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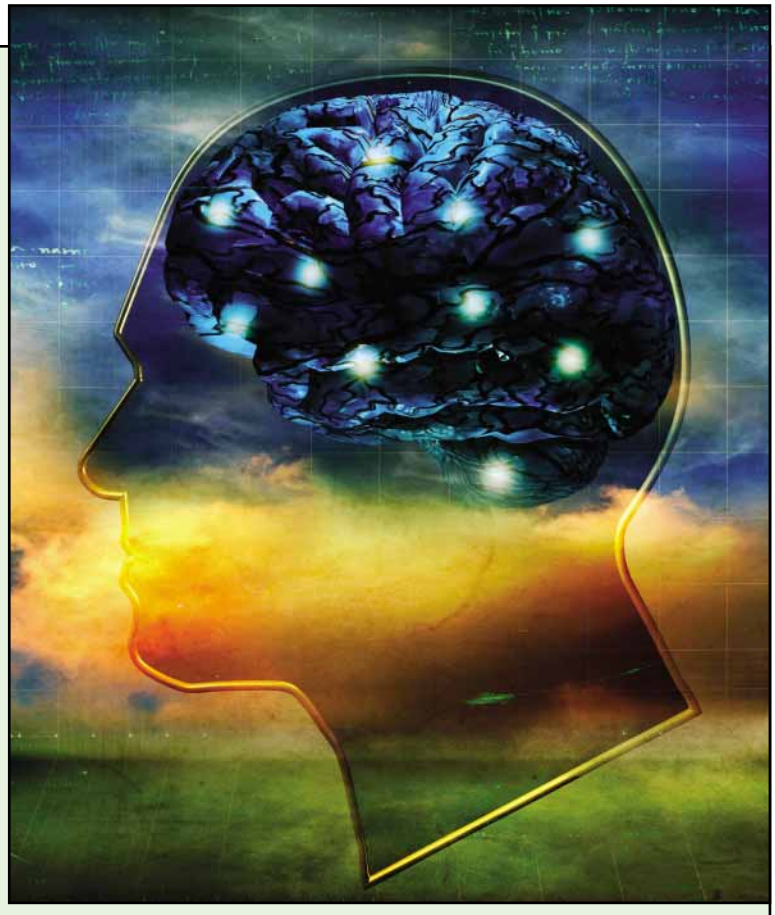

Special Populations in Depression
Managing Care for Patients With Depression and Comorbid Health Problems

Larry Culpepper, MD, MPH
Guest Editor
Chief of Family Medicine, Boston Medical Center
Professor and Chairman of Family Medicine
Boston University School of Medicine
Boston, Mass.

Clinical Approaches to Patient Concerns About Memory Loss

Richard J. Caselli, MD
Chair, Department of Neurology
Mayo Clinic Scottsdale (Arizona)
Professor of Neurology
Mayo Clinic College of Medicine
Rochester, Minn.

Social and Emotional Costs of Learning Disabilities

Carl C. Bell, MD
Chief Executive Officer and President
Community Mental Health Council Inc.
Director, Public and Community Psychiatry
University of Illinois, Chicago, Ill.

Case Files

Bill McCarberg, MD
Founder, Chronic Pain Management Program
Kaiser Permanente
Escondido, Calif.

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Practical Neuroscience for Primary Care Physicians is a publication series brought to you by Family Practice News and Internal Medicine News, the leading independent medical newspapers for primary care physicians. Each issue provides primary care physicians with timely and relevant clinical updates in neuroscience on depression and anxiety, headache, insomnia, pain management, and other topics that are immediately useful in day-to-day patient care. Featured are in-depth articles, case studies, and columns presented by thought leaders.

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INTERNATIONAL MEDICAL NEWS GROUP

From the Desk of...

Welcome to the Spring 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.

I lead off this issue by discussing managing the care of patients with depression and comorbid health problems. **Richard J. Caselli, MD**, Chair, Department of Neurology, Mayo Clinic Scottsdale (Arizona), and Professor of Neurology, Mayo Clinic College of Medicine, Rochester, Minnesota, lends his expertise on approaching patient concerns about memory loss. In the 'Case Files' section of the supplement, **Bill McCarberg, MD**, Founder, Chronic Pain Management Program, Kaiser Permanente, Escondido, California, shares case studies of patients presenting with pain.

To access all 2007 issues as well as current issues of *Practical Neuroscience for Primary Care Physicians*, visit www.familypracticenews.com or www.internalmedicinenews.com. The supplements can be found under the Medical Education Library. NOTE: The publication's original Web site, www.practicalneuroscience.com, is no longer active.

As always, if you would like to submit a case study or send in comments, you can still reach us at physiciansfeedback@elsevier.com.

Cordially,

Larry Culpepper, MD, MPH
Guest Editor
Chief of Family Medicine, Boston Medical Center
Professor and Chairman of Family Medicine
Boston University School of Medicine
Boston, Mass.

Larry Culpepper, MD, MPH

Managing Care for Patients With Depression and Comorbid Health Problems

Addressing the complexities of comorbidity is one of the many challenges that clinicians face in the primary care setting. Comorbidity can be defined as "the co-occurrence (or dual diagnosis) of two disorders or syndromes in the same patient, regardless of whether the disorders are coincidentally or causally linked, or whether they co-occur more than expected by chance."[1] In particular, depression can occur with any medical illness. This article describes practical considerations relating to the importance of being alert for risk factors and symptoms of depression when treating patients with various medical illnesses, highlighting the need for increased awareness about patterns of co-occurrence of mental disorders and medical illnesses.

Overlap With Other Health Problems

Depression is a multisystem disorder that affects immunologic, endocrine, vascular, and neural function.[1] Furthermore, studies have found that up to 60% of people with major depressive disorder (MDD) also met the criteria for an anxiety disorder, applying the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition; *DSM-IV*) criteria for all diagnoses.[2,3] The multifaceted nature of depression is useful to keep in mind when considering the wide range of medical illnesses that may co-occur with clinical depression, such as diabetes, cancer, heart disease, human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), chronic pain, or neurologic disorders including dementia and multiple sclerosis (**Table 1**).[4]

"The multifaceted nature of depression is useful to keep in mind when considering the wide range of medical illnesses that may co-occur with clinical depression."

For example, depression is associated with both the development and the adverse outcomes of heart disease, in which biologic pathways involving the sympathetic nervous system, the hypothalamic-pituitary axis, and the coagulation pathway are all implicated.[4] Depression—both MDD and depressive symptoms—increases short-term and long-term mortality in patients following myocardial infarction (MI) and also is a predictor of having an acute coronary event in the general population.[5]

Now regarded as an independent risk factor for cumulative mortality following heart attack,[6-9] depression was reported in one meta-analysis as being associated with a more than twofold increase in risk of a worse cardiovascular outcome among post-MI patients[10]; another study found that severely depressed patients with congestive heart failure show a fourfold increase in mortality.[11] Research has not yet made it clear whether this excess of cardiovascular deaths in post-MI patients with depression is because of behavioral factors (poor adherence to exercise or medication regimens), alterations in platelet function, an increase in inflammatory factors that result in cardiac irritability, or, as is most likely, the combination of these.[1]

With respect to the use of cognitive behavior therapy versus pharmacologic therapy for post-MI patients with depression, researchers who conducted the Enhancing Recovery in Coronary Heart Disease (ENRICHD) Patients study monitored the progress of 2,481 patients following an acute MI who were either depressed or had low social support.[12] They were randomized to either 16 weeks of cognitive behavior therapy or care provided only by their physician. Approximately 20% of both groups also received a selective serotonin reuptake inhibitor (SSRI) due to the severity of their depression. No difference in survival rates were detected between the two groups during follow-up of at least 18 months, although those in both groups with severe depression also treated with an SSRI did have better outcomes.

Although studies have found that depression associated with chronic medical conditions leads to worse outcomes for the chronic illness, no studies have been conducted yet showing that treating depression can prevent the development of other comorbidities. However, several studies have found that treating depression can improve comorbid medical outcomes.[13]

TABLE 1. MEDICAL DISORDERS THAT COMMONLY COEXIST WITH DEPRESSION AND ANXIETY[4]

Cardiovascular
Myocardial infarction, angina, coronary artery disease
Cardiac arrhythmias
Congestive heart failure
Mitral valve prolapse

Pulmonary
Asthma
Chronic obstructive pulmonary disease
Pneumonia
Pulmonary embolus
Pneumothorax

Neurologic
HIV/AIDS dementia
Parkinson's disease
Alzheimer's disease
Cerebrovascular accident
Chronic pain
Central nervous system tumor
Complex partial seizures
Encephalopathy
Encephalitis

Endocrine
Carcinoid syndrome
Hypoglycemia
Hypothyroid and hyperthyroid states
Hypoparathyroidism and hyperparathyroidism
Pheochromocytoma

Gastrointestinal
Gastroesophageal reflux disorder
Irritable bowel syndrome

Metabolic
Anemia
Dehydration
Electrolyte imbalance
Hepatic failure
Hypoxia
Porphyria

Other Conditions
Drug-induced (eg, steroids, drugs of abuse, "natural products" containing stimulants)
Drug withdrawal
Rheumatoid arthritis
Systemic lupus erythematosus
Chronic fatigue syndrome
Vitamin B_{12} deficiency

HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome.

Barriers to Recognizing and Treating Depression

Major depression is more common in medically ill individuals than in the general population, according to numerous studies.[14-17] However, the frequent comorbidity of depression with medical illness presents both diagnostic and treatment challenges to clinicians.

The conventional approach has been to view the relationship between medical illness and depression as one in which the medical illness leads to depression.

In other words, individuals who develop a medical illness may perceive it as a loss (reduced quality of life and self-image), with the development of depression as a reactive response to this loss. However, many clinicians are coming to understand that the reverse may be true; namely, people may start out with a genetic underpinning for depression that then interacts with environmental stresses, with the burden of stress having a cumulative influence from early life into the adult years. Although depression is sometimes viewed as episodic, it may be better described as a chronic illness with episodic symptomatology. Taking into account the lifespan development of illness, such combined forces as additional stress leading to long-term alteration in the sympathetic nervous system, an individual's management of stress and anxiety, increases in catecholamine levels, and decreased cardiac resilience can conceivably lead to the development of chronic illness. Depression may neither be recognized nor diagnosed until the patient seeks medical attention for the chronic illness.

TABLE 2. BARRIERS TO ACCURATE DIAGNOSIS OF DEPRESSION[4]

- Time constraints
- Lack of reimbursement
- Discomfort with uncertainty
- Focus on making a single diagnosis
- The need to rule out all medical diagnoses before provisionally accepting a psychiatric diagnosis
- "Either/or" mentality—either a psychiatric or medical diagnosis
- Mental illness stigma
- Concern about inflicting psychologic harm

One study has reported that up to 50% of the depressive episodes in patients with medical illness are not accurately diagnosed.[18] Time constraints, a focus on making a single diagnosis, and discomfort with uncertainty are just a few of the barriers to an accurate diagnosis of depression (**Table 2**).[4] Whereas reducing the duration of the primary care visit may improve physician productivity by increasing the number of patients seen per unit of time, shorter visits may be associated with such adverse effects as reductions in provision of certain preventive services, participation of patients in medical decision making, attention to psychosocial problems, and patient satisfaction.[19] Furthermore, even when clinicians are motivated to screen for depression, it can be a difficult task to differentiate somatic symptoms of depression (eg, sleep difficulties, loss of energy, weight change, change in appetite) from physiologic processes associated with the medical illness.[18] In such cases, cognitive and mood symptoms remain reliable (eg, impaired concentration, guilt, low mood, and anhedonia).[20]

One example that demonstrates the need to overcome these barriers is a 45-year-old woman who came for an office visit with chest pain, which was initially diagnosed as angina and treated in a standard way (including a beta blocker and calcium channel blocker, and treatment for hypertension). This patient did not comply with her medical regimen during the next 6 months. One weekend she came into the emergency room and had a mild cardiac event, resulting in hospital admission. As part of the admission procedure, the cardiologist recognized the depression through the routine use of the Patient Health Questionnaire-9 screening tool. Following the cardiac event, the patient was referred back to her primary care physician, who unfortunately did not understand the relationship between depression and comorbid medical illness and regarded the depression as a reactive response to the heart attack that did not require treatment. Over the next 6 weeks, this patient did not comply with her cardiac care regimen. She had another MI about 2 months later. At that point, she received treatment for depression with an antidepressant. During the first 2 to 3 weeks of cardiac rehabilitation, she was neither fully participating in nor receiving much benefit from rehabilitation. However, after 6 weeks, her cardiac care team was amazed that she became actively engaged in rehabilitation and was doing quite well. The progression coincided with the onset of antidepressant induced remission of depressive symptoms.

Screening Patients for Risk Factors

Not only is it important to look for risk factors relating to cardiac disease and diabetes, but clinicians need to treat depression as a condition that requires screening, both in its own right and because it now does appear to be a potent risk factor for medical illness. When a patient has risk factors for a medical illness, it is prudent to conduct a screening for depression. For patients with existing chronic illness, any new illness event (eg, acute MI, worsening of diabetes, hospital admission for congestive heart failure) ought to trigger surveillance for depression, including additional screening.

Risk factors for depression include a family history of mental illness, chronic physical or mental disorders, major life changes and stress, little or no social support, low self-esteem and/or persistent low mood, being female (women experience depression about twice as often as do men), and a history of difficult experiences as a child.[21]

The key is to recognize depression early, develop an adequate diagnostic assessment, implement effective short- and long-term treatment and management strategies, and integrate the ongoing surveillance of depression within the treatment care plan through frequent contact to address other health problems of the patient.[22]

Part of the initial assessment for depression involves evaluating whether a patient is having suicidal thoughts. Since our ability to predict suicidal activity is very

TABLE 3. KEY ANTIDEPRESSANT INSTRUCTIONS FOR PATIENTS

- Antidepressants work only if taken every day.
- Antidepressants are not addictive.
- Benefits from medication appear slowly over several weeks.
- Continue antidepressants even after you feel better.
- Mild side effects are common and usually improve with time.
- If you are thinking of stopping the medication, call your physician first.
- The goal of treatment is complete remission, but this sometimes takes several medication adjustments.

Source: Adapted from Lin EH, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care.* 1995;33:67-74.

weak, frequent follow-up and in some cases timely referral for a psychiatric consultation is appropriate for patients who are assessed for being at risk to take self-destructive actions. Studies have found that most depressed individuals who eventually commit suicide seek professional help within 1 month before death. However, most of these individuals are not taking any antidepressant medications at the time of death.[23] This may suggest that lack of treatment contributes to suicide risk, and perhaps more widespread antidepressant treatment can reduce suicide rates.

Ongoing Follow-Up

Depression can be treated successfully in most patients by primary care physicians.[24] Managing the care of patients with depression involves patient education, shared decision making regarding treatment, supportive counseling, and treatment-specific counseling. When pharmacologic therapy is determined to be the appropriate course of action, the plan is to provide antidepressant medications at adequate doses, monitor the response to treatment in terms of symptoms and any side effects, make regimen adjustments as needed, and switch agents or add new medications to the regimen only after an adequate trial.[24]

Ongoing patient education about the proper use of antidepressant therapy is critical (**Table 3**).[25] Of special concern are the data on patients with depression who discontinue antidepressant treatment without alerting their clinician. Rates of treatment discontinuation within 3 months after the start of antidepressant therapy reach up to 68%, depending on the type of antidepressant and the populations studied.[26] This often occurs because patients feel better. Ongoing patient education is important; patients often do not remember what they were told when they first started their antidepressant medication. Clinicians need to closely monitor the patient's response to therapy at 6 weeks to 12 weeks, assessing the patient's improvement and stressing the critical importance of long-term therapy in maintaining this improvement.

The goals for long-term management of depression include attaining full remission of depressive symptoms, helping the patient return to an acceptable functional status, integrating care for depression with the treatment of other chronic illnesses, maintaining pharmacologic treatment as needed, and preventing relapse or recurrence of depressive symptoms.[22] Treating depression may improve the patient's adherence to the regimen for addressing other chronic health problems.

Conclusion

Increased awareness about patterns of co-occurrence of mental disorders and medical illnesses can be useful in caring for patients in the primary care setting. Achieving optimal outcomes in patients with depression and comorbid health problems involves the recognition of depressive symptoms, persistence in clearly communicating the need and options for effective treatment, and vigilance in providing ongoing follow-up care.

Dr Culpepper has disclosed that he is a consultant to Eli Lilly and Company, Forest Laboratories, Inc., Neurocrine Biosciences, Inc., Pfizer Inc., and Wyeth. He is also on the speaker's bureau for Forest, Pfizer, and Wyeth.

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CASE FILES

Bill McCarberg, MD

Case 1: Female Presenting With Postherpetic Neuralgia

Presentation

G.M. is an 82-year-old female who has been seen for the last 15 years. She has hypertension, hypercholesterolemia, osteoporosis, and mild depression. She admits not wanting to take medication and stops treatment without consultation. Despite regular visits, her blood pressure and cholesterol are still poorly controlled.

Despite having a depressed mood, lack of enthusiasm, fatigue, insomnia, and diminished interest in pleasurable activities, G.M. denies depression: "If only my children would visit me more, I would feel fine."

G.M. calls the office complaining of a spider bite, which is itching and painful, but exhibits no skin rash. She is prescribed triamcinolone 0.1% cream and is scheduled for an appointment in 1 week. Two days later G.M. presents to the office as a walk-in with a chief complaint of a "spider bite." "It must still be in my bed because my pain is worse and I have several bites now." She describes the pain as horrible, achiness with occasional stabbing sensations. When asked about a pain score, G.M. says the pain is 11 out of 10.

Initial Evaluation

G.M. is 5'2" tall and weighs 184 lb. Her vital signs include blood pressure 148/82 mm Hg and pulse 82 bpm. She is on the following medications: atenolol 50 mg, simvastatin 40 mg, alendronate 70 mg weekly, and triamcinolone 0.1% cream.

Initial Assessment

The exam reveals a vesicular rash covering a large area below the patient's left breast. Diagnosis of recurrent herpes zoster is made. The diagnosis of herpes zoster can be made on history and physical exam alone.

G.M. is at risk for developing postherpetic neuralgia due to her age, severity of the pain at onset, and the wide area of skin involved. She is started on an antiviral, tapering prednisone, a hydrocodone product, and is scheduled to be seen in the office in 4 weeks.

On return, G.M. is accompanied by her daughter. G.M. looks unkempt and is depressed, moaning, and holding her left side. The daughter states, "My mother won't even wear a bra, it hurts so much. I don't think she has slept a wink since the last visit and she refuses to eat."

Examination reveals an extremely sensitive area to touch over the T8 and T9 dermatome with areas of numbness. Although the diagnosis of postherpetic neuralgia cannot be made until 3 months after onset of the rash, G.M. is clearly experiencing neuropathic pain with pain to light touch (allodynia) and loss of sensation (numbness). She is also having multiple quality-of-life issues related to her pain. Her underlying depression is worsening, her will to live has lessened, and her insomnia has worsened because of the pain, and she is not eating.

Treatment Plan

Aggressive management of her sleep, depression, and pain are necessary to return G.M. to a better quality of life. Duloxetine is prescribed as it will treat the pain and the depression at the same time. The patient was started on 30 mg of duloxetine to be taken first thing in the morning with a meal. One week later the dose was increased to 60 mg and by 2 weeks her pain level was well controlled and she was able to stop her hydrocodone product. The daughter was pleased with the results and noted that G.M. had gained weight as she was eating again.

Dr McCarberg has disclosed that he is on the speaker's bureau for Alpharma Inc., Cephalon, Inc., Eli Lilly and Company, Endo Pharmaceuticals, Merck & Co., Inc., Ortho-McNeil Pharmaceutical, Inc., Pfizer Inc., and Pricara.

To submit a case study for possible inclusion in an upcoming issue and for guidelines on submitting a case file, please email us at physiciansfeedback@elsevier.com.

Case 2: Male Presenting With Diabetes and Pain

Presentation

T.R. is a 62-year-old male with a history of diabetes for 26 years. As is typical for diabetics, he also has hypercholesterolemia and hypertension. He developed shortness of breath while at his sedentary desk job, leading to a diagnosis of coronary artery disease. T.R. continues to struggle in keeping his blood sugar below 180. His hemoglobin A1c ranged from 8 to 9.5. Patient states, "My mother had diabetes, my father has diabetes, and I have two sisters with diabetes; it's in the family, I feel fine. Besides those sugar testers cost too much."

Over the last five months, T.R. noticed aching and burning in his feet that is especially bothersome at night. A monofilament exam had been done for years and polyneuropathy was diagnosed but asymptomatic; therefore, the patient ignored the condition. Now, the patient is not sleeping, worried about his heart, and believes there is no control: "My father died at 64 years old, I guess I'm following in his footsteps."

Initial Evaluation

T.R. is 5'5" tall and weighs 220 lb. His vital signs include blood pressure 138/80 mm Hg and pulse 80 bpm. The physical exam is unremarkable except for shiny skin on his lower extremities, loss of hair, and numbness to the monofilament in the same area where he describes his pain. His medications include aspirin, simvastatin, ezetimibe, lisinopril, hydrochlorothiazide, atenolol, metformin hydrochloride, glyburide, insulin glargine injection, insulin lispro, and nitroglycerin.

Discussion

Adherence to home glucose monitoring is variable in the diabetic population. With metabolic syndrome, multiple drugs are generally used in treating older patients with multiple comorbid conditions. With the onset of pain, patients may be more interested in monitoring blood sugar and adhering to diet, exercise, weight loss, and recommended medications. Pain, described in terms of aching or burning and being worse at night, is typical of diabetic peripheral neuropathy. The patient's skin changes suggest microvascular diseases.

Although improving blood sugar control will not guarantee improved pain, the pain may emphasize to T.R. the need to improve monitoring. Treatment is difficult given the patient's age, comorbid heart disease, and polypharmacy.

Treatment Plan/Follow-Up

The patient begins pregabalin 75 mg at bedtime and is asked to return in 10 days with blood sugar monitoring results. The patient was feeling better at follow-up, reporting better sleep and improved energy on 75 mg of pregabalin, which he slowly increased to 150 mg twice a day.

PRACTICAL BITS

Quick and Practical Diagnostic Tools

MEMORY LOSS

Memory is the ability to normally recall the facts and events of our lives, and this takes place in three stages:

Stage 1: Encoding. This is when a person takes information in.

Stage 2: Consolidation. This is when the brain takes the information it encodes and processes it so that it gets stored in certain areas of the brain.

Stage 3: Retrieval. When a person recalls stored information in the brain.

Source: Cherie Berkley. Is Your Memory Normal? Available at: http://www.webmd.com/healthy-aging/guide/is-your-memory-normal. Accessed February 13, 2008.

DEPRESSION

The US Preventive Services Task Force (USPSTF) found that asking the following two simple questions (sensitivity: 96%; specificity: 57%) about the presence of mood and anhedonia may be as effective for screening (but not case finding) as using more involved instruments:

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

Other areas to discuss with patients are:

- Multiple somatic complaints, weight gain/loss, mild dementia
- Multiple (>5/year) medical visits; problems in more than 1 organ system, with the absence of or insufficient physical findings to explain the complaints
- Fatigue
- Work or relationship dysfunction/changes in interpersonal relationships
- Sleep disturbances
- How are things at work?
- How are things at home?
- We all have stresses in our lives. Has your stress level increased lately?
  – How are you handling it?
- How much are you drinking?
  – Is that more than usual?
- What medicines are you taking?
- What OTCs and herbal remedies are you taking?
- Has anyone in your family suffered emotional or stress-related problems?
- Have you had problems like this before?
- Who do you have to talk to?
- HOW ARE YOU?

Source: California Academy of Family Physicians. Recognition and Management of Depression. Available at: http://www.familydocs.org/files/ Depressionmonograph.pdf. Accessed February 13, 2008.

Clinical Approaches to Patient Concerns About Memory Loss

Richard J. Caselli, MD

Clinicians in the primary care setting often observe that memory loss is one of the most common complaints of aging. As people grow older, they may require more time to remember and their ability to concentrate may diminish. Although memory impairment is common and associated with morbidity in some circumstances, adequate screening and evaluation for medical conditions that can lead to memory problems (including dementia) are often lacking in primary care (**Table 1**).[1] For example, reported rates of overlooked dementia are between 35% and more than 90%,[2,3] and studies have found that dementia is not recognized in two out of three people with dementia who are seen by their physicians.[4] However, research in aging and dementia is moving forward, creating an awareness that further advances in knowledge about the pathophysiology of disorders will eventually be applied to clinical practice. Therefore, clinicians need to stay informed of the latest research developments and their implications for improved patient care.

This article reviews various developments in research that explore how aging changes brain structure, thought processes, and blood chemistry, focusing on the impact of knowledge gained so far in addressing the concerns of people who seek care in the primary care setting.

Reported rates of overlooked dementia are between 35% and more than 90%, and studies have found that dementia is not recognized in two out of three people with dementia who are seen by their physicians.

Understanding the Relationship Between Apolipoprotein E e4 and the Risk for Alzheimer's Disease

Although people have two copies of every gene, more than two versions of the gene itself can exist. Each version of the gene is called an allele, which is in all forms of tissues and proteins including the gene for apolipoprotein E (APOE).

The APOE e4 allele increases the risk for developing Alzheimer's disease (AD), which was a research finding of a pivotal study reported in 1993 that showed the risk for AD increased from 20% to 90% and the mean age at onset decreased from 84 years to 68 years with an increasing number of APOE e4 alleles in families with late-onset AD.[5] In other words, there is a dose-related effect between the APOE e4 allele and the age of AD onset. That means that if a person has two copies of the gene, the age of AD onset is younger than if a person has no copies of the gene. And if a person has only one copy of the gene, the age of onset is intermediate between the person with two copies of the gene and the person with no copies of the gene. The mean age of a diagnosis of AD onset for a person who has two copies of the e4 allele is 68 years.[5]

When researchers began studying people who developed AD early (that is, before age 65 years) to find out what causes the disease, they made a breakthrough when the gene that produced amyloid-ß protein fragments called amyloid-ß precursor protein was found on chromosome 21.[6] This is consistent with our knowledge about individuals with Down syndrome, all of whom inherit an extra chromosome 21 and typically develop early brain plaques leading to AD as they grow older. In addition to finding a gene coded on chromosome 21 as causative for an autosomal dominant mutation form called "early-onset familial AD," two other genes, located on chromosome 14 and chromosome 1, were found to be genetic bases of AD. However, taken all together, these three autosomal dominant mutations account for less than 5% of all cases of AD; they do not explain the remaining 95% of AD cases.[6]

The current thinking is that APOE is the genetic basis for up to 50% of all AD cases. Since the APOE e4 allele is a common gene (eg, about 20% of the population in North America and Europe have the e4 allele, which is completely compatible with a normal lifespan), it

TABLE 1. COMMON CAUSES OF MEMORY LOSS[1]

- Aging
- Alzheimer's disease
- Neurodegenerative illness
- Head trauma or injury
- Hysteria often accompanied by confusion
- Seizures
- General anesthetics such as halothane, isoflurane, and fentanyl
- Alcoholism
- Stroke or transient ischemic attack
- Transient global amnesia
- Drugs such as barbiturates or benzodiazepines
- Electroconvulsive therapy (especially if prolonged)
- Temporal lobe brain surgery
- Brain masses (caused by tumors or infection)
- Herpes encephalitis
- Other brain infections
- Depression

Note: Normal aging may result in trouble learning new material or requiring longer time to recall learned material. However, it does not lead to dramatic memory loss unless diseases are involved.

becomes possible to study the effects of APOE in the general population. Not only is the e4 allele (the second most common allele after the e3 allele) an allele that increases one's risk for AD, but the e2 allele (the least common allele) reduces one's risk for AD.

With respect to APOE-related risk of AD, researchers have found that the lifetime risk of AD increases from 9% with no e4 allele to 29% with the presence of one e4 allele[7]; there is a modest protective effect of the e2 allele[5]; the positive predictive value of AD in patients with the e4 allele and dementia exceeds 97%[8]; and the negative predictive value of AD in patients with the e4 allele and dementia is less than 45%.[8]

I would like to point out that although this APOE test is very helpful in research, its usefulness in clinical tests is limited, in my opinion. If a patient with dementia has an APOE test result of e4 positive, there is a more than 97% likelihood that the person has AD. However, if a patient has an APOE test result of e4 negative, there is still a fairly high percentage of patients who are going to have AD. Therefore, having an e4 negative test result does not rule out AD.

Exploring the Possible Influence of Apolipoprotein E e4 Prior to Onset of Mild Cognitive Impairment

Determining what constitutes normal age-related memory loss is a major area of interest in research. Researchers at the Mayo Clinic are conducting a large longitudinal study among healthy individuals (mean age, 56 years) with no known cognitive illnesses. One early finding is that there are metabolic changes in the brains of these healthy individuals that resemble what is seen in AD. When we correlate memory learning test performance with gray matter densities that are evident on positron emission tomography scans, we find there is a correlation.

In our APOE e4 allele carriers, we find that it takes more trials to learn the same thing that one used to learn more easily; it's not a matter of actually losing memory, but the person needs to work hard at maintaining his or her capacity to learn.

One study we conducted explored whether memory loss is detectable before the symptomatic presentation of mild cognitive impairment (MCI) in individuals at greater genetic risk for AD based on the presence or absence of the APOE e4 allele.[9] Study participants were cognitively normal individuals of known APOE genotype who were age 50 years of age or older and initially enrolled using a match paradigm that included e4 homozygotes, e3/4 heterozygotes, and e4 noncarriers in a 1:1:2 ratio. Two verbal and two visual memory tests were administered to the study participants over time. We found that test performance became worse with serial administration of the same test over the course of several years for study participants who are e4 carriers. Yet, test performances among study participants who are e4 noncarriers remain fairly stable.

TABLE 2. MEMORY PROBLEMS THAT ARE NOT PART OF NORMAL AGING[10,11]

- Forgetting things much more often than usual (such as difficulty remembering common words when speaking or mixing words up)
- Forgetting how to do things that have been done many times before (such as following a recipe or getting lost while driving on familiar streets)
- Having trouble learning new things (such as becoming less able to follow directions)
- Repeating phrases or stories in the same conversation (such as asking the same questions repeatedly)
- Having trouble making choices or handling money
- Not being able to keep track of what happens each day

We concluded that memory declined in APOE e4 carriers before the symptomatic presentation of MCI in a cohort whose mean age was 60 years over a median period of 33 months, noting that the decline began prior to age 60 years of age. Our analysis of the data revealed that the APOE e4 carriers did improve over the years in terms of memory test performance, but they were not improving as much as the e4 noncarriers. In other words, this does not mean that the ability to learn word lists and other exercises of nonstructured complexity declines over time, especially for an e4 carrier. In fact, the ability to remember coherent spatial concepts continues to improve with repeated exposure. However, people do not gain quite as much out of the continued exposure as they grow older.

Based on the findings of a longitudinal study that focused on long-term memory, we found that long-term memory scores among e4 carriers and e4 noncarriers track together very closely from age 30 years of age to age 60 years of age.[12] However, at around 60 years of age, the decline in memory scores starts to divert, with the e4 carriers showing a more rapid decline than do the e4 noncarriers through age 90 years of age. Another interesting finding is that there appears to be a gender effect in addition to a genetic effect, with women typically performing better on memory tests, such as the Auditory Verbal Learning Test, than do men.[12]

TABLE 3. SIMPLE TESTS FOR DEMENTIA[13]

Orientation Test for Memory Loss

The doctor may ask the current year, month, date, day of the week, and time of day. Small errors may be overlooked, but large errors (such as guessing the incorrect year or season) may suggest cognitive impairment.

Word Repetition Test for Memory Loss

The doctor will say a list of several words (usually common nouns such as apple, table, or penny) and ask the person to repeat the list. People with adequate hearing should be able to repeat back three words. An inability to do so indicates that the person may have problems with language, attention, or working memory.

Language Test for Memory Loss

The doctor may ask the person to name as many items as possible in a given category (for example, "animals" or "vegetables"). The time limit is 1 minute, but the doctor usually will not volunteer this information, as it can make the patient nervous. Instead, the doctor may say, "I will tell you when to start and when to stop." Naming fewer than 10 items in 1 minute is a sign of decreased mental function.

Test of Attention and Working Memory

This test involves spelling a word, such as "world," forwards and backwards or subtracting from 100 sequentially by 7. The doctor may also ask the person to arrange the letters of the word in alphabetical order or to say the months of the year backwards beginning with December. Omitting or transposing letters or months, as well as adding extra ones, may indicate memory deficiencies.

Memory

The doctor may ask the person to recall the list of words used earlier in the repetition test. (Usually, several other tests will be given between these two in order to gauge the person's memory.) The inability to remember at least two of three words suggests memory impairment.

Note: Although these tests seem simple enough for a spouse or other family member to administer, the interpretation of the results requires expert training, so only a doctor should give these tests.

Distinguishing Normal Age-Related Memory Loss From Abnormal Age-Related Memory Loss

Defining what is normal and what is abnormal is difficult. In clinical practice, asking patients and/or their family members some basic questions to describe the nature of their memory loss can be useful (**Table 2** on page 11).[10,11] Screening tools are available to help clinicians assess whether a person might have memory loss or other cognitive problems (**Table 3**).[13] Although a definitive diagnosis cannot be made based on screening tools alone, clinicians can obtain information to help determine the need for a thorough evaluation by a neurologist or other memory loss specialist.

For research purposes, we have defined an abnormal test score as a drop of two standard deviations (relative to the mean drop of the cohort) from one test to the next, and we have defined cognitive domain decline (itself defined as an abnormal decline on at least two tests within a cognitive domain) in terms of measures for executive function, memory, language, spatial, and behavior. First, we learned that out of approximately 200 cognitively normal individuals of known APOE genotype taking these memory performance tests every 2 years for up to 12 years, 48 study participants showed no decline on any tests. Second, we found no significant differences in decline between genetic subgroups in the age decile of 50 years to 59 years. However, in the age decile of 60 years to 69 years, we found that more individuals who are APOE e4 homozygotes tended to decline in a domain-specific fashion than other genetic subgroups. And when we looked at improvement over time, the groups that were least likely to improve were the e4 carriers. Ultimately, we had 7 individuals who went on to actually develop MCI or AD, which is a relatively small number, but our study is ongoing and we expect many more to convert over time.

We have found that APOE e4 carriers have lower glucose metabolism in regions that topographically overlap areas metabolically affected by AD, noting that

TABLE 4. DIRECT-TO-PATIENT MESSAGE: 10 TIPS FOR KEEPING YOUR MEMORY SHARP[15]

The following tips can help keep your mind sharp and your memory intact:

1. **Exercise your mind.** The brain continues to form new connections as long as it's stimulated. Play a musical instrument. Do crossword puzzles and other memory exercises. Learn a foreign language. Read!
2. **Stay physically active.** You'll be more alert during the day, and you'll sleep better at night. Get moving with aerobic activity, strength training, and stretching.
3. **Eat and drink well.** Eat a diet rich in fruits and vegetables. These contain antioxidants that protect and nourish brain cells. Drink lots of water because dehydration can make it harder to concentrate.
4. **Give yourself reminders and cues.** Work people's names into your conversations with them. Set up cues, like putting your keys on the ironing board so you'll remember to turn off the iron before leaving home.
5. **Take your time.** Slow down and pay full attention to the task at hand.
6. **Relax.** Stress interferes with concentration. Let your mind take a "mental break" every so often.
7. **Keep a positive attitude.** Research shows that happiness makes you more alert, which makes your senses more receptive to receiving information.
8. **Talk to your doctor.** Factors including certain medical conditions, medications, vitamin deficiencies, fatigue, and depression can contribute to memory problems.
9. **Know your numbers.** Keep track of your blood pressure, cholesterol, thyroid, and blood sugar levels to be sure they're in the healthy range.
10. **Keep your perspective.** You're not the first person to dial a number only to forget whom you're calling. Take note of it, but unless you feel it's unusually frequent, don't be concerned.

some of these metabolic differences are long-standing and may even be lifelong. We also found that there are similar reductions in hippocampal volume and gray matter density in APOE e4 carriers that correlate with cognitive performance in the presymptomatic period. Furthermore, memory declines in APOE e4 carriers before the symptomatic presentation of MCI, and group (but not individual) differences are apparent during the age decile of 50 years to 59 years. Data suggest that aerobic fitness can be a risk-modifying factor for those at high genetic risk for AD; more studies are needed to better understand any correlation between aerobic capacity and cognitive measures. And, finally, APOE e4 carriers, particularly individuals with APOE e4 homozygotes, in the age decile of 60 years to 69 years, may be more vulnerable symptomatically to the effects of aging, fatigue, anxiety, and physical fitness than are APOE e4 heterozygotes and e4 noncarriers. This progression precedes symptom onset and may predict symptomatic conversion within a few years.

Conclusion

Detecting and screening for memory problems are important first steps in addressing the concerns of patients or their family members who visit primary care clinicians. In addition to considering the possibility of memory problems caused by depression, dehydration, inadequate nutritional intake (ie, not eating enough healthy foods or having too few vitamins and minerals in the body), minor head injuries, thyroid problems, or adverse reaction to certain medications,[14] increased awareness of common causes of memory loss is warranted. Taking the initiative to have candid conversations with patients and/or family members about memory problems may include education about lifestyle strategies that promote good health, including physical exercise (**Table 4**).[15] Frequent contact with each patient can be useful to assess any progression in memory problems over time.

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Social and Emotional Costs of Learning Disabilities

Carl C. Bell, MD

The notion that learning disabilities are an academic problem exclusively is not only erroneous, it's dangerous. The struggles of children with impairments in reading, writing, math, memory, and organization extend far beyond the classroom and often contribute to a heavy psychological burden.

Multiple studies demonstrate that adolescents with learning disabilities frequently exhibit co-occurring emotional and behavioral problems, including depression, anxiety, conduct disorders, and delinquency. In the landmark 2001 National Longitudinal Study of Adolescent Health, a cross-sectional analysis of the in-home interview data of more than 20,000 adolescents included in the study showed that rates of emotional distress, suicide attempts, and involvement in violence were significantly increased in the 1,301 adolescents who were identified as having a learning disability, compared with their non–learning impaired peers (J. Adolesc. Health 2001;27:340-8). Similar results have been reported in a variety of community and clinical samples.

In the 2003 National Survey of Children's Health, learning disabilities were the most commonly diagnosed emotional, developmental, or behavioral problem of children aged 0-17 years. Compared with their peers without developmental problems, these children had lower self-esteem, had more depression and anxiety, and missed more school and were less involved in sports and other community activities (Pediatrics 2006; 117:e1202-12).

In addition, children with learning disabilities drop out of high school at a disproportionately higher rate than their peers, and high school dropouts are 3.5 times more likely to have trouble with the law than are those who graduate, according to the National Center for Educational Statistics.

Literature on the causal direction of the co-occurrence of behavioral/emotional and learning problems is inconsistent. For example, it is unclear whether learning impairments beget mental health troubles or vice versa, whether the causation is reciprocal, or whether a shared etiologic factor underlies the overlap. It is clear, however, that "a cascade of negative psychosocial effects" occur with learning disabilities," said David Osher, Ph.D., project director for the American Institutes for Research in Washington.

"In the 2003 National Survey of Children's Health, learning disabilities were the most commonly diagnosed emotional, developmental, or behavioral problem of children aged 0-17 years."

As many as 20% of people in the United States have a learning disability (including about 3 million children aged 6-21 years who receive special education services in school), and about 30% of learning- disabled children have behavioral and emotional problems, according to data presented in the Department of Education's 2005 report to Congress on the Individuals With Disabilities Education Act (www.ed.gov/about/reports/annual/ osep/2005/index.html). The lesson? The societal impact of this problem is huge.

Adult expectations of adolescents make them particularly vulnerable to negative sequelae, contends John McNamara, Ph.D., associate professor in the department of child and youth studies at Brock University in St. Catharines, Ont. A younger child with a learning disability who exhibits a behavioral need probably would be identified in elementary school, but a teenager at risk for emotional or behavioral problems "is operating within a setting where expectations shift to the adolescents advocating for themselves—so a kid in trouble can fall off the radar," he said.

In a large-scale study published in 2005, Dr. McNamara and his colleagues explored the relationship in adolescents between learning disabilities and risk-taking behavior. They determined that adolescents with learning disabilities (and adolescents with learning disabilities and comorbid attention-deficit hyperactivity disorder) were significantly more likely to smoke, use alcohol and marijuana, engage in acts of direct aggression, and engage in acts of minor delinquency (Learn. Disabil. Res. and Pract. 2005; 20:234-44).

In a recent follow-up to that study, which is slated for publication this summer, Dr. McNamara said he and his colleagues asked why adolescents with learning disabilities engage in these risk-taking activities to a greater extent than their non–learning disabled peers. The investigators found support for their hypothesis that psychosocial factors partly mediate the link.

Among the mediating psychosocial covariates were adolescents' familial relationships, engagement in school and extracurricular activities, and feelings of well-being and of being victimized. "To us, these findings support the idea that it is a combination of the learning disability, per se, and the secondary psychosocial characteristics associated with adolescents with learning disabilities that explains the more frequent engagement in risk taking," he said.

The findings also show that "these kids require someone to step into their space to ensure they're thriving."

These adolescents can thrive, Dr. McNamara stressed. "It is evident in the research that successful adolescents with learning disabilities are self-aware and have accepted their learning disability. They have learned to seek support when they need it, and they have learned to seek out

and operate in environments where they have the tools to succeed," he said. "The ability to do these things comes from someone teaching them how to do so through well-designed interventions."

The key components to effective intervention for these adolescents, according to Dr. McNamara, include "intensive intervention during the early school years; ongoing one-on-one, or close to it, tutoring; consistent academic and life skill–based counseling; and consistent ongoing parental support and understanding."

Feeling a sense of connectedness to and support from school also serves as an important protective factor, according to the findings of the adolescent health survey. Adolescents who receive such support "often have higher self-esteem, feel more in control of their own academic achievement, and understand how to advocate for themselves," Dr. McNamara said.

To best serve not only the academic needs of adolescents with learning disabilities but also the social and emotional ones, educators and mental health providers first must understand "that the co-occurrence of behavioral and emotional problems with learning disabilities is common and leads to poorer outcomes," according to Dr. Osher. Next, they must work together to create emotionally safe and supportive school environments.

Also, "the interventions should be culturally and linguistically competent, strengths based, capacity building, and a as child and family driven as possible," Dr. Osher said. "Wherever possible, labeling and pullout approaches and special classes should be avoided."

But multiple barriers impede the development of such emotionally safe and supportive learning environments. Problematic are disinterest, lack of information about what to do and how to do it, and the pressures faced by school administrators to produce "short-term gains on high-stakes tests," Dr. Osher said. "What gets assessed gets addressed," he said, so if schools are to become a protective factor in the lives of at-risk kids, social and emotional considerations must be assessed.

Toward this end, Dr. Osher and colleagues at the American Institutes for Research, together with the Collaborative for Academic, Social, and Emotional Learning and the Learning First Alliance, developed a strategy for overcoming barriers. The three-component intervention, which has been implemented by the Chicago Public Schools, includes a psychometrically robust 57-item survey of the social and emotional conditions for learning, the results of which are incorporated into school, district, or state score cards; a customized report informing administrators on the significance of specific subgroup responses to the survey; and an online tool kit linked to individual school reports that provides strategies and programs that have proven effective in similar contexts.

In Chicago, the results of the survey reports have begun to change discourse in the district, Dr. Osher reported. Still, several barriers to widespread implementation and efficacy of such strategies have yet to be overcome. For example, Dr. Osher said, the ongoing "marginalization of social [and] emotional factors" makes it difficult to generate financial resources for comprehensive assessments and intervention design.

And even when financial support exists, "another barrier is making sure that interventions enter the classroom, affect the learning process, and reach the individual child. This is a struggle in all systems change, including education."

By Diana Mahoney, New England Bureau.
IMNG News Service.
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Perspective

The key challenge when dealing with adolescents who have emotional or behavioral issues that co-occur with learning disabilities is to try to get people to understand that if you wait until you are thirsty to dig your well, you are foolish. Effective prevention must be proactive.

Early identification of learning disabilities is important—provided it is taken as an opportunity to surround the child with protective factors such as empathy and a sense of hopefulness.

I can think of no better formula for a child who has a learning disability than the one that my colleagues and I describe in a recently published article examining immediate and midterm trauma intervention (Psychiatry 2007; 70:283-315). We discuss providing a sense of safety, self-efficacy, collective efficacy, connectedness, and calming to individuals in the aftermath of trauma. A learning disability is not a trauma in the classic sense, but it is a personal disaster of sorts, and as such, the critical elements of an effective trauma intervention are appropriate.

Surrounding the teen with a social fabric comprising trusted adults, teachers, neighbors, and coaches is a promising strategy. Ideally, this "village" can help the teen find his or her strengths and, through the strength activity, teach the teen how to overcome the propensity for externalizing or internalizing behaviors.

The debate over whether the emotional/behavioral issues are secondary to the learning disability is of little significance. You don't have to worry about the chicken/egg or egg/chicken scenario, because there are no eggs without chickens and no chickens without eggs. The behavioral and learning conditions are clearly interrelated, so it makes sense to work on both at the same time.

If a teen's sense of academic frustration is leading to anxiety and depression, effectively treating the emotional manifestations requires addressing the sense of frustration and failure through academic and social interventions. Similarly, to effectively reduce the academic frustrations, the emotional and behavioral manifestations have to be diminished so the teen can actively participate in the process.

Dr. Bell is chief executive officer and president of Community Health Council Inc. in Chicago and serves as director of public and community psychiatry at the University of Illinois at Chicago.

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]*.

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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

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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).

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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.

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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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