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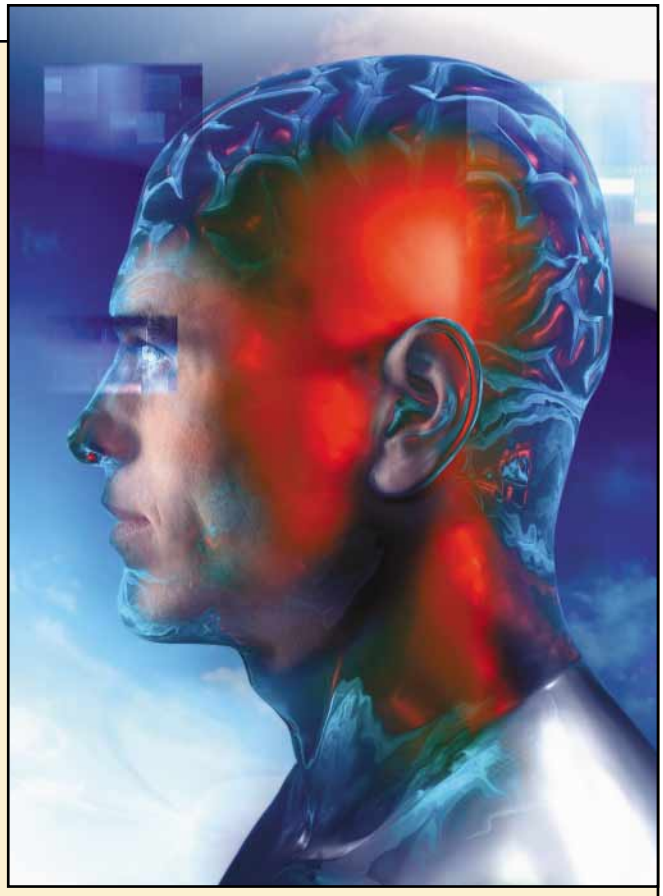

Special Populations in Depression
Effective Approaches to Depression in Men

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Strategies for Managing Anxiety Disorders

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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 third issue of *Practical Neuroscience for Primary Care Physicians*, a supplement series created as a practical resource for primary care physicians.

I, along with IMNG, want to thank all of those who participated in our survey that was published with the summer issue. We are grateful for the overwhelmingly positive feedback. On page 9 you can find out who won the survey contest.

In this issue, **Michael E. Thase, MD**, Professor, Department of Psychiatry, University of Pennsylvania School of Medicine and Philadelphia Veterans Affair Medical Center, Philadelphia, Pennsylvania, and University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, authors the 'Special Populations in Depression' series by discussing depression in men. **Thomas L. Schwartz, MD**, Associate Professor of Psychiatry, Director of Adult Outpatient Services, Director of the Depression and Anxiety Disorders Research Program, and Assistant Director of Residency Training, State University of New York (SUNY) Upstate Medical University, Syracuse, New York, addresses the management of anxiety disorders. In our 'Case Files' section, **Ellen A. Dornelas, PhD**, Director of Behavioral Health Programs, Preventive Cardiology, Hartford Hospital, University of Connecticut School of Medicine, Farmington, Connecticut, shares two case studies in smoking cessation.

Look for the last supplement of 2007 in the December issue of *Family Practice News* and *Internal Medicine News*. Also, be sure to visit the publication's web site at www.practicalneuroscience.com for additional editorials. Through our web site, we also welcome submissions of case studies or point-of-view columns. We look forward to hearing from our loyal readers.

Cordially,

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Special Populations in Depression

Michael E. Thase, MD

Effective Approaches to Depression in Men

Despite the pervasiveness of depression—with an estimated 6 million men (nearly 7% of men) and more than 12 million women (12% of women) in the United States who have depressive illnesses in any given 1-year period[1]—clinicians working in primary care settings often encounter obstacles in identifying depression in men. Because women are more likely to suffer from depression than are men and even more likely to seek treatment for depression than are men,[1,2] physicians may be somewhat less prepared to recognize depression in men. Yet, without treatment, men who suffer from depression often experience symptoms that can last for weeks, months, or years.[1]

This article focuses on the clinical challenges of identifying depression in men and discusses effective approaches for improved recognition and treatment of depression in men in the primary care setting.

Although the standard symptoms of depression apply to both men and women, men often experience depression differently and may have different ways of coping with their symptoms.

Looking for Signs of Depression

Although the standard symptoms of depression apply to both men and women, men often experience depression differently and may have different ways of coping with their symptoms.[1] For example, men may be more likely to express their depression in terms of fatigue, irritability, anger, loss of interest in work or hobbies, or sleep disturbances rather than to openly acknowledge feelings of sadness, worthlessness, or excessive guilt.[3,4] Men also are more likely to turn to alcohol or drugs when they are depressed; substance abuse can mask the signs of depression, making it harder to detect and treat effectively.[1] Some men may cope with depression by throwing themselves compulsively into their work; others may respond to depression by engaging in reckless behavior, taking risks, and putting themselves in harm's way.[1] Furthermore, more than four times as many men die by suicide in the United States as do women; this is but one of the consequences of untreated depression.[5]

Cultural expectations about masculinity and misperceptions about mental illness can be barriers to self-awareness of one's depressive symptoms. Some men may believe that expressing their emotions or admitting to feeling depressed is a personal failure and a sign of weakness. Their view of the traditional male as someone who restricts emotional expression and exhibits a preoccupation with success, power, and competition makes them resistant to being diagnosed with or treated for depression.[2] Some men are uneducated about mental health issues and may confuse the illness of depression with some kind of personal liability or flaw.

Therefore, men may not fully disclose information about their emotional state, may fail to recognize the symptoms of depression, or may deny the severity of the problem.[2] For some men, the combination of not believing the problem warrants attention or feeling stigmatized and not accepting recommendations for treatment makes them resistant to seeking relief of depressive symptoms.

SYMPTOMS OF DEPRESSION

Not everyone who is depressed experiences every symptom. Some people experience only a few; some people suffer many. The severity of symptoms varies among individuals and also over time.

- Persistent sad, anxious, or "empty" mood
- Feelings of hopelessness or pessimism
- Feelings of guilt, worthlessness, or helplessness
- Loss of interest or pleasure in hobbies and activities that were once enjoyable, including sex
- Decreased energy, fatigue; feeling "slowed down"
- Difficulty concentrating, remembering, or making decisions
- Trouble sleeping, early morning awakening, or oversleeping
- Changes in appetite and/or weight
- Thoughts of death or suicide, or suicide attempts
- Restlessness or irritability
- Persistent physical symptoms, such as headaches, digestive disorders, and chronic pain that do not respond to routine treatment.

Source: National Institute of Mental Health.[1]

Particularly in the primary care setting, men rarely describe their concerns with such phrases as "I'm depressed" or "I'm sad all the time and cry a lot." Rather, men may present with more nonspecific complaints, such as insomnia, stress, or fatigue. Unexplained, persistent, or multiple physical symptoms—such as back pain, headache, bowel disturbances, dizziness, palpitations, and fatigue—can be a marker for an underlying depressive or anxiety disorder.[6] When physical symptoms in men lack a medical explanation despite a thorough evaluation, consideration of the strong linkage between physical symptoms and depression is warranted.[6]

Studies have found that as the number of unexplained physical symptoms increases, the likelihood of a mood or anxiety disorder increases in tandem.[6-10] One study of 1,000 adult Americans in four primary care clinics found that up to two thirds of patients with medically unexplained symptoms had a depressive disorder; the presence of any of 15 common physical symptoms increased by twofold to threefold the likelihood of a diagnosis of a mood or anxiety disorder.[10] In an international study of 1,146 primary care patients who met the criteria for major depression, researchers reported that 69% of these patients presented with only physical complaints; 50% of the patients in this analysis reported multiple unexplained physical symptoms and 11% denied psychological symptoms of depression when questioned directly.[9]

People with major depression may present with physical symptoms in the primary care setting but only acknowledge psychological symptoms (eg, depressed mood or guilt) when specifically asked about them.[9] Furthermore, some patients may believe that the initial reporting of physical symptoms is a more appropriate route for seeking help from a primary care physican.[9] Yet, most patients with a depressive or anxiety disorder will admit to psychological symptoms if specifically asked about them; less than 20% of these patients will respond with denial of psychological distress when questioned.[6]

When further evaluation leads to a diagnosis of depression, the role of the primary care clinician is extremely important in helping the person come to terms with accepting the diagnosis and accepting the treatment strategy that may work best for him.

Diagnosing and Treating Depression

The first step for physicians is to conduct a physical examination of the patient, with special attention to making assessments about certain medications currently prescribed and detecting any medical conditions that can cause the same symptoms as depression (eg, viral infection, thyroid disorder, or low testosterone level).[1] After the physician is able to rule out these possibilities through examination, interview, and laboratory tests (if needed), the next step is to conduct a psychological evaluation or refer the patient to a mental health professional.

Making a diagnostic evaluation includes obtaining a complete history of symptoms (eg, when symptoms started, how long they last, level of severity, and whether symptoms have occurred in the past and how they were treated). Questions about alcohol and drug use are important to ask the patient, as well as questions about recent thoughts regarding death or suicide and any family history of depression or anxiety. Likewise, it is important to assess for disturbances in speech, thought patterns, or memory, which can be associated with depressive disorders.[1] Treatment strategies for depressive disorders will depend on the specific diagnosis, the severity of the symptoms, and the patient's preference; a combination of treatments—behavioral and pharmacologic therapies—may lead to the best course of action for some patients.

In my experience treating hundreds of men, I have found that it is important to be able to explain the condition at different levels to people with different levels of knowledge, sophistication, and psychological preparedness. In some cases, talking about depression as a consequence of prolonged stress is useful. In others, making a parallel between depression and other common chronic medical conditions, such as diabetes or hypertension, is useful. Giving examples of accomplished men who are reported to have suffered from depression—such as Abraham Lincoln and Winston Churchill—can help provide perspective on depression. Depending on the individual's knowledge and attitude toward depression, physicians may find it helpful to choose their words carefully when discussing depression with men. For example, making a referral to a mental health professional for some "coaching" may be more palatable as an initial approach than insisting on "extensive psychotherapy" with an as-of-yet unidentified psychiatrist or psychologist.

For men with mild to moderate symptoms of depression, treatment with antidepressants or a focused form of counseling/psychotherapy are equally useful options. Two advantages of pharmacologic therapy

are that (1) antidepressants are readily accessible, even in the most remote parts of the country, whereas in some places people may not have access to effective psychotherapy, and (2) a greater level of quality control exists with medications, no matter in which community a person resides or who is prescribing the medication ("if you write a prescription for fluoxetine, it is always for fluoxetine"), whereas if you recommend cognitive therapy, your patient may not find someone who really knows how to do cognitive therapy effectively. On the other hand, one of the advantages of psychotherapy is that the patient may learn something (eg, changing distorted views of self and how to overcome problems) that can be applied to the rest of the person's life. In that respect, the short-term cost of therapy is likely to be offset by the long-term benefit.

After consideration of issues relating to availability, access, and patient preference, primary care physicians may find that therapy with the selective serotonin reuptake inhibitors (SSRIs) is effective for the management of depression in men. If therapy with an SSRI as initial monotherapy does not relieve depression, the patient is often switched to therapy with a selective serotonin-norepinephrine reuptake inhibitor such as the extended-release formulation of venlafaxine or duloxetine, or the norepinephrine-dopamine reuptake inhibitor bupropion. For those patients for whom these strategies have not worked, other options are available. Primary care physicians are encouraged to try two or three different antidepressants for a particular patient, recognizing that 50% to 60% of patients may not achieve an adequate response after one trial of an antidepressant of sufficient dose and duration.[11]

For patients with the more severe and complicated forms of depression, the use of psychotherapy in combination with pharmacotherapy may provide the best results. Primary care clinicians may prefer to work hand-in-hand with a psychologist or other mental health professional. However, for patients with any signs of psychosis or bipolar disorder, referral to a psychiatrist may be the preferred course of action.

For example, some patients may require therapy with monoamine oxidase inhibitors or combination therapy with complex regimens under the care and expertise of a psychiatrist. The same is true for the most effective treatment for severe depression, electroconvulsive therapy, which still has a 50% to 60% chance of working even after several antidepressants have failed.[12]

I have encountered men in my work who are almost as adverse to psychotherapy as they are to medication. Unless the patient has a severe, incapacitating form of depression (with psychotic or bipolar tendencies), presenting a stepped treatment plan for the skeptical patient may be an effective approach. This approach involves the physician monitoring the patient's symptoms and functional status, starting out with a self-care plan that includes following recommendations for exercise and taking good care of himself, as well as good sleep hygiene and doing some reading, such as the books *Feeling Good* by David Burns, MD,[13] or *Beating the Blues*, which I wrote with Susan Lang.[14]

Engaging the patient in this approach includes an agreement up front on when you will re-evaluate the situation together if all of these commonsense measures do not have a favorable effect. The patient is asked, "Of all the possible treatments, which one would you find the most acceptable if this rather straightforward, commonsense plan doesn't work?" This involvement of the patient in decision making about treatment may help overcome initial skepticism, as well as help improve the patient's outcome.[15] When pharmacologic therapy is the preferred treatment strategy, clinicians can help encourage adherence by educating patients on how to take their medication, how the medication works, and the short- and long-term effects of the medication, and by explaining that antidepressants are not addictive.[16,17]

DIRECT-TO-PATIENT MESSAGE FROM THE NATIONAL INSTITUTE OF MENTAL HEALTH ON HOW MEN CAN HELP THEMSELVES IF THEY ARE DEPRESSED

Depressive disorders can make one feel exhausted, worthless, helpless, and hopeless. It is important to realize that these negative views are part of the depression and do not accurately reflect the actual circumstances. Negative thinking fades as treatment begins to take effect. In the meantime:

- Engage in mild exercise. Go to a movie or a ballgame, or participate in religious, social, or other activities.
- Set realistic goals and assume a reasonable amount of responsibility.
- Break large tasks into small ones, set some priorities, and do what you can as you can.
- Try to be with other people and to confide in someone; it is usually better than being alone and secretive.
- Participate in activities that may make you feel better.
- Expect your mood to improve gradually, not immediately. Feeling better takes time. Often during treatment of depression, sleep and appetite will begin to improve before depressed mood lifts.
- Postpone important decisions. Before deciding to make a significant transition—change jobs, get married or divorced—discuss it with others who know you well and have a more objective view of your situation.
- Do not expect to "snap out of" a depression. But do expect to feel a little better day by day.
- Remember, positive thinking will replace the negative thinking as your depression responds to treatment.
- Let your family and friends help you.

Source: National Institute of Mental Health.[1]

PRACTICAL BITS

Quick and Practical Diagnostic Tools

Stages of Change Model

People change behavior through a series of discrete changes. In addition to the principle of resolving ambivalence, the Stages of Change is a second key aspect of the motivational counseling approach. The Stages of Change Model, or Transtheoretical Model, developed by Prochaska and DiClemente,[1] describes the five stages of behavior change, as follows:

Precontemplation: The patient has not thought about changing behavior or does not want to change. The clinician's job is to raise awareness about the behavior.

Contemplation: The patient is considering behavior change. The clinician's job is to use strategies to resolve ambivalence.

Preparation: The patient is getting ready to change the behavior in question. The clinician's job is to use strategies that build motivation and confidence and to elicit solution-oriented techniques or strategies for change from the patient.

Action: The patient has actually made a change in the behavior (eg, stopped smoking). The clinician's job is to provide support and continue to elicit solution-oriented techniques and strategies that will help the patient in his/her efforts to change.

Maintenance: The patient has maintained the behavior change for at least 6 months. The clinician's job is to provide support and elicit from the patient relapse-prevention strategies that will help the patient maintain long-term behavior change.

Source: 1. Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: Toward an integrative model of change. *J Consult Clin Psychol*. 1983;51:390-395.

Providing Effective Follow-Up Care

Continuity (defined as "seeing the patient regularly over time for a large proportion of the patient's health encounters")[18] is ranked by patients as being among the most highly valued attributes of primary care.[19] Primary care clinicians can build relationships of trust with men who have depression, be an advocate for them, and partner with them in shared decision making. Not only are primary care clinicians often the first contact for care for these men, they can help individuals identify their symptoms and sort out their major issues, deliver much of the care, make referrals for psychotherapy whenever appropriate, and provide coordination of care over the long term.[19]

Frequency of follow-up is a vital component in managing depression. People with depression need to be seen no less frequently than monthly; telephone interactions with the patient by the office nurse, a physician's assistant, or another clinician during the first weeks of treatment are especially useful. Ongoing monitoring is required, based on the understanding that undertreatment (defined as "an insufficient duration of treatment, a subtherapeutic dosage of antidepressant, and/or poor adherence to the prescribed regimen") is the most common cause of initial treatment failure.[20] Furthermore, the risk of depressive relapse and recurrence extends over several years.[21] Engaging family members or other loved ones of the patient in the treatment process can be useful; the love and caring support of a spouse can be a very important asset to a man with depression.

Conclusion

Identification of depressive symptoms, persistence in clearly communicating the need and options for effective treatment, and vigilance in providing ongoing follow-up care are the key components in achieving optimal outcomes for men with depression. Physicians can serve a vital role in changing the paradigm from "depression in men is underrecognized and under treated" to "depression in men is better recognized and more effectively treated."

Dr Thase has disclosed that he is a consultant to AstraZeneca, Bristol-Myers Squibb Company, Cephalon, Inc., Cyberonics, Inc, Eli Lilly & Company, GlaxoSmithKline, Janssen L.P., MedAvante, Inc., Neuronetics, Novartis Pharmaceuticals Corporation, Organon, Sepracor Inc., Shire US Inc., Supernus Pharmaceuticals, Inc., and Wyeth. He is on the speakers bureau of AstraZeneca, Bristol-Myers Squibb, Cyberonics, Lilly, GlaxoSmithKline, Organon, sanofi-aventis, and Wyeth.

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Resources in the SPOTLIGHT

SMOKING CESSATION RESOURCES

Smokefree.gov

This web site provides information and professional assistance to those individuals trying to quit smoking. Smokefree.gov gives support in the form of an online guide for smokers and access to experts and print resources as well as research studies.

www.smokefree.gov

Treatobacco.net: Database & Educational Resource for Treatment of Tobacco Dependence

This web site is an essential resource for those professionals working on the treatment of tobacco dependence. This source of information provides evidence-based data and practical support, covering the key areas in the treatment of tobacco dependence: efficacy, safety, demographics and health effects, health economics, and policy.

www.treatobacco.net

Society for Research on Nicotine and Tobacco

This group's mission is to stimulate the generation of knowledge concerning nicotine in all of its manifestations—from molecular to societal. The society sponsors scientific meetings and publications as well as encourages scientific research on public health efforts for the prevention and treatment of tobacco use.

www.srnt.org

ANXIETY DISORDER RESOURCES

Anxiety Disorders Association of America (ADAA)

The ADAA is dedicated to informing the public, health care professionals, and legislators that anxiety disorders are serious, real diseases that can be treated. The organization promotes the early diagnosis, treatment, and cure of anxiety disorders, encourages the advancement of scientific knowledge about causes and treatment of anxiety disorders, and assists people with anxiety disorders in finding treatment.

www.adaa.org

Agoraphobics Building Independent Lives (ABIL)

ABIL's goal is to provide hope, support, and advocacy for people suffering from phobias, panic attacks, and/or agoraphobia by establishing self-help groups and providing public education. The organization continues to develop a strong link with the professional community to improve the quality of treatment available.

www.anxietysupport.org

Freedom From Fear

This national not-for-profit mental health advocacy association has a mission to positively impact the lives of all those affected by anxiety, depressive, and related disorders through education, research, and community support. The organization has developed an anxiety and depression screening program. The web site has a section for health care professionals seeking programs and patient education materials.

www.worldsleepfoundation.com

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Thank you to those who took the time to fill out the survey and fax it back to us. We appreciate your feedback.

CASE FILES

Ellen A. Dornelas, PhD

Clinical Case: A 56-Year-Old Man With Recent Myocardial Infarction

Background

The patient is a 56-year-old man with a recent inferior-wall myocardial infarction. He underwent cardiac catheterization and coronary stenting and was discharged after 4 days. While in the hospital, he stopped smoking but relapsed on the second day after discharge. A nurse from his cardiac rehabilitation program referred him for smoking cessation.

Presentation and History

The patient admits to a pack-a-day smoking history of almost 40 years. He has a history of hypercholesterolemia, a body mass index of 26 kg/m^2, and a self-described sedentary lifestyle. His mother is alive at age 82 years and in good health. His father was a lifelong smoker who died of sudden cardiac death at age 61 years. The patient has tried to quit smoking at least twice before. The most recent attempt was about a year ago and lasted 4 months. He relapsed during a period of increased job stress.

The patient has a history of at least one episode of depressed mood, which occurred in his late 30s and was treated successfully with antidepressant medication and psychotherapy. He no longer takes an antidepressant and reports that he is happy with his job. The patient has been married for 24 years and has two grown children and two grandchildren. He lives with his wife, who is a nonsmoker.

Discussion

Traditional approaches to smoking cessation tend to follow a medical model, characterized by presentation of a great deal of information and advice in a short period of time. In contrast, motivational counseling* focuses on eliciting motivational statements from the patient. Motivational interviewing is based on the premise that people are ambivalent about behavior change.† The overarching goal is to help the patient resolve the ambivalence. High levels of motivation provide a strong foundation for applying smoking cessation strategies and techniques.

Counselor: Tell me about a typical day. How does smoking fit in to your day?

RD: I smoke one cigarette with my coffee in the morning, another on the way to work and then I don't smoke much in the morning. But in the afternoon, between 2:00 pm and the time I go to bed at night, I usually finish the rest of the pack, and if I'm stressed, I might smoke more.

Counselor: What concerns do you have about smoking?

RD: Of course, since I had the heart attack, I'm really worried that I am going to die from another heart attack! You would think that would have made me quit!

Counselor: Well, it sounds like you have been trying but it has been difficult for you. How motivated are you to stop smoking, on a scale from zero to ten, with ten being the highest level of motivation?

RD: That is a good question! About a seven.

Counselor: What makes you as motivated as you are?

RD: I want to see my grandchildren grow up. I don't want to die any earlier than I have to. There are so many things left that I want to accomplish.

Counselor: So how can I help you move from a seven to a ten?

RD: It helps me to have someone coaching me. Somehow, if I know someone will be checking back with me, it helps me to stick to my plan.

Counselor: OK, I can certainly do that. So, given all that you have said, what types of different strategies have you considered that will help you to quit smoking?

Intervention

The optimal treatment plan for smoking cessation combines medication with behavior modification. Nicotine replacement therapy (NRT) comes in multiple formulations, including transdermal patch, chewing gum, lozenge, inhaler, and nasal spray. Additionally, the US Food and Drug Administration has approved varencline and bupropion for smoking cessation. Because the patient said stress played a role in his urge to smoke, the self-titrating forms of NRT were discussed: inhaler, gum, and nasal spray. The patient chose the inhaler, in part because he could continue to take breaks at work, substituting use of the inhaler for cigarette smoking.

Behavioral treatments discussed included a local smoking cessation group, use of a web-based intervention, and contact information for the local smoking cessation support line, or Quitline. The patient chose the web-based program, in part because of time limitations and the availability of online peer support. The patient chose a quit date and was asked to contact the cessation counselor by telephone the day after the quit date and then monthly for the next 6 months. Cardiac rehabilitation nurses monitored the patient's progress and supported his smoking cessation attempt.

Follow-Up

The patient contacted the smoking cessation counselor on the 1-year anniversary of his heart attack, reporting that he had remained tobacco free throughout the year.

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

Clinical Case: A 43-Year-Old Woman Undergoing Gastric Bypass Surgery for Morbid Obesity

Background

In preparation for gastric bypass surgery, the patient's surgeon has told her that she must stop smoking. The patient was referred to a smoking cessation program.

Presentation and History

The patient is 5' 7" tall and weighs 310 lb. She has a history of hypertension and diabetes and early-stage osteoarthritis involving her knees. The patient admits to a pack-a-day smoking history that dates back to age 16 years. She reports that she is easily winded and knows that her smoking is hazardous to her health. The patient quit for the duration of each of her two pregnancies. She admits that smoking helps control her eating, and she feels anxious about making two difficult behavior changes at the same time.

The patient has a full and sometimes stressful life. She admits to no history of mental health issues, although she consulted with a psychologist for about 6 months following a divorce. She is employed full time as a nurse. She lives with her two children, both of whom are in high school. The patient's primary source of psychosocial support is her mother, who is 67 years of age and lives nearby.

Discussion

Motivation is a prerequisite for behavior change.† Even so, many motivated people lack confidence in their ability to change. Strategies to build confidence generally rely on eliciting statements from the patient. Primary practitioners can learn motivational counseling*, which can be incorporated into virtually any type of smoking cessation program.

Counselor: So from the fact that you are here, I know you are taking your surgeons' requirement seriously. But my concern is that stopping smoking requires a high level of motivation. Do you think we should go ahead?

LD: I'm completely motivated, I would really like to stop smoking and my doctor has told me that he won't perform the surgery unless I quit. But it is just a great deal of change for me to make all at once!

Counselor: So it sounds like you really want to stop, but perhaps you aren't as confident in your ability to quit? On a scale from 0 to 10, with 10 being the highest level of confidence, how would you rate your confidence level?

LD: Probably a 3! I wish it was higher!

Counselor: Why a 3 and not a zero? What gives you the confidence you have?

LD: Well, I know that when I was pregnant both times, I just put the cigarettes away. I didn't start again until after I stopped breastfeeding. So if I did it twice before, I should be able to do it again.

Counselor: That is true, you have stopped for nearly a year, twice before in your life!

LD: The difference now, is that I am trying to also change what I eat. Cigarettes helped me to control my eating.

Counselor: You are right, those are two major lifestyle changes to undertake. Who is supporting you in your efforts to change?

LD: My mother is my biggest support, she will stay with me after surgery. My kids are both great as well, one will go walking with me.

Counselor: So it is wonderful that you have a strong support system. I wonder if there has ever been a time in your life when you had to make changes similar to these, where it was very difficult but you were successful?

LD: Yes, I put myself through school while my kids were young and I never thought I would get my degree, but I did!

Counselor: So it sounds like when you really put your mind to it, you have incredible ability to overcome challenges. I'll bet this trait will really carry you through.

LD: I think you are right, perhaps I just needed the push to get started.

Counselor: So given all that you said, where does that leave you now?

LD: I think I just have to do it.

Counselor: What kind of approaches have you considered to help you in your efforts to stop smoking?

CLINICIAN RESOURCES FOR SMOKING CESSATION

Internet
www.smokefree.gov

Telephone Quitlines
1-800-QUIT-NOW. A single access point for the National Network of Tobacco Cessation Quitlines

Local Smoking Cessation Programs
National 2-1-1 call centers can usually provide referrals to local smoking cessation programs, as can most state-run Tobacco Cessation Quitlines.

Pharmacotherapy

Over-the-Counter
- Nicotine polacrilex gum
- Transdermal patch
- Lozenge

By Prescription
- Nicotine inhaler
- Nicotine nasal spray
- Non-nicotine replacement medications, bupropion and varencline

LD: I would like to know more about the different medications. I know there are some new things around but I'm not familiar with them.

Counselor: Great, I can tell you about medication and you might consider combining medication with a behavioral program.

Intervention

For medical therapy, the patient chose nicotine gum and bupropion, and a smoking cessation group was her choice for behavior modification training and support. She found that the bupropion helped minimize the negative affect that often accompanies withdrawal in the first week after stopping smoking. The nicotine gum provided a substitute for cigarettes and overeating. The smoking cessation group provided peer support and reassurance that she was not alone in her struggle to change behavior. The smoking cessation counselor remained available for contact as needed after the completion of the group.

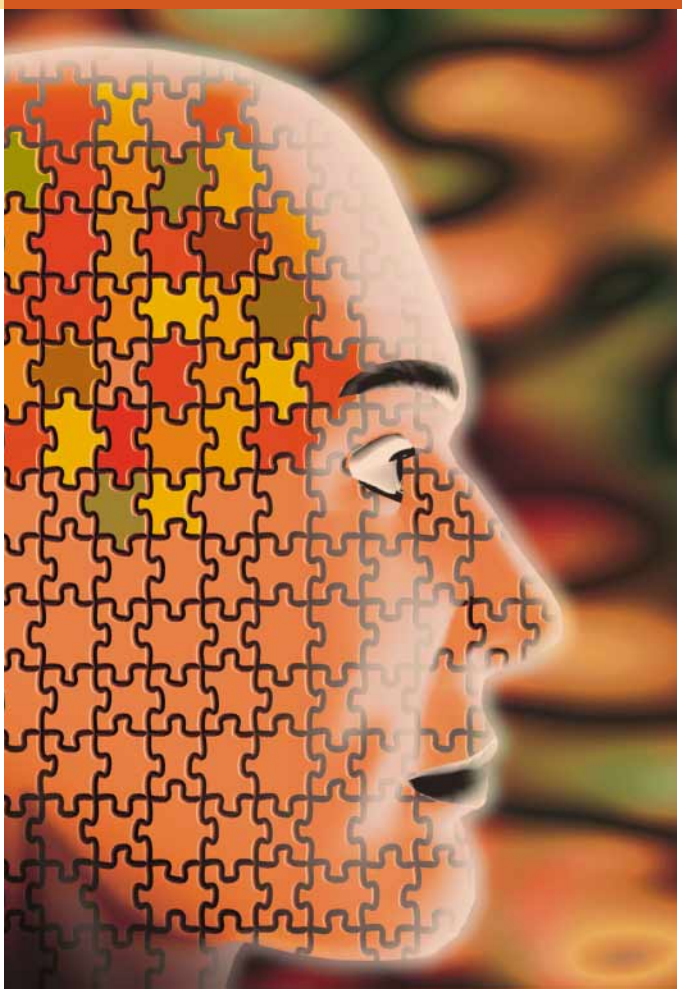
Follow-up

The patient underwent successful gastric bypass surgery. On the first anniversary of the surgery, she remained tobacco free.

Dr Dornelas has disclosed that she has received clinical grants from Pfizer Inc.

*Rollnick S, Butler CC, Stott N. Helping smokers make decisions: The enhancement of brief intervention for general medical practice. *Patient Educ Couns*. 1997;21:191–203.
†Turn to page 8 to read more on the five stages of behavioral change.

Strategies for Managing Anxiety Disorders



Thomas L. Schwartz, MD

> **Although anxiety disorders can be effectively treated, only about one third of those who suffer from an anxiety disorder receive treatment.**

Anxiety disorders are prevalent among patients seen in the primary care setting, occurring in about 19% of this population, according to prevalence studies, and have a substantial impact on an individual's functioning, work productivity, and health care costs.[1-3] An estimated 40 million adult Americans struggle with anxiety disorders.[4] Although anxiety disorders can be effectively treated, only about one third of those who suffer from an anxiety disorder receive treatment.[4]

Every patient visit in the primary care setting can be an opportunity for clinicians to detect any signs or symptoms of anxiety disorders. This article discusses practical approaches for primary care clinicians to assess and manage the care of people with anxiety disorders.

Identifying Anxiety Disorders

Having feelings of anxiety is a normal part of life; anxiety is one of the ways that the body responds to a physical, emotional, or intellectual stimulus. However, anxiety disorders can develop when such feelings become persistent and overwhelming and interfere with a person's daily functioning. Anxiety disorders occur when there is an excessive or inappropriate response to a relatively neutral stimulus.

According to the criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition; *DSM-IV*),[5] several types of anxiety disorders are identifiable based on specific characteristics, including:

- **Generalized anxiety disorder (GAD)** is characterized as excessive and uncontrollable worry, "occurring more days than not for at least 6 months," and difficulty in controlling the worry. Symptoms of GAD may include restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating, irritability, muscle tension, and sleep disturbance.
- **Obsessive-compulsive disorder (OCD)** involves having repetitive thoughts that are intrusive, unwanted, and disturbing, often combined with rituals and behaviors to reduce anxiety provoked by these obsessions.
- **Panic disorder** is characterized by unexpected, sudden episodes of intense fear that occur without any warning or apparent reason, often provoking such symptoms as dizziness, palpitations, shortness of breath, and trembling; each episode usually lasts no more than about 10 minutes.
- **Social anxiety disorder** is marked by an excessive and unreasonable fear of being scrutinized by others or doing something embarrassing in front of strangers, which causes distress or leads to avoidance of certain situations; physical signs may include tachycardia, increased blood pressure, trembling, shaking voice, shortness of breath, blushing, nausea, diarrhea, cold clammy hands, muscle tension, gastrointestinal discomfort, sweating, and poor eye contact.[6]
- **Posttraumatic stress disorder (PTSD)** may occur after a terrifying event that a person experienced or witnessed where intense fear occurred, followed by repeated flashbacks or intrusive images of the trauma. Symptoms of PTSD may include sleep problems, feelings of detachment or numbness, hypervigilance, irritability, and aggressiveness.

Consideration needs to be given to anxiety caused by medical problems or use

or discontinuation of certain medications. Various medical conditions may cause anxiety, including neurologic disorders (eg, head injury, brain infection, or inner ear disorder), cardiovascular disorders (eg, heart failure or arrhythmias), endocrine disorders (eg, overactive adrenal or thyroid gland), and respiratory disorders (eg, asthma or chronic obstructive pulmonary disease), as well as fever.[7] Several prescription drugs (eg, ephedrine and theophylline) and over-the-counter products that contain ephedrine or caffeine can induce anxiety.[7] Furthermore, the discontinuation of a medication (eg, benzodiazepines) can induce anxiety.[7]

Anxiety may also be related to substance misuse (defined as the problematic use of alcohol or other psychoactive substances, such as other sedatives, opioids, cannabinoids, stimulants, and hallucinogens).[8] For example, people may find themselves using alcohol to ease their anxiety; however, although alcohol may initially appear to alleviate anxiety, regular and long-term use can actually increase anxiety levels. In other words, a reciprocal causal relationship between alcohol dependence and anxiety disorders can develop over time, with alcohol dependence leading to anxiety disorders and vice versa.[8]

Making an accurate diagnosis of a patient's particular anxiety disorder is the first step in providing effective treatment, which often involves engaging the patient in some form of psychotherapy and pharmacotherapy, alone or in combination.[9]

Recognizing Coexisting Conditions

Anxiety disorders rarely occur in isolation.[10] In clinical practice, most patients with an anxiety disorder have comorbid conditions, such as major depression, alcohol and other substance abuse problems, or more than one anxiety disorder.[11] For example, researchers who analyzed data from the National Comorbidity Survey Replication found that up to 60% of people with a diagnosis of major depressive disorder met the criteria for an anxiety disorder (applying the *DSM-IV* criteria for all diagnoses).[12] Therefore, the prudent course of action is to look for any signs or symptoms of an anxiety disorder whenever a diagnosis of clinical depression is made, as well as to screen for depression whenever an anxiety disorder is detected.

Various rating scales (eg, **Figure**) and screening tools can be effective in the primary care setting to help determine the need for more extensive evaluation in these individuals. Such assessments are important for clinicians in determining a comprehensive treatment plan for individuals. Of course, with time constraints it may be difficult to have a rating scale for every disorder. It may be wise to use a few select and specific scales if you see a high rate of these disorders in practice or to use one general scale that may pick up much overlapping symptom information.

Scales such as that shown in the **Figure** may act as checklists or provide the clinician with a framework to ask diagnostic questions. Many scales can be completed in the waiting room, scored by staff, and placed on the chart for review by the physician, not unlike taking vital signs at the initiation of a primary care visit. Often, patients can complete rating scales after the nursing intervention, while waiting for the physician to enter the examination room, as well.

It is fortunate that some pharmacologic therapies are available that can treat both depression and anxiety. In this regard, the US Food and Drug Administration (FDA) has approved some selective serotonin reuptake inhibitors (SSRIs, such as fluoxetine, sertraline, paroxetine, and escitalopram) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs, such as venlafaxine) to treat both depressive and anxiety disorders. Other antidepressants and anxiolytics may be effective for each condition separately per FDA indications.

In addition, careful consideration needs to be given to medical disorders that commonly coexist with anxiety and depression, including heart disease, pulmonary disorders, neurologic conditions, endocrine disorders, gastrointestinal

FIGURE. THE GENERALIZED ANXIETY DISORDER (GAD)-7 SCALE

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at All	Several Days	More Than Half the Days	Nearly Everyday
Feeling nervous, anxious, or on edge	☐ 0	☐ 1	☐ 2	☐ 3
Not being able to stop or control worrying	☐ 0	☐ 1	☐ 2	☐ 3
Worrying too much about different things	☐ 0	☐ 1	☐ 2	☐ 3
Having trouble relaxing	☐ 0	☐ 1	☐ 2	☐ 3
Being so restless that it is hard to sit still	☐ 0	☐ 1	☐ 2	☐ 3
Becoming easily annoyed or irritable	☐ 0	☐ 1	☐ 2	☐ 3
Feeling afraid as if something awful might happen	☐ 0	☐ 1	☐ 2	☐ 3

Note: The first two items constitute the GAD-2 subscale.
Source: Kroenke et al.[1] Used with permission.

TIPS ON HELPING A LOVED ONE WITH AN ANXIETY DISORDER

These suggestions from the Anxiety Disorders Association of America may be useful to give to family members of patients with anxiety disorders:

- Learn about the anxiety disorder.
- Encourage treatment.
- Aim for positive reinforcement of healthy behavior, rather than only criticizing irrational fear, avoidance, or rituals ("catch them doing something right").
- Measure progress on the basis of individual improvement, not against some absolute standard.
- Help set specific goals that are realistic and that can be approached one step at a time.
- Do not assume you know what is needed. Ask how you can help. Listen carefully to the response.
- Acknowledge that you do not understand if you have never personally experienced a panic attack or other form of irrational anxiety.
- Understand that knowing when to be patient and when to push can be challenging. It's a fine line. Achieving a proper balance often requires trial and error.
- Remember, recovery requires hard work on the part of the individual and patience on the part of the partner and family. It may seem like a slow process, but the rewards are well worth it.

Source: Anxiety Disorders Association of America.[18]

disorders, metabolic conditions, and other medical problems (eg, rheumatoid arthritis, lupus, chronic fatigue syndrome, or vitamin B_{12} deficiency).[13] A thorough assessment of the individual's lifestyle habits, including the overuse of alcohol, caffeine, and cigarettes, provides useful information in the context of managing anxiety disorders and various comorbidities.

Determining Treatment Options

Several treatment strategies are available for the management of anxiety disorders, with evidence suggesting that pharmacologic therapy in combination with psychotherapy, particularly cognitive-behavioral therapy (CBT), can help improve outcomes for individuals with anxiety disorders.[14] CBT strategies for anxiety disorders focus directly on eliminating exaggerated fears and the avoidance responses that help maintain anxiety disorders, as well as applying psychoeducational interventions that provide individuals with a different perspective for interpreting their ongoing anxiety experiences.[14] Patients are taught to monitor their situations and their anxiety levels. If anxiety rises, patients assess the situation and utilize cognitive or behavioral techniques to halt the escalating anxiety. As a result, the link between neutral stimulus and excessive anxiety response is extinguished. Developing a strong referral network of psychotherapists who are skilled in CBT is a key component in the infrastructure of all primary care practices, and sessions should be attended for 10 to 20 weeks by patients. Analytical or psychodynamic psychotherapy is less studied but also may be effective, particularly if the patient is motivated for longer-term approaches or access to CBT is limited.

Anxiety disorders are often treated with SSRIs, such as fluoxetine, paroxetine, escitalopram, or sertraline or SNRIs, such as venlafaxine, as first-line treatment.[15] Although originally approved by the FDA for the treatment of depression, SSRIs have been proven effective in the treatment of GAD, PTSD, panic disorder, OCD, and social anxiety disorder. SNRIs have been approved by the FDA for the treatment of GAD, panic disorder, and social anxiety disorder. In addition, buspirone, a serotonin receptor agonist, is FDA approved to treat GAD, and benzodiazepine sedatives (eg, alprazolam, clonazepam, and diazepam) have received FDA approval for treating certain anxiety states as well.

Because anxiety symptoms can be extremely distressing, benzodiazepines typically may provide the most rapid relief, often within 1 or 2 days of treatment, as compared with SSRIs and SNRIs, which often require 2 or more weeks for a noticeable response.[16] However, no single pharmacologic agent appears to be effective for all individuals with anxiety disorders. For some patients, patience and persistence are required until the most effective combination of modalities is found.

Effectiveness rates with SSRIs, SNRIs, and anxiolytic sedatives may reach as high as 70%.[16] However, one must consider side effects. Sedatives are considered second-line treatment because of the risk of addiction, but these agents cause problems of sedation, ataxia, and respiratory suppression as well. First-line SSRIs/SNRIs often have sexual dysfunction, weight gain, headaches, gastrointestinal upset, insomnia, tremor, diaphoresis, sedation, and/or activation syndrome (eg, irritability, restlessness, or emotional lability, which may represent a change that promotes suicidality) as adverse effects. In patients up to 25 years of age, there is a warning about increased chances of worsening depression and suicidal thinking.

Discussing the Need for Therapy With Patients

Primary care clinicians can take the initiative to ask questions about anxiety when meeting with their patients, understanding that patients are often reluctant or embarrassed to discuss mental health issues such as anxiety. Patients may be secretive and feel shame about their symptoms, may think it is normal to be anxious, or may lack insight about anxiety disorders. For example, people with OCD, on average, visit three or four doctors and spend more than 9 years seeking treatment before they receive a correct diagnosis because of these issues.[17]

Education is a key aspect of any intervention with patients who have an anxiety disorder. In addition to presenting psychotherapy as an effective therapy, which may be the treatment of choice for patients with mild to moderate anxiety,

primary care professionals can define anxiety disorders as specific medical conditions with clearly defined and appropriate treatment strategies using psychotherapy and medications, alone or in combination.

When pharmacologic therapy is prescribed, patients need to be properly educated about how the medication works, possible side effects, and the anticipated timing to notice a pharmacologic response. As a general rule, clinicians should start with a low dose of a certain medication to avoid any initial anxiety-invoking adverse effects and then be willing and able to use the full dose range gradually as stated in the package insert for each prescription medication. In general, clinicians should leave a patient at the lowest therapeutic dose for 4 to 6 weeks and escalate throughout the dose range in similar fashion. For best results, patients should not be left on low to moderate doses for months at a time; a full trial of an SSRI/SNRI may be considered a failed trial only when used at moderate to high doses for several weeks. Keeping doses too low may lower side effects but also may compromise the outcome.

Of special note is the role of family members or other loved ones in helping people with anxiety disorders seek help and follow the recommended treatment plan. Educating family members about the anxiety disorder and how they can be supportive of the patient's treatment plan can be useful in encouraging adherence to keeping appointments for psychotherapy and/or taking medications as prescribed.

Providing Effective Follow-Up Care

Primary care clinicians should be aware of the consequences when patients discontinue psychotherapy or pharmacologic therapy too early, leading to a relapse in symptoms of anxiety disorders. The more this happens, the more difficult it often is to achieve optimal outcomes because of treatment resistance. This is analogous to the situation in which patients are instructed to use an antibiotic for bacterial bronchitis for 10 days; if the medication is stopped too soon after only a few days of relief, the bronchitis may return and become more difficult to treat because of antibiotic resistance.

With medications for anxiety disorders, as well as those for depression, there is usually a prescribed amount of time that an individual should continue with a certain medication regimen, even if the individual starts feeling much better. It may make sense with most anxiety disorders to achieve a wellness state where the patient is remarkably better and continue the medication for at least 1 year from this point before slow discontinuation of the medication. OCD may require longer or lifelong treatment. In general, the more severe and more chronic the illness, the longer it is required for patients to stay on an appropriate medication despite feeling well. This long-term prophylactic treatment should be the standard of care.

Ongoing follow-up care allows for close monitoring of progress, as well as addressing any concerns about the treatment plan. Early identification of any side effects relating to the medication allows for adjustments in an individual's treatment. Some medications may take several weeks to achieve a favorable response, with several alterations of the dose to work properly. Monitoring also allows for conversation about tolerability and side effect issues and allows the patient to better balance the risks of continuing treatment for anxiety prevention versus stopping the medication early while at risk for symptom relapse.

Conclusion

Improvements have been made over the last 2 decades in recognizing and managing anxiety disorders. Clinicians should no longer look for anxiety or depression alone, considering the frequency with which these two common mental health problems occur together; a search for one condition should include assessment for the other. Medical and substance misuse comorbidities should also be considered.

The first step is making an accurate diagnosis and determining an effective treatment strategy. In addition to the emergence of new classes of medications to treat patients with anxiety disorders, various forms of psychotherapy are tailor-made to address certain anxiety disorders. Adequate attention to the individualized needs of patients, including candid discussions about the nature of their anxiety disorder and available treatment options, is warranted. Ongoing follow-up care is essential to helping these individuals with anxiety disorders achieve and maintain long-term treatment gains.

Dr Schwartz has disclosed that he has received clinical grants from Wyeth and Forest Laboratories, Inc., and is a consultant to Wyeth.

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Cast a Wide Net With Chronic Pain

Carl C. Bell, MD

Chronic pain cuts wide. One out of every five people lives with some sort of chronic pain. Of that 20%, one-third are not able or are only minimally able to maintain an independent lifestyle because of it, according to the International Association for the Study of Pain.

And chronic pain cuts deep. Beneath the veneer of the physical symptoms lies the social, emotional, and psychological havoc caused by the associated disability, isolation, fear, and helplessness, which leads to a substantially diminished quality of life.

Unfortunately, chronic pain is also invisible. There's no gash to suture, no broken leg to set. Instead, there exists an amorphous condition that is difficult to measure and even more difficult to manage, particularly in a health care culture that values cut-and-dry diagnoses and magic pills. Adding to the complexity is the fact that chronic pain often coexists with a range of psychological disorders, including depression, anxiety, personality disorders, cognitive problems, and substance abuse.

In one study designed to assess the prevalence of chronic pain conditions and their relationship with major depressive disorder (MDD), investigators from Stanford (Calif.) University conducted a cross-sectional telephone survey of a random sample of nearly 19,000 subjects from the general population.

> **"Adding to the complexity is the fact that chronic pain often coexists with a range of psychological disorders, including depression, anxiety, personality disorders, cognitive problems, and substance abuse."**

About 4% of the survey participants met the diagnostic criteria for MDD, and of those, 43.5% reported having at least one chronic pain condition—a number four times greater than reported by individuals in the study who did not have depression (*Arch Gen Psychiatry*. 2003;60:39-47).

More recently, another Stanford study sought to evaluate the strength of the association between major depression and chronic pain and to examine the clinical burden associated with the two conditions. Of nearly 6,000 randomly sampled primary care patients who responded to a questionnaire, about 7% met criteria for MDD, and two-thirds of those with depression reported chronic pain. Among all of the subjects in the sample who reported chronic pain, the prevalence of MDD was significantly higher than in those without pain (*Psychosom Med*. 2006;68:262-8).

The direction of the pain/depression connection has yet to be fully understood, but the degree of disability appears to play an important role, according to lead investigator Bruce A. Arnow, Ph.D. Among those respondents with chronic pain, the prevalence of MDD was 23% in people with disabling pain, compared with 5% in those who were not disabled by their pain. "It's possible that those who are disabled by pain become depressed, and it is possible that those who are depressed are more likely to become disabled," he said.

Regardless of initial direction, the likelihood that one will coexist with the other warrants that both be addressed. Numerous studies have shown that depressed chronic pain patients report greater pain intensity, more malignant disease course, and poorer response to pain treatments. Additionally, depression can impede rehabilitation efforts because of low motivation, poor morale, low energy, and hopelessness.

In contrast, considering the physical and mental health components of chronic pain as symptoms of a single pain syndrome can improve patient outcome. A large, multisite investigation of depression care from the University of Washington, Seattle, showed that older adults with chronic arthritis pain who were screened and treated for depression had significant improvements in pain severity and functioning, compared with those patients who received standard arthritis care. The treatment group benefited from a multidisciplinary program that included medication, psychotherapy, and in-person and telephone follow-up (*JAMA*. 2003; 290:2428-9).

The multidisciplinary intervention "not only helped patients with arthritis feel less depressed but also helped them cope better with their pain, to be more active, and to have a higher quality of life," according to lead investigator Dr. Elizabeth H.B. Lin of the Group Health Cooperative in Seattle. Treating patients' depression isn't going to take the pain away, she said, but treatment can change the experience of pain, which can lead to improved outcomes.

In addition to antidepressant medications when warranted, various nonpharmacologic strategies, including patient psychoeducation, and cognitive-behavioral interventions, can give chronic pain patients a sense of control over their pain and the tools needed to modify behaviors that contribute to emotional and physical distress.

The bottom line, according to chronic pain expert Robert D. Kerns, Ph.D., associate professor in the departments of psychiatry, neurology, and psychology at Yale University, New Haven, Conn., is that patients with chronic pain have to be viewed from a broad biopsychosocial perspective.

"For greatest effectiveness [in managing chronic pain], we should be treating the whole person, not fixing a 'broken' body part," Dr. Kerns said.

By Diana Mahoney, New England bureau, IMNG News Service. Reprinted from *Clinical Psychiatry News*, August 2006.

Perspective

People who have chronic pain are extraordinarily clear about the devastating impact this problem has on their psychological balance. The resulting sense of helplessness often generates a great deal of grief, depression, stress, pessimism, and loneliness.

People who have never experienced severe, chronic pain, however, have no idea how disruptive it can be. Because of this, they may erroneously assume (and even suggest) that the pain is purely psychological or a sign of weakness of character or will—sentiments that further isolate and alienate the sufferers.

This isolation is exacerbated by the current health care culture. Although some understanding exists of the medical conundrum of pain, the psychiatric ramifications are very much an afterthought. The proactive approach of considering mind and body takes a back seat to the mechanistic approach of trying to heal the physical body while ignoring the mind.

This approach is rather typical of Western medicine and has its origins as far back as the Descartes doctrine of the distinction between the mind and body.

Because Western medicine focuses so intently on the mechanistic view of life and well-being, we don't have evidence of the efficacy of other, more esoteric forms of healing, such as acupuncture, meditation, prayer, and support group activities. We won't be able to collect such evidence until Western health care providers routinely begin to embrace non-Western approaches to health care that address issues of both the mind and the body.

Fortunately, science may be taking us in that direction. The mechanism of pain has been connected to the serotoninergic neurotransmitter system in the brain and body, which is also linked to depression. This connection suggests a potential route for therapeutic benefit of antidepressant medications for chronic pain.

Bridging the mind/body gap in our management of chronic pain is not impossible, but doing so does require a critical culture shift in which neither element takes a backseat to the other.

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

Pain Relief Is a Phone Call Away

Patients suffering from chronic, nonmalignant pain generally have to come to terms with the fact that finding a cure for their symptoms is an elusive goal. A more reasonable treatment target is pain management, often through some combination of analgesic medication and behavior modification.

In fact, numerous studies have shown that behavioral interventions—particularly cognitive-behavioral therapy (CBT) and self-regulatory techniques such as biofeedback and hypnosis—can significantly reduce pain intensity and improve emotional and physical functioning.

Ideally, after participating in a behavioral intervention, patients will regularly access and employ the various coping strategies they've acquired. Realistically, the likelihood that they will do so diminishes over time.

Although it may not be feasible to conduct open-ended behavioral intervention groups, pain specialists at the University of Vermont in Burlington may have developed the next best thing. Therapeutic Interactive Voice Response (TIVR) was developed to enhance the therapeutic outcome of patients who have completed a course of group CBT for chronic pain and to minimize their reliance on pharmacologic painkillers.

The first component of the TIVR enhancement is a daily self-monitoring questionnaire. Patients access the computerized interactive telephone system and respond by touch-pad to a series of questions that measure coping, perceived pain control, mood, medication, and stress. The objective is to improve self-monitoring of pain behavior, coping skills, and medication use, said TIVR principal investigator Dr. Magdalena R. Naylor, director of the university's MindBody Medicine Clinic.

If patients desire a coping skills "refresher," they can access a didactic review that provides a verbal review of the various pain management skills learned during the CBT intervention, such as relaxation response, positive self-talk, cognitive restructuring, and distraction techniques.

The final component is a monthly feedback message: A therapist analyzes computer-collated, patient-specific data from the telephone response system and records a personalized message for participants summarizing the daily reports and offering insight into potential problem areas. This element is critical to the efficacy of the system, according to Dr. Naylor, as it is a vehicle for valuable feedback and an ongoing positive connection with the therapist.

In a pilot test of TIVR in a group of 10 middle-aged patients with severe, chronic musculoskeletal pain, regular use of the TIVR both maintained and strengthened the therapeutic gains associated with the CBT intervention (*J Pain*. 2002;3:429-38).

The Vermont investigators are currently replicating the TIVR study in a randomized, controlled trial.

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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.

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

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

WARNINGS: Clinical Worsening and Suicide Risk—Patients with 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 MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

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

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

Families and caregivers of 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.

MAOIs—In patients receiving a serotonin reuptake inhibitor (SSRI) in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRIs and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Cymbalta and MAOIs have not been evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

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

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

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* PRECAUTIONS, Drug Interactions).

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

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

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

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

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

Laboratory Tests—No specific laboratory tests are recommended.

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

Cymbalta May Have a Clinically Important Interaction with the Following Other Drugs—Alcohol—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol. In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen (*see* PRECAUTIONS, Hepatotoxicity). CNS-Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action. Serotonergic Drugs—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta and the potential for serotonin syndrome, caution is advised when Cymbalta is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (*see* WARNINGS,

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Serotonin Syndrome). The concomitant use of Cymbalta with other SSRIs, SNRIs, or tryptophan is not recommended (*see* PRECAUTIONS, Drug Interactions). Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* WARNINGS, Serotonin Syndrome). Potential for Interaction with Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

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

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

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

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

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

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

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

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

Geriatric Use—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN premarketing studies, 33% (357) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPN studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, Cymbalta has been associated with cases of clinically significant hyponatremia (*see* Hyponatremia, *under* PRECAUTIONS).

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

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

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

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping similar types of events into a smaller number of standardized event categories is necessary. MedDRA terminology was used to classify reported adverse events.

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

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

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

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

The most commonly observed adverse events in Cymbalta-treated MDD patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating.

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

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

The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia.

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

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

The most commonly observed adverse events in Cymbalta-treated GAD patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; fatigue; dry mouth; somnolence; constipation; insomnia; appetite decreased; hyperhidrosis; libido decreased; vomiting; ejaculation delayed; and erectile dysfunction.

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

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

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

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

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

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

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

OVERDOSAGE: There is limited clinical experience with Cymbalta overdose in humans. In clinical trials, cases of acute ingestions up to 3000 mg, alone or in combination with other drugs, were reported with none being fatal. However, 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 approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed drugs) included serotonin syndrome, somnolence, vomiting, and seizures. ***Management of Overdose***—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

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

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

MMRM=Mixed-effects Models Repeated Measures analysis

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

treat beyond the obvious

Cymbalta® duloxetine HCl DELAYED RELEASE CAPSULES

Important Safety Information

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, 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 thioridazine and not in patients with a known hypersensitivity or 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 when initiating drug therapy and when increasing or decreasing the dose. A health professional should be immediately notified if the depression is persistently worse or there are symptoms that are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication.

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

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

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

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

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

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

Most common adverse events (≥5% and at least twice placebo) in premarketing clinical trials were: **MDD:** nausea, dry mouth, constipation, fatigue, decreased appetite, somnolence, and increased sweating. **DPNP:** nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia. **GAD:** nausea, fatigue, dry mouth, somnolence, constipation, insomnia, appetite decreased, increased sweating, libido decreased, vomiting, ejaculation delayed, and erectile dysfunction.

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

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