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Practical Neuroscience
for Primary Care Physicians

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Special Populations in Depression
Clinical Implications of Depression in Patients With Cardiovascular Disease

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Strategies for Managing Patients With Migraine

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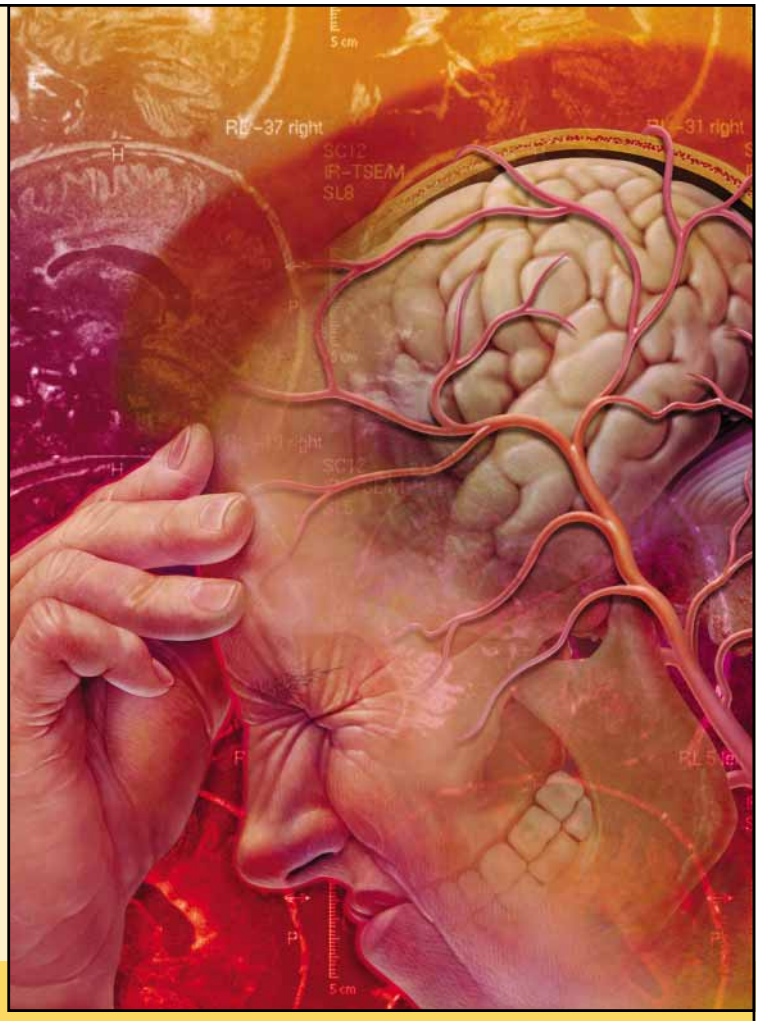

Case Files

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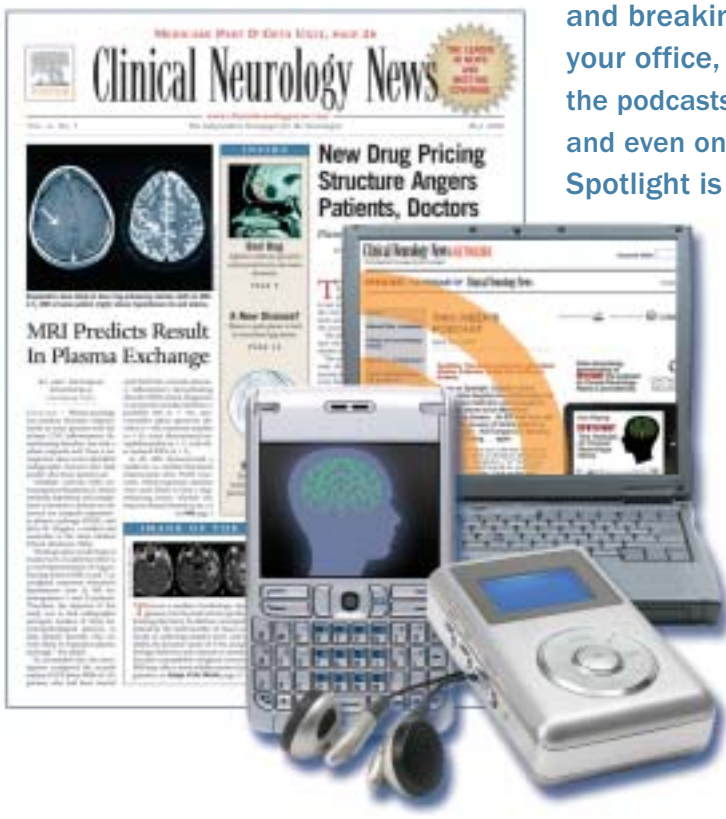

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- The role of smoking and heavy drinking in increasing the risk for Alzheimer's disease
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From the Desk of...

Welcome to the Summer 2008 issue of *Practical Neuroscience for Primary Care Physicians*. Now in its second year of publication, this supplement series continues to provide a practical resource for primary care physicians.

In this issue, **Alexander Glassman, MD**, Professor of Clinical Psychiatry, College of Physicians and Surgeons, Columbia University, Chief, Clinical Psychopharmacology, New York State Psychiatric Institute, New York, authors the "Special Populations in Depression" article, focusing on depression in patients with cardiovascular disease. **Carolyn Bernstein, MD**, Assistant Professor of Neurology, Cambridge Hospital, Harvard Medical School, Cambridge, Massachusetts, Medical Director, Women's Headache Center, Somerville, Massachusetts, discusses strategies for managing patients with migraines. In the "Case Files" section of the supplement, **Thomas L. Schwartz, MD**, Associate Professor of Psychiatry, Director of Adult Outpatient Services, Director of the Depression and Anxiety Disorders Research Program, Assistant Director of Residency Training, State University of New York (SUNY) Upstate Medical University, Syracuse, New York, shares case studies of patients with anxiety disorders.

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As always, if you'd like to contact us, you can reach us at physiciansfeedback@elsevier.com.

Cordially,

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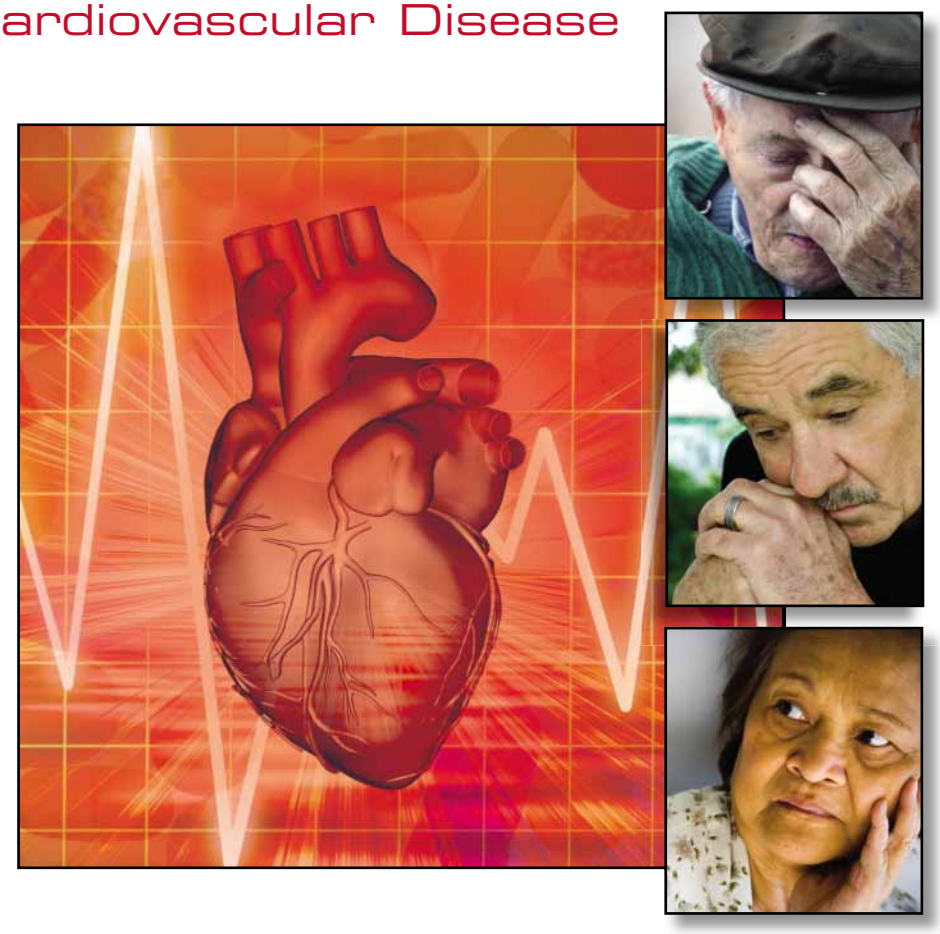
Alexander Glassman, MD

Clinical Implications of Depression in Patients With Cardiovascular Disease

Depression—both major depressive disorder (MDD) and depressive symptoms—increases mortality in patients following myocardial infarction (MI) and also is a predictor of developing cardiovascular disease (CVD) in the general population free of any evidence of medical illness.[1-4] Furthermore, depression is a painful and persistent condition, and if left untreated in patients who have overt coronary disease, depression will impair the patient's adherence to the advice and treatment recommendations by the patient's team of health care professionals, further impairing the patient's health status.[5,6] This article describes the importance of being alert for symptoms of depression when caring for patients with CVD in the primary care setting, highlighting the need to provide appropriate treatment and ongoing follow-up care for depression.



"Multiple barriers exist that can impede a patient with CVD from receiving appropriate treatment for depression."

Identifying and Treating Depressive Symptoms in Patients With CVD

Epidemiologic studies have found that at any point in time major depression will be observed in approximately 5% of the general population, 10% of medical outpatients, 20% of outpatients with coronary heart disease (CHD), and one third of outpatients with heart failure.[7] Symptoms of depression include *persistent* sad, teary, or "empty" feelings; feelings of hopelessness, pessimism, and/or guilt and worthlessness; irritability and/or restlessness; loss of interest in previously pleasurable activities; fatigue, decreased energy, difficulty concentrating, diminished interest in sex, and/or difficulty making decisions; insomnia, often early-morning wakefulness, or excessive sleeping; overeating or appetite loss; and thoughts of suicide and persistent somatic symptoms: headaches, cramps, or digestive problems that do not ease even with treatment.[8]

Multiple barriers exist that can impede a patient with CVD from receiving appropriate treatment for depression. Patients with CVD are not routinely evaluated for clinical depression. This is especially true in the setting of an acute coronary event where there is enormous pressure to institute medical treatments and where it is easy

> **Even when a patient's cardiologist or family member detects signs of depression, this information may not be communicated directly to the primary care practitioner.**

to see the patient's symptomatology as a normal reaction to an obviously stressful event. Even when a patient's cardiologist or family member detects signs of depression, this information may not be communicated directly to the primary care practitioner. Not only doctors but the patients themselves may be inclined to consider depression as an expected and natural consequence of a serious medical threat, regarded as a normal reaction that will pass without giving serious attention to the benefits of treatment with antidepressants and/or psychotherapy. However, the evidence suggests that half of all post-MI depressions persist for more than half of the next year and fully two thirds of all depressions observed following a coronary event actually began prior to that event.[9]

Some clinicians may not have adequate knowledge and experience about the efficacy and safety of antidepressant therapy in patients with CVD. For example, previous studies have found that patients treated with older antidepressant medications (eg, tricyclic antidepressants) have an increased risk for cardiovascular events.[10] Until recently, it has been considered good practice to avoid antidepressant treatment in patients with acute coronary syndromes (ACS) whenever possible. It is only recently that studies with selective serotonin reuptake inhibitors (SSRIs) have been available to document the safety of these drugs in these patients.[10-11] While there is no evidence of cardiovascular harm with SSRIs, it should be remembered that SSRIs have a significant effect on platelet activity. While randomized trials in post-ACS patients have not documented any evidence of bleeding, those trials involved less than 1,000 post-ACS patients. It is likely that as the number of post-ACS patients exposed to SSRIs increases, there will be some evidence of bleeding. Although it does not appear common, the combination of patients receiving multiple antiplatelet drugs with the advancing age of cardiovascular patients makes this occurrence almost inevitable. Increased awareness of the knowledge gained from recent studies relating to patients with depression and CVD can help clinicians make better treatment decisions for their patients.

The Impact of SSRI Therapy in Patients With CVD

The findings from three studies are particularly useful for clinicians to consider when determining treatment options for depressive symptoms in patients with CVD or post-ACS. Designed to evaluate the safety and efficacy of the SSRI sertraline in depressed patients hospitalized for recent MI or unstable angina, the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) studied a total of 369 patients with MDD. Patients were randomly assigned to receive sertraline in flexible dosages of 50 to 200 mg/day or placebo for 24 weeks.[11] This randomized, double-blind, placebo-controlled trial was conducted in 40 outpatient cardiology centers and psychiatry clinics in the United States, Europe, Canada, and Australia from April 1997 through April 2001. Researchers found this SSRI to be safe and effective for treating depression in this population, with no difference in safety as measured by change from baseline in left ventricular ejection fraction, heart rate, blood pressure (either systolic or diastolic), arrhythmias, or any electrocardiographic measures including QTc. Although SADHART was not powered to evaluate life-threatening cardiovascular events, a trend for a reduction in the composite end point (defined as recurrent MI, stroke, hospitalization for angina, hospitalization for heart failure, or CHD death) was observed.[11]

Researchers who conducted the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) study monitored the progress of 2,481 patients following an acute MI who were either depressed or had low social support.[12] These study participants were recruited from 73 hospitals affiliated with 8 clinical centers located in various regions of the United States; the study was conducted from October 1996 through October 1999. Study participants were randomized to either 16 weeks of cognitive behavior therapy supplemented by treatment with an SSRI when needed or usual care only provided by their physician (which also included SSRI therapy when needed). Either group, if they were severe or did not get better, could receive SSRI therapy.

Data from the ENRICHD study showed a modest decrease in depression, but no difference in survival rates were detected between the psychotherapy and usual care groups during either a 6-month treatment period or during follow-up for patients in both arms of at least 30 months. Although designed as a study of psychotherapy compared to usual care, ethical considerations required the patients entering the protocol with more severe depressions be offered an antidepressant drug. In addition, those patients who did not recover adequately in 6 or 8 weeks were also offered an antidepressant drug. SSRIs were by far the most commonly used drug; the SSRIs used in this study included sertraline (49.5%), paroxetine (28.9%), fluoxetine hydrochloride (13.0%), citalopram (7.6%), and others (1.0%).[13] In a post hoc analysis, researchers found that among depressed individuals who participated in the ENRICHD study and received SSRIs, there was an associated 42% reduction in both recurrent MI and death, after adjustment for age, Killip class, ejection fraction, creatinine levels, diabetes mellitus, congestive heart failure, previous MI, stroke, and baseline depressive symptoms.[7,13] This observation was highly statistically significant, but the 353 depressed patients who received the drug were not randomized to that treatment.

The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial, a randomized, controlled, 12-week, parallel-group efficacy

TABLE 1. MECHANISMS BY WHICH DEPRESSION MAY LEAD TO CARDIAC EVENTS

Potential Biological Mechanisms:

- Alterations in cardiac autonomic tone
- Common genetic vulnerability
- Enhanced activity of the hypothalamic-pituitary axis
- Greater platelet activation
- Increased catecholamine levels
- Increased whole blood serotonin
- Inflammatory processes
- Lower omega-3 fatty acid levels
- Mental-stress induced ischemia
- Toxicity of tricyclic antidepressants

Potential Behavioral Mechanisms:

- Dietary factors
- Lack of exercise
- Medication nonadherence
- Poor social support
- Unhealthy lifestyle

Source: Whooley MA.[7] Reprinted with permission. Copyright © 2006 American Medical Association.

TABLE 2. MNEMONIC DEVICES FOR SYMPTOMS OF CLINICAL DEPRESSION

Diagnosis of major depressive disorder requires five or more of the following nine symptoms, including depressed mood or anhedonia, causing clinically significant distress or impairment in functioning nearly every day for at least 2 weeks.

Less Depression-Specific Symptoms (SPACE)

1. **S**leep (insomnia or hypersomnia)
2. **P**sychomotor (agitation or retardation)
3. **A**ppetite (increase or decrease, unintentional weight loss or gain)
4. **C**oncentration (diminished ability to think or concentrate)
5. **E**nergy (fatigue or loss of energy)

More Depression-Specific Symptoms (DIGS)

6. **D**epressed mood (feeling sad or empty)
7. **I**nterest (markedly diminished interest or pleasure in almost all activities)
8. **G**uilt (feelings of worthlessness or excessive guilt)
9. **S**uicidal ideation (recurrent thoughts of death or suicide)

Source: Kroenke.[19] Reprinted with permission. Copyright © 2002 American Medical Association.

study of the SSRI citalopram and interpersonal psychotherapy, found citalopram reduced depressive symptoms among 284 patients with coronary artery disease and major depression, but psychotherapy did not.[14] There were no particular safety issues, but the number of events was inadequate to evaluate the effect of the antidepressant on life-threatening events.

Another randomized, placebo-controlled study called Myocardial Infarction and Depression Intervention Trial (MIND-IT) was conducted in a small number of patients hospitalized for MI in the Netherlands during September 1999 through March 2002 and found the dual-acting antidepressant mirtazapine to be safe and effective in the treatment of post-MI depression, but the study was much too small to evaluate if treatment reduced medical events.[15]

A study conducted by Rasmussen and colleagues in Denmark between January 1996 and May 1998 evaluated the effect of sertraline (50 mg/day with adjustments up to a maximum dose of 150 mg/day as needed) in the prevention of poststroke depression.[16] A total of 137 patients who experienced an acute ischemic stroke were randomly assigned to 12 months of double-blind treatment with either sertraline or placebo as soon as it was established that they suffered from an ischemic rather than a hemorrhagic stroke. Approximately 10% of the sertraline-treated group developed clinical depression, whereas 30% of patients in the placebo group developed clinical depression. These researchers concluded that the use of this SSRI was effective, safe, and well tolerated in preventing the development of depression in the first year following a stroke.[16] Although it was not a preplanned analysis, there was a trend for patients who received sertraline to experience reduction in life-threatening events over the next year—a particularly interesting result because these patients were not depressed. They were treated because they were at higher risk for depression.

All of these studies found improvements in depression, and three of the five found a substantial reduction in medical events, suggesting a possible, but not definite, cardioprotective effect associated with the use of SSRIs. Even if antidepressants do not reduce life-threatening medical events, the evidence is strong that they are safe and can improve both mood and the patient's quality-of-life.

Possible Mechanisms of Effect

Various biological and behavioral factors have been suggested as possible mechanisms by which depression may lead to cardiac events (**Table 1**).[7] Multiple pathways—including noradrenergic hyperactivity, abnormalities in the hypothalamic-pituitary-adrenal systems, reduced heart rate variability, increased inflammatory cytokine activity, and increases in platelet reactivity—have been identified as possible mechanisms behind the association of depression and heart disease.[7,17] Beyond these potential physiological mechanisms, depressive mood itself without question interferes with the patient's health behaviors. These patients do not listen to their health care providers, are less compliant with medication, are less able to stop smoking, and fail to go to rehabilitation. All of these have been shown to increase mortality in post-MI patients.

Potential Clinical Tools

The nine-item Patient Health Questionnaire (PHQ-9) is a practical tool for clinicians to use in the primary care setting.[18] Patients can complete the PHQ-9 within 2 minutes in the waiting room, and an office assistant can alert the clinician when a patient scores 10 or higher, indicating a positive screen for depression. Clinicians may find it useful to remember the mnemonic SPACE DIGS as a prompt in discussing symptoms of depression with patients and family members (**Table 2**).[19] Once

PRACTICAL BITS

Quick and Practical Diagnostic Tools

POUNDING MNEMONIC DEVICE TO HELP DIAGNOSE MIGRAINE

Pulsating quality

duration of 4-72 h**O**urs

Unilateral location

Nausea and vomiting

Disabling intensity

Source: Detsky ME et al. *JAMA*. 2006;296:1274-1283.

IDENTIFYING PANIC ATTACKS

Panic attacks are sudden feelings of terror that strike without warning and can occur at any time. The fear and terror that a person experiences during a panic attack are not in proportion to the true situation and may be unrelated to what is happening around them. When consulting with a patient, ask if he/she experienced any of the following symptoms (someone suffering from panic attacks will experience several of the symptoms):

- Racing heart
- Feeling weak, faint, or dizzy
- Tingling or numbness in the hands and fingers
- Sense of terror, impending doom, or death
- Feeling sweaty or having chills
- Chest pain
- Breathing difficulties
- Feeling a loss of control

Adapted from: WebMD Medical Reference. Available at: http://www.webmd.com/anxiety-panic/guide/panic-attack-symptoms. Accessed April 14, 2008.

depression is identified, effective treatment and follow-up care should be implemented to improve patient outcomes.[20]

Conclusion

Clinicians need to keep in mind that the increased risk of adverse cardiovascular events in patients with known cardiac disease is associated even with relatively mild symptoms of depression.[21,22] Not only have the highest mortality rates been observed among patients with severe depression who are hospitalized with acute MI, but elevated mortality rates also have been observed in patients with very modest levels of depressive symptoms. Results of a recently published study of 766 patients admitted for acute MI found that clinical depression was an independent risk factor for death 5 years after the acute MI, with an increased risk of death even when patients were found to have minor depression.[23]

Untreated depression is a barrier to the delivery of cardiac care. Treating depression will improve the mood and the quality of life for these patients and is likely, although the evidence is not definite, to reduce the risk of medical adverse events.[24] Frequent contact with patients with both depressive symptoms and CVD is particularly important. The more often clinicians can interact with these patients (including providing encouragement to patients and their family members), the more likely these patients will follow the instructions of their health care professionals. Clinicians need to understand the importance of detecting any signs of depression in patients with CVD. Ignoring or dismissing depressive symptoms should be avoided. Not only is clinical depression associated with adverse outcomes in vascular disease, depression is a painful and persistent condition that can be treated. Once depression is identified, SSRIs are reasonably effective, safe, and easily administered and will improve patient outcomes. Only if the depression is severe or persistent will referral be necessary. ■

Dr Glassman has nothing to disclose.

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CASE FILES

Thomas L. Schwartz, MD

Case 1: Depression or Anxiety?

Presentation

A.L. is a 39-year-old administrator who came to the office with a chief complaint of having difficulty coping after gastric bypass surgery. She states surgery went well and she lost 100 pounds. However, she feels as though she is different, has had difficulty with her job, and has left her boyfriend of 20 years. She reports hopelessness, loss of enjoyment, and poor sleep as target symptoms. On review of systems she admits to a history of generalized anxiety with multifocal, uncontrolled worries that often would leave her tense and with insomnia. This has been ongoing since childhood. There is evidence of no other psychiatric disorder.

Psychosocial Assessment

The patient's history and examination leads to a preliminary diagnosis of major depressive disorder (MMD), single episode, moderate severity with premorbid generalized anxiety disorder (GAD). A focused psychosocial assessment using the BATHE technique was conducted.

Background: "What has been going on in your life?"
Patient Response: "I have left my boyfriend. I cannot focus at work. I do not look forward to things. I should be happy that I lost a lot of weight and am healthy now."

Affect: "How has that made you feel?"
Patient Response: "Hopeless, worthless."

Trouble: "What troubles you the most?"
Patient Response: "After my surgery, I lost weight. I used to blend into the background and now I seem to get more attention, which is good, but bad, too."

Handling: "How are you dealing with this?"
Patient Response: "I began drinking wine, but was able to give it up 2 months ago."

Empathy: Educate the patient about the diagnosis and treatment options while conveying an understanding of this change in her life.

This patient meets several criteria for depression. Once the diagnosis of MDD is established, it is key to look for comorbidities as depression, more often than not, travels with other disorders. This patient had clear generalized anxiety since childhood, and this depression has developed "on top of" a baseline of anxiety. Through further discussions with the patient, we see the potential for social anxiety as she is beginning to dislike being the center of attention as her weight decrease has called attention to her. She also began coping by using alcohol. Both anxious and depressed patients have a high utilization of alcohol as self-treatment. This should be further investigated as well.

GAD is one of the most common comorbidities and is often overlooked as many depressed patients are agitated, ruminative, and worried. The formal diagnosis per DSM-IV is as follows:

- excessive anxiety/worry for 6 months or more
- difficulty controlling worry
- often associated with three or more of the following:
  - restlessness
  - fatigue
  - poor concentration, decision making
  - irritability
  - muscle tension
  - insomnia

Management Plan

The assessment concludes that this patient has both MDD and GAD as comorbid conditions. Clinically, it will be necessary to monitor for evolution of other psychiatric comorbidities, such as a relapse into alcohol abuse. The patient screened negative for suicidality, but her complaint of hopelessness should be monitored.

Initial treatment is psychoeducation and explanation about her two disorders, validating her experience of these troublesome symptoms. Informed consent may be given regarding psychotherapy or medication management options as both have good evidence that they may help her symptoms. Cognitive Behavioral Therapy (CBT) is a short-term, outcome-based intervention where over 12 weeks the patient may learn to analyze her level of anxiety and depression. If she determines that her negative thoughts are "excessive" to her situation, then she may learn techniques to combat and short circuit these thoughts, which may lead to improved affect and decreased worry. From a medication point of view, starting with FDA-approved products that carry indications for both MDD and GAD are warranted. It is likely that any serotonin and/or norepinephrine facilitating antidepressants will help, but the FDA approval process guarantees clinicians that scrutinized and controlled data exists to provide for reproducible efficacy and tolerability. Given this, a good starting place would be to choose venlafaxineXR, paroxetine, escitalopram, or duloxetine. Dosing should be started lower than the therapeutic dose as her anxiety may make her more prone to activating side effects. However, the full dosing range should be systematically used over time in order to gain remission from symptoms. Too often patients are continued on lower, minimally effective doses. If there is minimal response, systematic dose escalation is warranted instead of switching medications too quickly. It is likely that monotherapy with one of the above medications will help both of her psychiatric disorders.

Case 2: ADHD or Anxiety?

Presentation

S.H. is a 42-year-old team manager who came to the office with a chief complaint of having difficulty coping, paying attention, and getting work done. She states that her job and classwork are faltering, and she is used to being an overachiever. She states that she used to be able to work a job, sit through classes, maintain attention, study at home, and do well. She states that the last year she has done horribly and may have to drop out of her MBA classes. On review of systems she admits to a history of worrying throughout her life, but this has not interfered with her social roles. She states that in the last 6 months, she will wake up in the morning, feel tense, have difficulty breathing, and will have nausea. There is evidence of no other psychiatric disorder.

Psychosocial Assessment

The patient's history and examination leads to a preliminary diagnosis of anxiety disorder.

Background: "What has been going on in your life?"
Patient Response: "I am a single mom of a teenager. I took a new job and haven't received the support I was promised to lead the team, and I have 2 courses left in my MBA, which I am about to fail."

Affect: "How has that made you feel?"
Patient Response: "If I could focus better, I would pass my classes and be fine."

Trouble: "What troubles you the most?"
Patient Response: "I need to pay attention."

Handling: "How are you dealing with this?"
Patient Response: "I haven't. I procrastinate and get nothing done. I am irritable."

Empathy: Educate the patient about the potential diagnosis and treatment options while conveying that she is, in reality, under a lot of stress and is burning the candle at both ends trying to achieve a lot in a short amount of time.

This patient meets some criteria for attention deficit hyperactivity disorder (ADHD). She has the following criteria:

- fails to give attention to details
- cannot sustain attention
- does not follow through on tasks
- has difficulty organizing and
- is forgetful.

However, in taking a longitudinal history, one finds no childhood evidence of inattention, hyperactivity, or impulsivity. Her symptoms have been occurring for about 1 year. This makes the diagnosis of ADHD unlikely. Her chief complaint is one of executive dysfunction (poor attention, organization) and amotivation. Interestingly, she downplays the anxiety, agitation, subsyndromal panic symptoms, and the worrying that she experiences daily. It would be pivotal to screen for anxiety disorders such as generalized anxiety, panic disorder, and possibly post-traumatic stress disorder. She may also be suffering from an adjustment disorder where she has marked social stressors in her life; this mixture of inattention, anxiety, and possibly depression (amotivation, poor concentration) symptoms may be a result of the stress itself and not part of a major mental illness, such as ADHD or panic disorder.

A supportive evaluation to realistically assess her goals of taking a new job, raising a teenager, and completing an MBA may be important. It is possible that she has overstretched her limits, which has caused the above symptoms. This realization and working towards a problem-oriented solution to decrease her stress may be helpful (ie. could she delegate some of her tasks at work? could she drop one course in school?) Another, more dynamic approach would be to see if she has always pushed herself to perform; as she has gotten older, perhaps she cannot maintain the same pace as in her twenties. Again, she may be able to use this information to make some lifestyle changes to decrease her stress, which may decrease her symptoms.

Management Plan

The assessment concludes that this patient has an adjustment disorder with mixed anxiety and depressed mood. A clinical mistake would be to take her chief complaint of inattention at face value of representing a full ADHD diagnosis. She should not be treated with ADHD medication. On the flip side, should we consider using an antidepressant or anxiolytic? As she does not have a clear major psychiatric illness, it would be clinically appropriate not to prescribe as of now. The treatment of choice for adjustment based anxiety or depression would be to provide psychotherapy, if available.

Initial treatment is psychoeducation and explanation about her symptoms, validating her experience of these troublesome symptoms. Supportive or dynamic therapy sessions using the above techniques would be the treatment of choice. If she can navigate through her stressors and cope better, her symptoms should improve.

How does one tell an "adjustment" versus a depressive or anxiety disorder? In this case, if the stressors resolve some and the patient's symptoms continue or even worsen, then the differential diagnosis would begin to include depression, panic, and generalized anxiety. If this becomes the working diagnosis, then an FDA-approved antidepressant is certainly warranted. Choosing an antidepressant approved for these three syndromes would include venlafaxineXR and paroxetine. Many of the other SSRI/SNRI antidepressants are approved in two of these areas and may also be useful. Finally, if her anxiety and depressive symptoms remit and she continues to have issues with inattention, it is possible she suffers from "adult onset" inattentive ADHD, and use of an approved ADHD medication would then ultimately be warranted.

Dr Schwartz has disclosed that he is a consultant to Wyeth. He has also received funding for clinical grants from Wyeth, Forest Laboratories, Inc., and Bristol-Myers Squibb Company.

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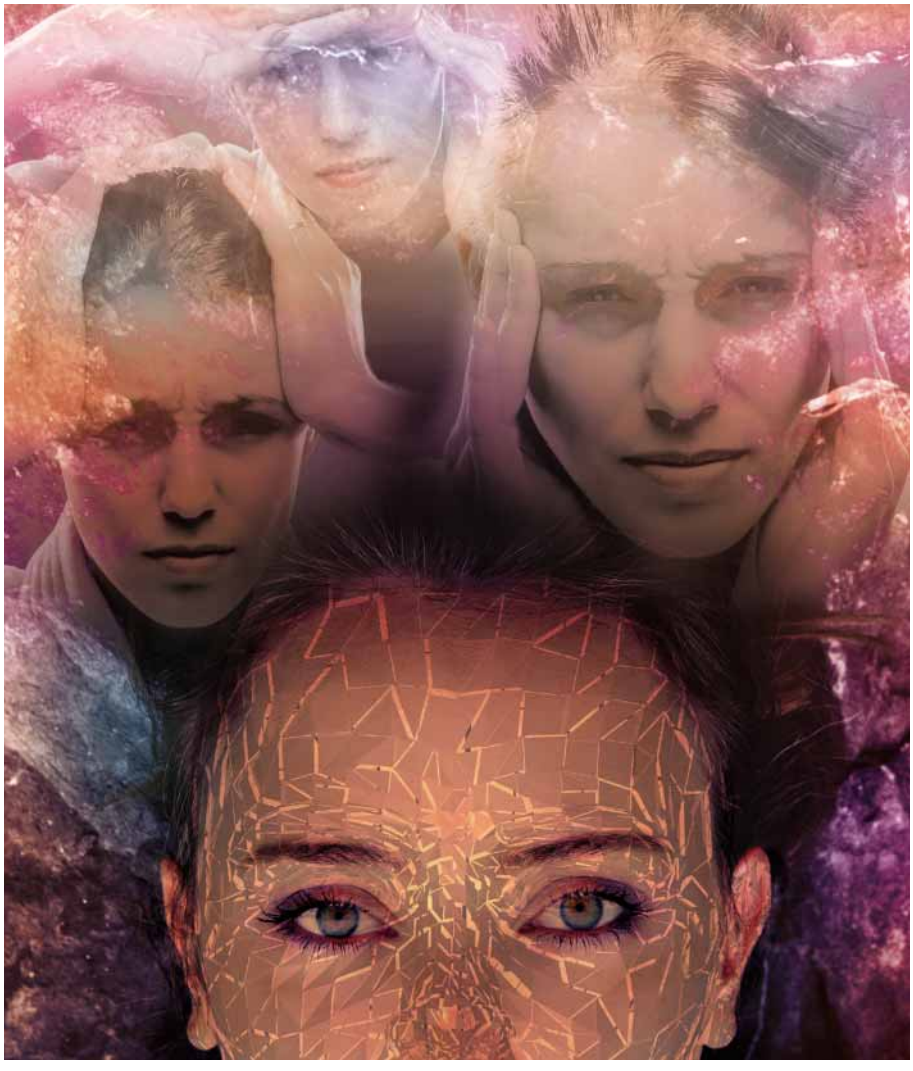
Strategies for Managing Patients With Migraine

Carolyn Bernstein, MD

Migraine is a complex disorder with variations in frequency, intensity, and symptoms from person to person and from episode to episode. Although an estimated 28 million individuals (18% of women and 6% of men) in the United States experience migraine headaches, nearly half of this population are not diagnosed and treated for this painful condition.[1,2] Furthermore, triggers for migraine can vary from person to person; various psychological, environmental, biochemical, neurophysiologic, and genetic factors may trigger migraine episodes.[3,4] Individuals may seek care when they experience several headaches per month, each lasting for several hours or days; when these headaches disrupt their home, work, or school life; or when their symptoms include nausea, vomiting, vision changes, or other sensory problems.[2]

Clinicians in the primary care setting often face challenges in recognizing and treating these patients with migraine, given the variability of its clinical presentation. This article offers practical considerations in making assessments and managing the ongoing needs of patients with migraine, highlighting the need to encourage patients with migraine to take an active role in identifying and avoiding (if possible) triggers for migraine, being alert to early symptoms of a pending attack, making lifestyle changes, and developing realistic expectations about the impact of different treatment options.



Although an estimated 28 million individuals (18% of women and 6% of men) in the United States experience migraine headaches, nearly half of this population are not diagnosed and treated for this painful condition.

Signs and Symptoms of Migraine

Migraine pain is usually unilateral and throbbing; pain also may occur on both sides of the patient's head. Ranging in intensity from mild to incapacitating, migraine pain is often accompanied by nausea and vomiting, or photophobia/phonophobia. Clinicians trained in headache care will be aware of the International Headache Society (IHS) classifications, with descriptions of at least 17 types of migraine and the criteria for diagnosis.[5]

Migraine is typically classified as classic migraine (also called migraine without aura) or common migraine (also called migraine with aura) (**Table 1**).[5] One way for clinicians to remember the diagnostic criteria for migraine is the mnemonic POUNDing (Pulsating, duration of 4–72 hOurs, Unilateral, Nausea, Disabling).[6] A diagnosis of migraine can be made based on the occurrence of at least two migraine attacks over a person's lifetime, rather than previously circulated information of at least two migraine attacks per year. If a patient has experienced only one migraine attack, it would be described as a migraine-type headache.

For those 15% to 20% of people with migraine who experience an aura, the most common aura symptoms are visual disturbances and paresthesias, which usually disappear within 60 minutes of onset.[7] Note: Patients who experience auras without a subsequent headache should be further evaluated to rule out transient ischemic attack and seizure disorders (**Table 2**).[8]

When patients report that they experience "sinus" headaches, clinicians need to be alert to the likelihood that patients with episodic headaches predominated by nasal and sinus symptoms may actually suffer from migraine. Studies have found that patients with a history of self-described or physician-diagnosed "sinus" headache and no previous diagnosis of migraine commonly met IHS criteria for migraine or migrainous headache.[9,10] Therefore, the presence of nasal or ocular symptoms, often considered to be features of "sinus" headache, requires prompt assessment for migraine and consideration of migraine-specific therapy when a diagnosis of migraine is made.[9] A sinus examination is an important part of the evaluation for these patients.

Measuring the Impact of Migraine

Developing an understanding of a patient's history of migraine-related symptoms and other headache characteristics, as well as determining any family history of similar headaches, is the basis by which a diagnosis of migraine is made. The Migraine Disability Assessment (MIDAS) questionnaire is a useful tool to gather information about the impact of a patient's headaches on the individual's life over the past 3 months.[11] Not only can this easy-to-use, five-item questionnaire be completed within 2 minutes in the initial assessment of migraine, but MIDAS also is useful to make comparisons over time; patients can see how their MIDAS scores change over time in response to treatment interventions.

In clinical practice, I give patients with migraine a diary and encourage them to do the best they can to keep track of the number of days they have a headache, rating their headaches from 1 to 10 in terms of severity. I also ask them to record which medications and the amount they take, as well as response to treatment. In addition, I encourage them to identify any factors that make one day different from another in terms of events and activities associated with the migraines (eg, weather changes, level of stress, unusual intake of alcohol, disruptions in their regular schedule for sleeping and eating). Gathering relevant information is essential in identifying possible triggers for migraine episodes and determining individualized treatment plans.

Causes of Migraine

Various theories have been developed to explain what causes migraine. The vascular theory posits that migraine is caused by dilatation and constriction of blood vessels, in which the pain is due to pressure of the blood vessels exerted on pain-sensitive structures and the focal symptoms are caused by ischemia. This theory provides the rationale for older migraine medications such as ß-blockers and calcium channel blockers.

TABLE 1. DIAGNOSTIC CRITERIA FOR MIGRAINE

MIGRAINE WITHOUT AURA

At least five headache attacks that:

- Last 4 to 72 hours if untreated or unsuccessfully treated
- Have at least two of the following characteristics:
  - Unilateral location
  - Pulsating quality
  - Moderate to severe intensity
  - Aggravated by walking up stairs or similar routine physical activity
- Are accompanied by at least one of the following symptoms:
  - Nausea, vomiting, or both
  - Photophobia and phonophobia
- No evidence of related organic diseases

MIGRAINE WITH AURA

At least two attacks with at least three of the following characteristics:

- One or more completely reversible aura symptoms that indicate focal cerebral cortical dysfunction, brain stem dysfunction, or both
- At least one aura symptom develops gradually over more than 4 minutes or two or more symptoms occur in succession
- No aura symptom lasts more than 60 minutes
- Headache follows aura in less than 60 minutes
- No evidence of related organic diseases

Source: Adapted with permission from Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia.* 2004;24(suppl 1):1-150.[5]

TABLE 2. VISUAL SYMPTOMS OF MIGRAINE AURA VERSUS TRANSIENT ISCHEMIC ATTACK

Feature	Migraine Aura	Transient Ischemia Attack
Duration	15–30 minutes	3–10 minutes
Quality	Dynamic, bright, multicolored Forms geometric patterns	Static, dark Dimming of vision

Source: Kunkel RS. Migraine aura without headache: Benign, but a diagnosis of exclusion. *Cleve Clin J Med.* 2005;72:529-534. Reprinted with permission. Copyright © 2005 Cleveland Clinic. All rights reserved.

The inflammatory theory focuses on how scalp muscles tighten initially at the beginning of the migraine. This inflammatory response follows with cellular migration, which may explain part of the process. Nonsteroidal anti-inflammatory drugs (NSAIDs)—including aspirin, naproxen, fenoprofen, ketoprofen, flurbiprofen, and mefenamic acid—have been studied for their effectiveness to abort migraine, based on the idea that they inhibit prostaglandin synthesis and platelet aggregation.[1] In my clinical experience, I have found that indomethacin may penetrate the blood-brain barrier better than do other NSAIDs and, therefore, is a treatment to consider for patients who do not receive relief with other NSAIDs. NSAIDs often work to abort migraine, but should be used with caution to avoid potential compromise of gastrointestinal and renal function.[1]

The latest theory about the causes of migraine is the neurovascular rationale, which proposes that people with migraines have some abnormality in neuronal firing. Cells depolarize and cellular depression spreads medially, which triggers thalamic pain centers as well as the nausea/vomiting center in the hypothalamus, and spreads down into the brain stem to hit the trigeminal nerve, causing the unilateral pain.

In my opinion, the truth probably lies in a combination of all three theories. For those patients with stiffness in their scalp and tenderness in their neck at the start of a migraine episode, adding an NSAID as soon as possible may be helpful. For patients with vascular symptoms plus visual changes, a ß-blocker or calcium channel blocker may be useful. For patients with a whole cascade of symptoms, medications with migraine-specific indications—such as topiramate or divalproex—may work best. Clinicians need to probe carefully for details, including the sequence of events, when determining the appropriate treatment plan for patients with migraine.

Of special note is a recently published study that found people with migraine had on average a thicker somatosensory cortex (where a pain sensation relays) than a control group of people without migraine.[12] This finding is relevant because it demonstrates that the brain is actually changing in response to being stimulated over and over again by this neurochemical cascade that triggers the migraine. In other words, the muscle contractions of migraines are causing some kind of permanent effect on the brain. This reinforces an understanding of migraine as a chronic illness, not just a headache, that requires serious attention with treatment individualized to each patient.

TABLE 3. COMMON TRIGGERS OF MIGRAINE

- Alcohol
- Anxiety
- Change in sleep pattern
- Depression
- Flashing lights, visual stimulation
- Foods and beverages containing nitrites, aspartate, glutamate, tyramine
- High altitude
- Medications—nitroglycerin, hydralazine, histamine, estrogen, reserpine, steroid withdrawal
- Menstruation, ovulation
- Organic solvents
- Perfumes
- Physical exertion
- Sexual activity
- Skipping meals
- Smoke
- Stress
- Weather changes

Source: Loj J, Solomon GD. Migraine prophylaxis: Who, why, and how. *Cleve Clin J Med.* 2006; 73:793-816. Reprinted with permission. Copyright © 2006 Cleveland Clinic. All rights reserved.

Possible Triggers of Migraine

The key to effective treatment for patients with migraine is to establish a positive working relationship between the clinician and patient to tailor treatment to the severity and frequency of migraine episodes.[6] Identification of factors that may trigger migraines is an important aspect of care (**Table 3**).[1] A recent study reported that 75.9% of the 1,207 patients evaluated for precipitants of acute migraine attack reported triggers that included stress (79.7%), hormones in women (65.1%), not eating (57.3%), weather (53.2%), sleep disturbance (49.8%), perfume or odor (43.7%), neck pain (38.4%), light(s) (38.1%), alcohol (37.8%), smoke (35.7%), sleeping late (32.0%), heat (30.3%), food (26.9%), exercise (22.1%), and sexual activity (5.2%).[13]

Asking patients to think about what may have caused a particular headache can be useful. The list of possibilities is legion, ranging from caffeine withdrawal and mood change to sleep deprivation or excess. In addition, asking patients about what they have done in the past to relieve migraine pain can be useful. Which medications have they used and was anything helpful? Have any nonpharmacologic interventions (eg, locally applied heat or cold, massage, hot showers, rest in a quiet, darkened room) been useful in reducing migraine pain? Have they tried relaxation techniques, yoga, meditation, biofeedback, acupuncture, or other interventions to achieve symptom relief? Patients with migraine are best served when they participate in the management of their individualized treatment plan (**Table 4**).[7]

Determining Appropriate Pharmacologic Therapy

For patients with migraine, the best defense is a good offense.[14] Preventive, abortive, and rescue medications are available treatment options to consider. Medications currently used to prevent migraine include ß-blockers, anticonvulsants, antidepressants, calcium channel blockers, and NSAIDs.[1] Abortive medications include triptans, ergot alkaloids (never give ergot to people with hypertension), and anti-inflammatory agents. Rescue therapy includes subcutaneous sumatriptan, phenothiazine, parenteral nonsteroidal agents and corticosteroids, and opioid analgesics.[1] Many of these agents are available in different formulations, including injection, nasal spray, and melts.

TABLE 4.
PRINCIPLES OF ACUTE MIGRAINE TREATMENT

- Educate patients about their condition and its treatment and encourage them to participate in their own treatment
- Use migraine-specific agents (triptans, dihydroergotamine, ergotamine) in patients with more severe migraine and in those whose headaches respond poorly to nonsteroidal anti-inflammatory drugs or combination analgesics
- Select a nonoral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex
- Consider a self-administered rescue medication for patients with severe migraine that does not respond well to other treatments
- Guard against medication-overuse headache (rebound or drug-induced headache)

Source: Adapted from Matchar DB, Young WB, Rosenberg JH, et al. Evidence-based guidelines for migraine headache in the primary care setting: Pharmacologic management of acute attacks. Available at: http://www.aan.com/professionals/practice/pdfs/gl0087.pdf. Accessed April 16, 2008.

In my clinical experience, topiramate is one of the best medications for migraine prophylaxis. Keep in mind that increasing the daily dose to 100 mg or more can interfere with the effectiveness of oral contraceptives. I also tell my patients with migraine about the increased predisposition to kidney stones with the use of topiramate and encourage them to drink plenty of water, as well as the rare (but mostly reversible) occurrence of acute myopia with vision loss; I instruct them to stop taking this medication right away if their vision begins to blur. I also point out that, unlike several other migraine prophylactic agents, topiramate is associated with weight loss.[1]

Tips on Emergency Room Visits for Migraine

Clinicians certainly understand that patients want to avoid a visit to the emergency room when they have a migraine. The emergency room typically has bright lights, noisy people, and long waiting times—all elements that can make a person with migraine feel even worse. Furthermore, surveys have found that people who work in the emergency room often regard people with migraine as drug seekers. To help improve the situation for patients with migraine who are unable to avoid emergency room visits or have travel plans, clinicians are encouraged to plan ahead. For example, clinicians can download a form available at the National Headache Foundation web site (https://www.headaches.org/pdf/physicianmigraineerform.pdf), print it out, and provide it to the patient. This completed form will state that a valid diagnosis of migraine has been made for this patient, as well as information on which medications have been helpful in previous episodes for this patient and any recommendations for rescue therapy (eg, an injection of ketorolac).

Conclusion

Clinicians in the primary care setting can help identify patients with migraine and provide effective treatment options to help prevent migraine episodes and relieve symptoms when migraine episodes occur. Despite the variability of its clinical presentation, migraine can be diagnosed and treated with the use of preventive, abortive, and rescue therapies. Establishing a positive working relationship between the clinician and patient is a key component in tailoring treatment to the severity and frequency of migraine episodes. ■

Dr Berstein has nothing to disclose.

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CYMBALTA®

(duloxetine hydrochloride) Delayed-release Capsules

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

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

INDICATIONS AND USAGE: Major Depressive Disorder—Cymbalta is indicated for the acute and maintenance treatment of major depressive disorder (MDD).

Diabetic Peripheral Neuropathic Pain—Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy.

Generalized Anxiety Disorder—Cymbalta is indicated for the acute treatment of generalized anxiety disorder (GAD).

CONTRAINDICATIONS: Monoamine Oxidase Inhibitors—Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome *[see Warnings and Precautions]*.

Uncontrolled Narrow-Angle Glaucoma—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk—Patients with major depressive disorder (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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients 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 Warnings and Precautions, Discontinuation of Treatment with Cymbalta]*.

Families and caregivers of 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.

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 (duloxetine) is not approved for use in treating bipolar depression.

Hepatotoxicity—Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.3% (73/23,983) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1.1% (75/6871) of Cymbalta-treated patients compared to 0.3% (13/5036) 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 Warnings and Precautions and 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.

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 (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated *[see Contraindications]*.

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 Drug Interactions]*.

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

Cymbalta® (duloxetine hydrochloride) PV 5907 AMP

Abnormal Bleeding—SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis and vertigo.

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 (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with 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.

Activation of Mania/Hypomania—In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2327) of duloxetine-treated patients and 0.1% (1/1460) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP or GAD placebo-controlled trials. Activation of mania or 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 major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.04% (3/8504) of patients treated with duloxetine and 0.02% (1/6123) of patients treated with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

Effect on Blood Pressure—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg BID. At the highest 200 mg BID dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 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]*.

Clinically Important Drug Interactions—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Potential for Other Drugs to Affect Cymbalta—*CYP1A2 Inhibitors*—Co-administration of Cymbalta with potent CYP1A2 inhibitors should be avoided *[see Drug Interactions]*.

CYP2D6 Inhibitors—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine *[see Drug Interactions]*.

Potential for Cymbalta to Affect Other Drugs—*Drugs Metabolized by CYP2D6*—Co-administration of Cymbalta with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., 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 *[see Drug Interactions]*.

Other Clinically Important Drug Interactions—*Alcohol*—Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with substantial alcohol use *[see Warnings and Precautions and Drug Interactions]*.

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 *[see Warnings and Precautions and Drug Interactions]*.

Hyponatremia—Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Cymbalta. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk *[see Use in Specific Populations]*. Discontinuation of Cymbalta should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

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. 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 (e.g., 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.

Hepatic Insufficiency—Cymbalta should ordinarily not be used in patients with hepatic insufficiency *[see Warnings and Precautions and Use in Specific Populations]*.

Severe Renal Impairment—Cymbalta should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) *[see Use in Specific Populations]*.

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]*.

Glycemic Control in Patients with Diabetes—As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta and by 0.2% in the routine care groups.

Urinary Hesitation and Retention—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.

In post marketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

Laboratory Tests—No specific laboratory tests are recommended.

ADVERSE REACTIONS: Clinical Trial Data Sources—The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2327), DPNP (N=568) and GAD (N=668). The population studied was 17 to 89 years of age; 64.8%, 38.7%, and 64.7% female; and 85.5%, 77.6%, and 84.6% Caucasian for MDD, DPNP, and GAD, respectively. Most patients received doses of a total of 60 to 120 mg per day.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

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

Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Diabetic Peripheral Neuropathic Pain—Approximately 14.3% (81/568) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 7.2% (16/223) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) were nausea (duloxetine 3.5%, placebo 0.4%), dizziness (duloxetine 1.6%, placebo 0.4%), somnolence (duloxetine 1.6%, placebo 0.0%), and fatigue (duloxetine 1.1%, placebo 0.0%).

Generalized Anxiety Disorder—Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

Adverse Reactions Occurring at an Incidence of 5% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—The incidence of treatment-emergent adverse reactions in placebo-controlled trials (N=3563 Cymbalta; N=2178 placebo) for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo were: nausea, dry mouth, diarrhea, dizziness*, insomnia (includes middle insomnia, early morning awakening, and initial insomnia), fatigue* (includes asthenia), somnolence* (includes hypersomnia and sedation), constipation*, decreased appetite* (includes anorexia), and hyperhidrosis. *Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

The most commonly observed adverse reactions in duloxetine-treated patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

Adverse Reactions Occurring at an Incidence of 2% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Pooled MDD and GAD Trials—Table 3 in full PI gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials (N=2995 Cymbalta; N=1955 placebo) for approved indications that

occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo were: Cardiac Disorders—palpitations; Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, diarrhea, constipation*, abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain), vomiting; General Disorders and Administration Site Conditions—fatigue (includes asthenia); Investigations—weight decreased*; Metabolism and Nutrition Disorders—decreased appetite (includes anorexia); Nervous System Disorders—dizziness, somnolence (includes hypersomnia and sedation), tremor; Psychiatric Disorders—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), anxiety, decreased libido (includes loss of libido), orgasm abnormal (includes anorgasmia), abnormal dreams (includes nightmare); Reproductive System and Breast Disorders—erectile dysfunction, ejaculation delayed, ejaculation disorder (includes ejaculation failure and ejaculation dysfunction); Respiratory, Thoracic, and Mediastinal Disorders—yawning; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—hot flush. *Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

The most commonly observed adverse reactions in duloxetine-treated MDD/GAD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were nausea, dry mouth, constipation, somnolence, decreased appetite, and hyperhidrosis.

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.

Effects on Male and Female Sexual Function—Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions 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. Physicians should routinely inquire about possible sexual side effects. See Table 5 in full PI for specific ASEX results.

Vital Sign Changes—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure *[see Warnings and Precautions]*.

Duloxetine treatment, for up to 13-weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3 beats per minute.

Weight Changes—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

Laboratory Changes—Cymbalta treatment in 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 Warnings and Precautions]*.

Electrocardiogram Changes—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13-weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg BID, no prolongation of the corrected QT interval was observed.

Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine—Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 23,983 patients were treated with duloxetine. Of these, 6,702 took duloxetine for at least 6 months, and 3,006 for at least one year. The following listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. Cardiac Disorders—*Frequent:* palpitations; *Infrequent:* myocardial infarction and tachycardia; Ear and Labyrinth Disorders—*Frequent:* vertigo; *Infrequent:* ear pain and tinnitus; Endocrine Disorders—*Infrequent:* Hypothyroidism; Eye Disorders—*Frequent:* vision blurred; *Infrequent:* diplopia and visual disturbance; Gastrointestinal Disorders—*Frequent:* flatulence; *Infrequent:* eructation, gastritis, halitosis, and stomatitis; *Rare:* gastric ulcer, hematochezia, and melena; General Disorders and Administration Site Conditions—*Frequent:* chills/rigors; *Infrequent:* feeling abnormal, feeling hot and/or cold, malaise, and thirst; *Rare:* gait disturbance; Infections and Infestations—*Infrequent:* gastroenteritis and laryngitis; Investigations—*Frequent:* weight increased; *Infrequent:* blood cholesterol increased; Metabolism and Nutrition Disorders—*Infrequent:* dehydration and hyperlipidemia; *Rare:* dyslipidemia; Musculoskeletal and Connective Tissue Disorders—*Frequent:* musculoskeletal pain; *Infrequent:* muscle tightness and muscle twitching; Nervous System Disorders—*Frequent:* dysgeusia, lethargy, and parasthesia/hypoesthesia; *Infrequent:* disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; *Rare:* dysarthria; Psychiatric Disorders—*Frequent:* abnormal dreams and sleep disorder; *Infrequent:* apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; *Rare:* completed suicide; Renal and Urinary Disorders—*Infrequent:* dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal; Reproductive System and Breast Disorders—*Frequent:* anorgasmia/orgasm abnormal; *Infrequent:* menopausal symptoms, and sexual dysfunction; Respiratory, Thoracic and Mediastinal Disorders—*Frequent:* yawning; *Infrequent:* throat tightness; Skin and Subcutaneous Tissue Disorders—*Infrequent:* cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; *Rare:* ecchymosis; Vascular Disorders—*Frequent:* hot flush; *Infrequent:* flushing, orthostatic hypotension, and peripheral coldness.

Postmarketing Spontaneous Reports—The following adverse reactions have been identified during postapproval use of Cymbalta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

DRUG INTERACTIONS: Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2—When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, andduloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin *[see Warnings and Precautions]*.

Inhibitors of CYP2D6—Concomitant use of duloxetine (40 mg QD) with paroxetine (20 mg QD) increased the concentration of duloxetine AUC 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 (e.g., fluoxetine, quinidine) *[see Warnings and Precautions]*.

Dual Inhibition of CYP1A2 and CYP2D6—Concomitant administration of duloxetine 40 mg BID with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and C_{max}.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)—Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued *[see Warnings and Precautions]*.

Lorazepam—Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam—Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

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 (e.g., 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 *[see Warnings and Precautions]*.

Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg BID).

Cymbalta® (duloxetine hydrochloride) PV 5907 AMP

Drugs Metabolized by CYP2D6—Duloxetine 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 *[see Warnings and Precautions]*.

Drugs Metabolized by CYP2C9—Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19—Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Monoamine Oxidase Inhibitors—Switching Patients to or from a Monoamine Oxidase Inhibitor—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI *[see Contraindications and Warnings and Precautions]*.

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 co-administered 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. The concomitant use of Cymbalta with other SSRIs, SNRIs or tryptophan is not recommended *[see Warnings and Precautions]*.

Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Warnings and Precautions]*.

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 Warnings and Precautions]*.

CNS Drugs—*[see Warnings and Precautions]*.

Drugs Highly Bound to Plasma Protein—Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

USE IN SPECIFIC POPULATIONS: Pregnancy—Teratogenic Effects, 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 rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbit). 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 rat; 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 and Precautions]*.

When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

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 Boxed Warning and Warnings and Precautions]*. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPNP studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Cymbalta have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions]*.

Gender—Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Smoking Status—Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race—No specific pharmacokinetic study was conducted to investigate the effects of race.

Hepatic Insufficiency—*[see Warnings and Precautions]*.

Severe Renal Impairment—*[see Warnings and Precautions]*.

DRUG ABUSE AND DEPENDENCE: Abuse—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential.

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 (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Dependence—In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

OVERDOSAGE: Signs and Symptoms—In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

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.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and 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 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.

PATIENT COUNSELING INFORMATION: See FDA-approved Medication Guide and Patient Counseling Information section of full PI.

Literature revised December 13, 2007

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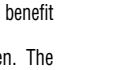

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† Cymbalta 60 mg/day vs placebo ($P \leq .05$) by MMRM for MDD on mean change in HAM-D_{17} Total Score, Maier Subscale, Psychic Anxiety, and Visual Analog Pain Scales. Full antidepressant response may take 4-6 weeks. MMRM=Mixed-effects Models Repeated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

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Important Safety Information

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders.**
- **Patients of all ages started on therapy should be monitored appropriately and 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 in patients with uncontrolled narrow-angle glaucoma.

Clinical worsening and suicide risk: All patients being treated with an antidepressant for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially within the first few months of treatment and when changing the dose. Consider changing the therapeutic regimen 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. **Families and caregivers of patients being treated with antidepressants for any indication should be alerted about the need to monitor patients.**

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

Cymbalta should ordinarily 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.

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.

SSRIs and SNRIs, including Cymbalta, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with concomitant use of Cymbalta and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.

On discontinuation, adverse events, some of which may be serious, have been reported with SSRIs and SNRIs. A gradual reduction in dose rather than abrupt cessation is recommended when possible.

Coadministration of Cymbalta with potent CYP1A2 inhibitors or thioridazine should be avoided.

Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics).

Cymbalta should ordinarily 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).

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

If symptoms of urinary hesitation develop during Cymbalta treatment, this effect may be drug-related. In postmarketing experience, urinary retention has been observed.

The most commonly reported adverse events (≥5% and at least twice placebo) for Cymbalta vs placebo in controlled clinical trials (N=3563 vs 2178) were: nausea, dry mouth, somnolence,* constipation,* decreased appetite,* and increased sweating.

* Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding 3 MDD studies which did not have a placebo lead-in period or dose titration.

See Brief Summary of full Prescribing Information, including Boxed Warning, on following pages.

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