get a good night's sleep, the other things may be easier to deal with."

Handling: "How are you handling this?"
Patient response: "Not well. I yell at the kids, snap at my husband; we both decided that I should see a doctor."

Empathy: Tell the patient that, under the circumstances, it must be very difficult.

Because the patient has multiple symptoms associated with some degree of psychodynamic dysfunction, you employ screening instruments to better define the nature of her problem.

The United States Preventive Services Task Force has endorsed a simple, two-question screen for depression.

1. During the past 2 weeks, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past 2 weeks, have you often been bothered by having little interest or pleasure in doing things?

An affirmative answer to one or both questions is a positive screen for depression. The patient denies both sets of symptoms, stating she is more anxious than depressed. She adds that her "bad nerves and poor sleep" predated the onset of her fibromyalgia symptoms, but the chronic pain has made these preexisting problems much worse.

Her psychiatric symptoms appear consistent with a diagnosis of generalized anxiety disorder (GAD). A handy mnemonic can help recall of GAD symptoms: SWICKIR, the "quicker" way to identify GAD.

Somatic symptoms and fatigue.
Patient response: "I am tired all the time despite being jittery and jumpy."

Worry. Excessive or difficult-to-control anxiety.
Patient response: "That describes me perfectly."

Irritability.
Patient response: "That was one of the reasons my husband encouraged me to come to the office."

Concentration or memory difficulties.
Patient response: "I can't concentrate on anything, and I'd forget my head if it wasn't sewn on."

Keyed up or on edge.
Patient response: "Like a cat on a hot tin roof!"

Insomnia.
Patient response: "I have trouble with sleep, ie, difficulty falling asleep, staying asleep, waking too early in the morning and not being able to go back to sleep, and then getting up feeling like I haven't slept at all."

Restlessness.
Patient response: "I can't sit still, even though I feel too tired to get up."

The combination of worry and three other symptoms, present more days than not and of at least 6 months' duration, satisfy DSM-IV criteria for a diagnosis of GAD. On the basis of the information gathered during the assessment, the diagnosis is fibromyalgia/insomnia/GAD.

Treatment Plan

The patient was told that she has multiple problems with three major diagnoses. Though complex, these problems generally are amenable to therapy. Treatment might take some time to produce results, but the outlook is good for significant relief from her multiple symptoms.

A multifaceted approach is used. The patient receives instruction in the principles of good sleep hygiene, begins a water aerobics program, has occasional physical therapy sessions, and participates in cognitive-behavioral and relaxation training programs. She also begins pharmacotherapy with a sedative/hypnotic (short term), a selective serotonin reuptake inhibitor, calcium and magnesium supplements, a high-potency multivitamin, and a prn analgesic.

The patient experiences almost immediate relief of insomnia symptoms, making her other symptoms more bearable. Over the next month or two, she has a gradual but perceptible improvement in all of her symptoms. She likely will require long-term therapy, but the overall outlook is fair to good for a reasonable response and return to her premorbid level of functioning.

See page 17, Practical Bits, for an explanation of BATHE and SWICKIR.

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Management of Disabling Migraine Episodes

Headache is one of the most common complaints of patients presenting to physicians' offices.[1] Headache can arise from multiple potential causes, making a careful history and physical examination essential for accurate diagnosis. Migraine headaches differ dramatically from the more common tension headaches. In particular, migraines are associated with excruciating, even debilitating, pain. In recent years, multiple therapeutic options have emerged for the treatment of migraine, including pharmacologic and nonpharmacologic interventions. Myriad options afford clinicians the opportunity to tailor therapy to the individual clinical and personal characteristics of each migraine patient. Effective treatment of migraine requires a clinician-patient partnership based on mutual trust and respect.

Differential Diagnosis

The differential diagnosis of migraine begins with determining the classification of a patient's headache as primary or secondary. Primary headache comprises migraine and tension headaches, whereas secondary headaches arise from other conditions, such as sinus problems, subarachnoid hemorrhage, and tumors. Conducting a medical history that includes several key questions can provide substantial guidance regarding the primary or secondary nature of a headache. These questions can elicit a clinical context surrounding the headache's origin and nature.

The differential should be structured to rule out secondary causes, which include some life-threatening conditions. Pain, tenderness, or pressure in sinuses suggests an upper respiratory infection, sinus congestion, or other infection. A patient's dental history also can reveal important clues, such as a history of teeth grinding, jaw clenching, pain when chewing food, or poor jaw alignment. Each of those conditions can be associated with headache.

Headache related to tumors has certain characteristics that can aid in the diagnostic workup. Focal neurologic findings, a headache that usually occurs in the morning, and head pain associated with body movement (such as rising from bed or bending over) all suggest the possibility of a tumor.

Look for clinical red flags that point to a serious acute medical problem that requires immediate attention, such as, most notably, subarachnoid hemorrhage. Examples include sudden-onset headache that a patient describes as being like a thunderclap or a "new and different" kind of headache or the "worst headache of my life," evidence of focal neurologic deficits, loss of consciousness, and seizures. Patients whose headaches are associated with any of these signs and symptoms should go immediately to an emergency room.

If the workup rules out a secondary cause for a patient's headache, the differential diagnosis should then focus on determining whether the patient has a migraine or tension headache. In most instances, characteristics of the headache can point to the correct diagnosis. The term "migraine" has its origin in the Greek word hemicrania, meaning pain on one side of the head. Migraine presents as throbbing unilateral pain that lasts 4 to 72 hours.[2] The headache may be associated with an aura. Migraine often is accompanied by nausea, vomiting, photophobia, and phonophobia. Importantly, the patient has a history of at least one similar headache.

In contrast to migraine, a tension headache tends to be associated with global pain that patients usually describe as aching or squeezing. The time frame and duration may vary. Tension headaches are not associated with an aura, nausea or vomiting, or focal features. Photophobia and phonophobia rarely occur.

Pathophysiology of Migraine

Over the past several years, Silberstein and colleagues[3] have conducted studies that have greatly improved the understanding of migraine pathophysiology and, in the process, have suggested focal points for treatment, particularly the triptan class of drugs. This research has shown that migraine originates with scalp allodynia or hypersensitivity. The scalp begins to tingle

KEY QUESTIONS

- Is this headache new or different?
- How long has it lasted?
- Have you had a similar headache before?
- What is the quality of the pain?
- Was there any aura or warning?
- What are the associated features?
- Is there a family history of similar headaches?

at the onset of migraine, which is a key question that should be posed during the initial workup of the patient. Pain pulses, then depolarizes and migrates medially toward the thalamic pain center. Neuronal activation in the thalamus can trigger nausea and vomiting, which are under the control of the nearby hypothalamus. Subsequently, the trigeminal nerve is activated, resulting in the unilateral pain that characterizes migraine. Once this occurs, triptan drugs will become ineffective; this emphasizes the need for intervention with triptan drugs as early as possible in the course of a migraine episode.

The work of Silberstein and others has shown that migraine pathophysiology involves a combination of serotonin-mediated reactivity, vasospasm, and an inflammatory response. As refinement of migraine therapy continues, treatment increasingly focuses on these three categories of factors that drive the migraine episode.

"Migraine often is accompanied by nausea, vomiting, photophobia, and phonophobia."

Pretreatment Considerations

Recent advances in our understanding of the origin, pathophysiology, and clinical manifestations of migraine have helped revolutionize the overall approach to treatment. Historically, the standard of care was to begin treatment with a drug that had mild potency and then progressively step up to more intense therapy until the patient responded. That stepwise approach gave no consideration to differences in migraine severity or subtypes (of which at least 17 have been identified[2]).

Stepped therapy has since given way to stratified treatment based on the degree of debility caused by migraine. In my own practice, I use the Migraine Disability Assessment Scale (MIDAS), available online at www.midas-migraine.net. The MIDAS approach helps the clinician to quantify the extent to which migraine adversely affects a patient's life. On the basis of the MIDAS score, a patient's condition can be categorized as mild, moderate, or severe. By determining the extent of disability caused by migraine, a clinician can choose the most appropriate approach to therapy for each patient. For example, a patient who is severely disabled by migraine, even if the episodes are infrequent, would merit consideration for intense treatment. On the other hand, a patient who has mild episodes would likely be a candidate for less intense therapy, even if the migraine episodes occur frequently.

Complementary and alternative medicine (CAM) has a growing role in the management of migraine. Some patients refuse to take medication. Others might have tried every drug available, and nothing has worked. Clinicians need to be aware of the CAM options available to patients with migraine and give adequate consideration to nondrug treatments.

Treatment planning also should take into consideration what I like to call the "ecology of the patient." This phrase refers to the overall physical and emotional status of the patient, including comorbid conditions. For example, if a patient has hypertension, a single drug might be available to treat hypertension and migraine at the same time.

Finally, a treatment plan for migraine should take into account the resources available. The onus is on the clinician to know what resources can be brought to bear in the treatment of migraine. Acupuncture has proven useful for some patients with migraine; but if therapy is unavailable in a particular area, acupuncture should not be discussed as a viable option with the patient.

Treatment

Preventive

Almost 28 million people aged 12 years or older in the United States who suffer from headaches that fit the International Headache Society definition of migraine might benefit from treatment aimed at preventing migraine.[4] Good communication between the clinician and patient is a necessity for effective migraine prevention.

Several types of medication have demonstrated efficacy for migraine prevention, beginning with antidepressants. Tricyclic antidepressants (TCAs) have a long history of use in the management of various types of pain. However, tolerability is a problem for the entire class, particularly when used at higher doses.[5] Newer antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs), also can prevent migraine episodes.[6] However, even though SSRIs are regarded as being less problematic than TCAs, patients should be informed about the potential side effects of SSRIs (which include sexual dysfunction and weight gain).[5]

Two anticonvulsants are approved for migraine prevention: valproic acid and topiramate. Both are effective, but side effects are a major issue with their use for migraine prevention. Tolerability is a problem; valproic acid is a teratogen and therefore strictly contraindicated during pregnancy. When started at a low dose (25 mg/d) and titrated gradually, topiramate is effective and well tolerated in the preventive treatment of migraine headaches.[6] Prominent side-effect issues with topiramate are nephrolithiasis (which can be minimized by appropriate hydration) and potentially rapid and dramatic weight loss.[7,8]

Pulse courses of anti-inflammatory therapy are a good preventive strategy for migraine. One example would be naproxen 500 mg bid for 3 weeks. Therapy with naproxen is useful for inflammatory contributions to migraine but should not be used chronically because of a risk of potentially severe gastrointestinal adverse effects.[5]

Beta-blockers, calcium-channel antagonists, and other vasoactive agents may be useful in some patients with migraine. If a beta-blocker is used, the drug should be continued for at least 3 months before judging its efficacy.[9] In my own practice, I prefer calcium-channel antagonists. I usually start a patient on 120 mg qd of long-acting verapamil.

On the horizon, new therapeutic options have demonstrated potential for migraine prevention.

Abortive Therapy

Triptans are widely used abortive therapies for migraine.[10] The key to their efficacy is administration at the first sign of an episode, the scalp allodynia. Triptans offer the advantage of several formulations: sublingual, tablet, intranasal, and injection. If a patient frequently has nausea and vomiting, injection might be the best option. Patients who have difficulty swallowing tablets might prefer a sublingual formulation. The drugs are contraindicated in patients who have coronary artery disease, which would be especially pertinent to older individuals.[11]

Several alternatives to triptans might also be considered for abortive therapy. These include ergot alkaloids; combination drugs, such as acetaminophen/butalbital/caffeine and isometheptene/dichloralphenazone/acetaminophen; nonsteroidal anti-inflammatory drugs; and steroids. Each of these drugs has demonstrated some degree of efficacy for aborting migraine episodes, and all are reasonable options if triptans are ineffective, contraindicated, or not used for other reasons.

Rescue Therapy

Several pharmacologic therapies have proven useful in managing patients with migraine pain that is unresponsive to other treatment. Options include narcotic analgesics (such as acetaminophen with codeine and propoxyphene), antiemetics, benzodiazepines, and anticholinergics.

Nondrug Treatment

Numerous nonpharmacologic interventions have been used as primary and adjunctive therapy for migraine. Little objective evidence supports their use for migraine prevention. Most of the underlying clinical basis for these interventions comes from anecdotal reports. Nonetheless, nondrug therapies appeal to some patients, whose wishes should be taken into account when planning a therapeutic regimen. The options can be presented as potential therapeutic aids, with the caveat that supporting scientific evidence is scant.

NONDRUG TREATMENTS

- Biofeedback
- Meditation
- Acupuncture
- Yoga
- Magnesium/folic acid
- Physical therapy
- Massage
- Nutrition

Special Populations

Hormonal Headaches

Several types of hormone-driven headaches have been identified. Menstrual migraine usually begins 3 days before the onset of a menstrual period and lasts 2 days into bleeding.[2] Ovulation headaches, as their name suggests, occur when a patient is ovulating. The best way to recognize hormonal headaches is to ask patients to keep a headache diary that tracks their menstrual cycle and the occurrence of headaches.

Hormonal therapy is one option for treating hormonal headaches. Oral contraceptives, vaginal rings, and other forms of hormonal manipulation can modulate withdrawal bleeding and in the process eliminate the associated headaches.[11]

Migraine During Pregnancy

Because many pregnancies are unplanned, clinicians should take a birth control history before starting a patient on any medication. The first trimester tends to be the most problematic, and very little can be done pharmacologically to manage migraine during this time. The options consist of acetaminophen with codeine and butalbital, acetaminophen, and caffeine combination tablets. These limited options must be clearly communicated to patients who are pregnant. Nonpharmacologic interventions play a much greater role in migraine management during pregnancy. Ice, massage, relaxation, acupuncture, and other nondrug treatments can be especially useful for patients who have few pharmacologic options. Migraine frequency and severity usually improve during the second and third trimester, and a patient's migraine profile may return to baseline soon after delivery.

Summary

Effective management of migraine begins with an accurate diagnosis, which depends largely on the clinician's skills in history taking and physical examination. Be alert to clinical red flags that suggest serious medical problems requiring immediate attention. Clinicians must create a management partnership with patients. Do not expect or promise too much in the way of treatment results. Be creative in the approach to therapy, bringing to bear all the available resources that might be indicated by an individual patient's personal ecology.

Dr Bernstein has nothing to disclose.

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Resources in the SPOTLIGHT

In each issue, this section will be dedicated to highlighting resources for additional information on the topics discussed in that particular issue. Many of these resources provide patients with information. This month, the resources are focused on depression/mental health and headache/migraine.

DEPRESSION/MENTAL HEALTH RESOURCES

MHA: Mental Health America

MHA, the country's oldest and largest nonprofit organization addressing all aspects of mental health and mental illness, is dedicated to promoting mental health and preventing mental disorders through advocacy, education, research, and service.

www.nmha.org

NARSAD: The National Alliance for Research on Schizophrenia and Depression

NARSAD is dedicated to supporting innovative scientific research to find the causes, better treatments, and cures for severe mental illnesses. NARSAD is the world's largest donor-supported organization for research on psychiatric disorders. Since 1987, the organization has awarded a total of $199.3 million in 2,948 research grants to scientists in the United States and 25 other countries.

www.narsad.org

US Department of Health and Human Services, SAMHSA (Substance Abuse and Mental Health Services Administration) Center for Mental Health Services (CMHS)

CMHS leads Federal efforts to treat mental illnesses by promoting mental health and by preventing the development or worsening of mental illness when possible. Congress created CMHS to bring new hope to adults who have serious mental illnesses and to children with serious emotional disorders. CMHS delivers mental health services, generates and applies new knowledge, and establishes national mental health policy.

www.mentalhealth.samhsa.gov

HEADACHE/MIGRAINE RESOURCES

ACHE: American Council for Headache Education

ACHE is dedicated to advancing the treatment and management of headache as a valid biologically based illness. Their mission is to reach out to health career policy makers, employers, opinion leaders, and headache patients.

www.achenet.org

AHS: American Headache Society

AHS is a professional society of health care providers dedicated to the study and treatment of headache and face pain. AHS promotes the exchange of information and ideas concerning the causes and treatment of headache and related painful disorders and strives to improve the knowledge, skills, and professional performance by physicians, psychologists, and other health care professionals who treat patients with head, neck, and orofacial pain.

www.americanheadachesociety.org

NHF: National Headache Foundation

NHF is a source dedicated to helping headache sufferers, sufferers' families, physicians, and allied health care professionals by providing educational and informational resources, supporting headache research, and advocating for the understanding of headache as a legitimate neurobiological disease.

www.headaches.org

NINDS: National Institute of Neurological Disorders and Stroke

NINDS conducts and supports research on brain and nervous system disorders. The mission of NINDS is to reduce the burden of neurologic disease—a burden borne by every age group, every segment of society, and people all over the world. To accomplish this goal, NINDS supports and conducts research on the normal and diseased nervous system, fosters the training of investigators in the basic and clinical neurosciences, and seeks better understanding, diagnosis, treatment, and prevention of neurologic disorders.

www.ninds.nih.gov

Coming in the June issue: Depression in Seniors, Pain Management, and more clinical cases.

Point of View
Challenges in Primary Care Persist Over Time

Exposure to messages that are communicated in pharmaceutical advertising may help remove some of the barriers that patients face in requesting care.

Clinicians in the primary care setting may find themselves in a quagmire of controversy regarding the impact of pharmaceutical advertising directed to their patients. With an estimated $4.5 billion spent on direct-to-consumer initiatives by pharmaceutical companies in 2006,[1] patients are exposed to a wide range of pharmaceutical advertising campaigns. Taken in addition to the previously existing marketing to clinicians regarding the diagnosis and treatment of illnesses for which adequate pharmacologic treatments are available, one may surmise that a large number of new prescriptions are occurring. As a result, there is a growing perception that primary care physicians now diagnose and treat more affective disorders—including depression and anxiety disorders—than in the past. However, a closer examination of the practices of primary care clinicians reveals that this is not, in fact, the case.[2]

Data from observational studies over the last 50 years have shown prescription rates in the primary care setting for affective disorders to be somewhat similar to the rate of prescriptions written today.[2] Clinicians continue to use clinical diagnostic tools and the natural presentation process of the patient as the basis for making treatment decisions in primary care, just as they have for decades.

Historical Context

Clinicians may find it helpful to recognize that some of the challenges faced today have been fairly common in primary care over the last 50 years.

As detailed in a book published in 2005 by Drs Callahan and Berrios,[2] the "myth of the old-time doctor" perpetuates the misperception that primary care doctors functioned in a substantively different manner during the 1940s and 1950s than they do today. According to popular culture, the old-time doctor is portrayed as someone with deep humanistic qualities who had plenty of time for patients, spent lots of time talking with patients, and did not write a lot of prescriptions. Yet, the empiric data tell a different story. For example, a study on private practice in North Carolina reported in 1956 that the average number of patient visits to an individual physician was 170 visits per week; physicians in the 1950s worked about 51 hours a week (about 9.3 hours per day for 5.5 days, not including after-hours calls).[3] Based on a few calculations, the typical patient visit would have lasted about 15 minutes, quite similar to that of today.

Observational studies during these decades have reported that 70% to 95% of patient visits resulted in a prescription.[2] For example, a study by Brotherston and colleagues[4] published in 1956 found that the prescription rate among patients who visited their physician once a year was about five prescriptions per patient; only 5% of patient visits did not result in receiving a prescription for medication. With respect to sedative/hypnotics—which were the preferred psychotropic medications of the day—physicians prescribed sedative/hypnotics more frequently than any other drugs; these classes of medications accounted for 15% of all prescriptions.[2] Barbiturates and bromides were the most common of these medications.[2]

Therefore, these studies and others[2] reveal that a good deal of psychosocial distress was presented by patients to primary care physicians in the 1950s, with many of these visits resulting in prescription for medication. Psychiatric disorders have been diagnosed and treated in the primary care setting for more than five decades. In short, the patients, the doctors, the illnesses, the frequency of prescribing medication, and the time spent in counseling/supporting patients are roughly the same as 50 years ago. Ostensibly what has changed is that primary care clinicians are treating affective disorders with different classes of drugs. Psychiatric disorders are treated in a more specified manner with agents that are greatly improved in terms of adverse event profiles (vis-à-vis the barbiturates, bromides, and benzodiazepines prescribed in past decades). The emergence of new treatment therapies have, in many cases, resulted in improved patient outcomes.

Practical Considerations for Interactions With Patients

Given this historical context, it may become evident that not all outcomes of pharmaceutical advertising are negative. Increasing patient awareness of medical conditions and diseases that can be treated may be the impetus for useful discussions with primary care physicians, resulting in appropriate diagnostic and treatment interventions.[5] Exposure to messages that are communicated in pharmaceutical advertising may help remove some of the barriers that patients face in requesting care. Most Americans have become accustomed to commercials that advise them to request medications from their doctors that will treat quite personal conditions (such as insomnia or erectile dysfunction),[6] which may increase a person's comfort level in seeking help. Pharmaceutical advertising may actually open new vistas for

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care in certain therapeutic areas that are sensitive for patients, such as affective disorders.

A survey of 500 physicians conducted by the US Food and Drug Administration in 2003 found that 88% of patients who asked about an advertised medication had the condition that the medication treats.[7] With respect to the prevalence of clinical depression, studies have found that about 20% of patients who seek care in the primary care setting suffer from depressive symptomatology.[8] One study reported that up to 90% of patients with major depression will improve with good adherence and adequate doses of the appropriate antidepressant drug.[9]

Some clinical caution is warranted; however, a recent study found that if a patient asks for a prescription by name, he or she has a 49% chance of walking out of the doctor's office with that particular prescription.[10] Although this may be appropriate, we as clinicians must ensure that our patients are receiving proper therapy, not just a completed business model. When a patient asks me about a particular drug, I respond with two straightforward questions: "Why do you want this drug?" and "What do you think is wrong with you?" My objectives are to elucidate from patients why they think they need a particular medication and what goals they have for therapy. We then discuss symptomatology and develop a diagnostic understanding, which leads to the treatment approach that seems most appropriate as a starting place.

An informed patient should not provoke fear in the informed clinician. Patients can voice their input on which approach they would like to take—or if they even want to be treated at all. Trust is the key to a therapeutic relationship; as a clinician, I trust the autonomy of my patients, but I also expect my patients to trust my professionalism. I believe that the interchange between their input and my response is where healing begins. If interchange is dynamic, it can be a place where a healing relationship can grow.

In conclusion, the challenges we face in the primary care setting are daunting. Each entity of the therapeutic triad—the patient, the clinician, and the pharmaceutical industry—serves an important role in achieving favorable outcomes in health care. Affective disorders are often present in patients who make primary care visits, but may or may not be recognized and diagnosed by clinicians.

When symptomatology relating to affective disorders is discussed, diagnostic and treatment decisions can be made based on our current knowledge about treatment options. Efforts that raise awareness among patients about available treatments to address affective disorders can be useful because patients may feel more comfortable in offering their input regarding their care. The clinician and patient can then work together in formulating a realistic plan, making adjustments as needed over time. In 1919, Franz Kafka captured the essence of primary care when he wrote these words in his short story entitled "The Country Doctor": "To write prescriptions is easy, but to come to an understanding with people is hard."[11] A constant in primary care practice for at least 100 years, this truth remains relevant today.

Dr Jackson has received funding for clinical grants from Eli Lilly and Company. He is a consultant to AstraZeneca and Eli Lilly.

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PRACTICAL BITS

Quick and Practical Diagnostic Tools

from Dr Lieberman

THE BATHE METHOD

Screening tool for anxiety and depression

The BATHE technique is a brief psychotherapeutic method that addresses the patient's background issues, affect, and most troubling problem. The physician then shifts the discussion to how the patient is handling the problem and ends with a demonstration of empathy.[1]

BATHE is designed to fit smoothly into a 15-minute appointment.[2] The acronym BATHE refers to the components of the interview, which are described below.

Background:	"What is going on in your life?"
Affect:	"How do you feel about that?"
Trouble:	"What troubles you the most about this?"
Handle:	"How are you handling that?"
Empathy:	"That must be very difficult for you."

References: 1. Lieberman JA III, Stuart MR. The BATHE method: Incorporating counseling and psychotherapy into the everyday management of patients. *Prim Care Companion J Clin Psychiatry*. 1999;1:35-38. **2.** Stuart MR, Lieberman JA III, eds. *The Fifteen Minute Hour: Practical Therapeutic Interventions in Primary Care*, 3rd ed. Philadelphia, Pa: Saunders; 2002: 85-90.

THE SWICKIR METHOD

Generalized Anxiety Disorder Screening Scale

This mnemonic, along with other screening tools, can help to reduce the number of undiagnosed psychiatric disorders in the primary care population. Patients who admit to three or more of the symptoms may meet the criteria for an anxiety disorder.[1]

SWICKIR stands for:

Somatic symptoms
Worry
Irritability
Concentration or memory difficulties
Keyed up, on edge
Insomnia
Restlessness

Reference: 1. Lieberman JA III. The differential diagnosis of fatigue and executive dysfunction in primary care. *J Clin Psychiatry*. 2003;64(suppl 14):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). Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN).

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).

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, 1% (39/3732) of Cymbalta-treated patients had a >3 times the upper limit of normal elevation of ALT 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 MDD clinical trials, Cymbalta treatment was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo. 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% (1/1139) of Cymbalta-treated patients and 0.1% (1/777) of placebo-treated patients. 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—Cymbalta has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with MDD, seizures occurred in 0.1% (1/1139) of Cymbalta-treated patients and 0% (0/777) of placebo treated patients. In placebo-controlled clinical trials in patients with diabetic peripheral neuropathy, seizures did not occur in any patients treated with either Cymbalta or placebo. 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 MDD placebo-controlled clinical trials of up to 9 weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in 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. However, the electrocardiograms of 321 patients who received Cymbalta in MDD placebo-controlled clinical trials and had qualitatively normal ECGs at baseline were evaluated; Cymbalta was not associated with the development of clinically significant ECG abnormalities (*see* ADVERSE REACTIONS, Electrocardiogram Changes). In DPN placebo-controlled clinical trials, Cymbalta-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients (*see* ADVERSE REACTIONS, Electrocardiogram Changes). 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, small increases in fasting blood glucose were observed in Cymbalta-treated patients. HbA_{1c} was stable in both Cymbalta-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the Cymbalta and the routine care groups, but the mean increase was 0.3% greater in the Cymbalta-treated group. There was also a small increase in fasting blood glucose in the Cymbalta-treated group. Total cholesterol was increased in Cymbalta-treated patients (2 mg/dL) and decreased in the routine care group (6 mg/dL). 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,

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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 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. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

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 clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN studies, 33% (357) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. 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. For both MDD and DPN 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).

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 ≤ placebo: 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 ≥5% 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 ≤ placebo: 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 ≥5% and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia.

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 4 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 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***—Cymbalta treatment, for up to 9 weeks in MDD placebo-controlled clinical trials of 40 to 120 mg daily doses caused increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic compared to placebo and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg (*see* PRECAUTIONS). Cymbalta treatment, for up to 9 weeks in MDD placebo-controlled clinical trials and for up to 13 weeks in DPN placebo-controlled trials caused a small increase in heart rate compared to placebo of about 2 beats per minute. ***Weight Changes***—In MDD placebo-controlled clinical trials, patients treated with Cymbalta for up to 9 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 321 Cymbalta-treated patients with MDD and 169 placebo-treated patients in clinical trials lasting up to 8 weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, and QRS intervals between Cymbalta-treated and placebo-treated patients. Electrocardiograms were obtained from 528 Cymbalta-treated patients with DPN and 205 placebo-treated patients in clinical trials lasting up to 13 weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTc measurements between Cymbalta-treated and placebo-treated patients.

Postmarketing Spontaneous Reports—Adverse events reported rarely since market introduction that were temporally related to Cymbalta therapy include: hallucinations, rash, and urinary retention. The following adverse events were reported very rarely: alanine aminotransferase increased, alkaline phosphatase increased, anaphylactic reaction, angioneurotic edema, aspartate aminotransferase increased, bilirubin increased, extrapyramidal disorder, glaucoma, hepatitis, hypersensitivity, hypertensive crisis, hyponatremia, jaundice, mania, orthostatic hypotension (especially at the initiation of treatment), seizures, serotonin syndrome, Stevens-JohnsonSyndrome, supraventricular arrhythmia, syncope (especially at initiation of treatment), syndrome of inappropriate antidiuretic hormone secretion (SIADH), 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.

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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.

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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.

Most common adverse events (≥5% and at least twice placebo) in MDD premarketing clinical trials were: nausea, dry mouth, constipation, fatigue, decreased appetite, somnolence, and increased sweating. Most common adverse events in diabetic peripheral neuropathic pain (DPNP) premarketing clinical trials were: nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia.

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

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