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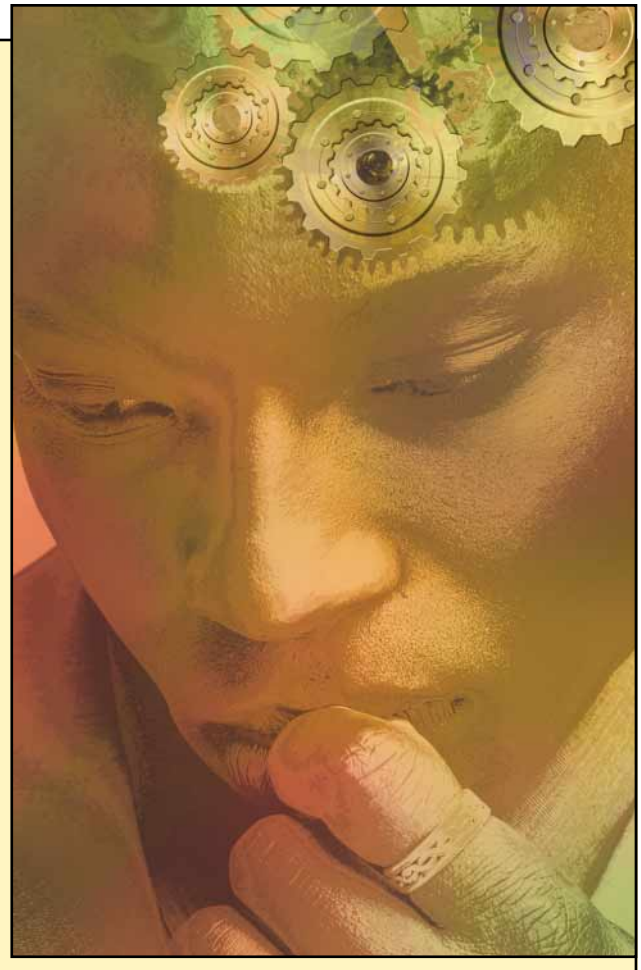

Special Populations in Depression
Applying Cultural Flexibility to Depression in Minority Populations

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Adults With ADHD Need to Know Treatment Options

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INTERNATIONAL MEDICAL NEWS GROUP

From the Desk of...

Welcome to the fourth and final 2007 issue of *Practical Neuroscience for Primary Care Physicians*, a supplement series created as a practical resource for primary care physicians.

In this issue, **William B. Lawson, MD, PhD, DFAPA**, Professor and Chair, Department of Psychiatry and Behavioral Sciences and Director, Mood Research Program, Howard University College of Medicine and Hospital, Washington, DC, authors the 'Special Populations in Depression' series by discussing depression in minorities. **Andrew J. Cutler, MD**, Courtesy Assistant Professor, Department of Psychiatry, University of Florida and President and Medical Director, Florida Clinical Research Center LLC, Maitland, Florida, addresses the management of bipolar disorders. In our 'Case Files' section, **David L. Dunner, MD, FACPsych**, Director, Center for Anxiety and Depression and Professor Emeritus, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, Washington, shares case studies in seasonal affective disorder, and **Peggy L. Johnson, MD**, Assistant Professor, Vice Chair for Clinical Services, Department of Psychiatry, Boston University School of Medicine, Boston, Massachusetts, shares case studies on depression in minorities.

Be sure to visit the publication's web site at www.practicalneuroscience.com where you can find the content of this supplement as well as the first 3 issues. We look forward to hearing from our loyal readers.

Cordially,

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Applying Cultural Flexibility to Depression in Minority Populations

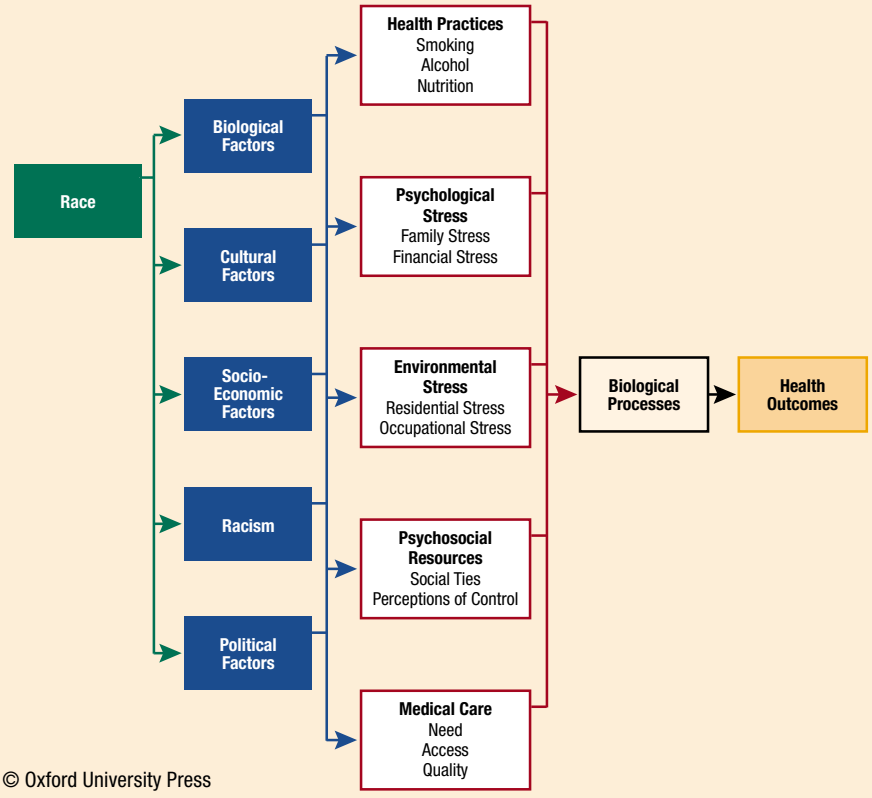
Developing a better understanding of cultural differences and their impact on detecting and treating clinical depression can help clinicians and their patients achieve better health outcomes. According to the US Census Bureau data, 25% of the population living in the United States now belong to a racial/ethnic minority group; projections have been made that, by 2050, one in every two Americans will be African American, Hispanic/Latino, Asian American, Pacific Islander, or Native American.[1] However, minority groups continue to experience striking health disparities, including shorter life expectancy and higher rates of diabetes, cancer, heart disease, stroke, substance abuse, infant mortality, and low birth weight.[2]

Given the enormous growth in minority groups and the existence of health disparities, health care professionals in the primary care setting need to adopt patient-centered strategies that are culturally flexible. The term "cultural flexibility" is a useful concept to describe the ability of clinicians to show versatility in their relationships with patients of diverse ethnic and linguistic backgrounds and treatment preferences; the ability to elicit, adapt, and respond to the cultural characteristics of patients does impact on outcomes of care.[3]

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

"Minority groups continue to experience striking health disparities, including shorter life expectancy and higher rates of diabetes, cancer, heart disease, stroke, substance abuse, infant mortality, and low birth weight."

FIGURE. A FRAMEWORK FOR UNDERSTANDING THE RELATIONSHIP BETWEEN RACE/ETHNICITY AND HEALTH[11]



Awareness of Differences in Communication

Clinical depression is a serious medical illness. Depression is a major factor in predicting heart attacks,[4] a major predictor of dementia when more than one episode occurs,[5] a risk factor for stroke,[6] and a major factor in predicting suicide.[7] Depression also interferes with a person's relationships at home, in the workplace, and in the community. Clinical depression is never normal and should not be accepted as a normal part of life for any individual, regardless of ethnicity, age, or life situation.

Clinicians are well versed in the textbook symptoms of clinical depression. These symptoms may include persistent sad, anxious, or "empty" mood; feelings of hopelessness and pessimism; feelings of guilt, worthlessness, and helplessness; loss of interest or pleasure; decreased energy and fatigue; difficulty concentrating, remembering, and making decisions; insomnia, early-morning awakening, or oversleeping; appetite and/or weight loss or overeating and/or weight gain; thoughts of death or suicide, or suicide attempts; restlessness and irritability; and persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain.[8]

However, various cultural groups and individuals may express such symptoms in vastly different ways. For example, depression may be discussed by Americans with European ancestry in terms of expressing sadness and guilt. But that is not true for everyone. Some people may not use the word "sad" to describe a person's feelings; "sadness" may be perceived culturally as a sign of weakness or not important or not the proper vocabulary for the medical setting. Depression and its symptoms may be perceived differently within various cultures; some cultures may consider mood, affect, and anxiety symptoms as social, moral, or spiritual problems.

In my clinical experience, I recall a woman who came to me and said she did not have any energy, she could not sleep, and she did not want to do the kind of things she liked to do. When I asked, "Are you depressed?" She replied, "No, I'm not depressed, and I'm not sad." But she said all her energy was just gone. She told me that, in the past, a doctor had given her an energy pill. I asked her, "What was this energy pill called?" and she answered, "Prozac®." The lesson for me is to recognize that simply because a person does not use the words "sad" or "depressed" does not mean the person is not depressed. Some people will only talk about how depression is manifested by physical symptoms, such as difficulty in sleeping, sleeping too much, no appetite or eating too much, or inability to concentrate. I have also observed that students may frequently acknowledge only that they cannot concentrate and they cannot think clearly. Such presentations of symptoms require further conversations to determine an appropriate approach for diagnosis and treatment.

Health literacy (defined as having the basic reading and numerical skills necessary to function in the health care environment)[9] is another relevant issue for some people in minority populations. Clinicians need to be aware of the level of health literacy among individuals who receive their care.

The Importance of Cultural Flexibility in Primary Care

Major depression is a treatable cause of pain, suffering, disability, and death. However, studies have found that primary care providers detect major depression in only up to 50% of their patients with major depression.[10]

When people have access to primary care, they first seek care from their primary care physician. Many people may wait until their symptoms are so severe that they have medical symptoms. The primary care clinician must be able to gather information about the patient's history and conduct the proper screening to assess if the person's underlying problem may be a psychiatric issue, such as depression or anxiety. As a preliminary screening, I often ask two basic questions: (1) Are you having problems sleeping? and (2) Are you having problems with your appetite? The answers to these two questions, as well as the use of

screening tools—including various questionnaires that take about 10 minutes to complete and can be administered by other staff—can often shed some light on the potential for a depressive episode.

The next step is to determine the severity of a person's symptoms to evaluate whether or not the patient may be a threat to himself or herself and to look for signs that suggest that the patient is unwilling to comply with the recommended treatment regimen because of despondency.

Developing cultural flexibility begins with one's recognition of his or her own lack of knowledge and experience in working with people of different cultures. For example, in the Washington, DC area, on the West Coast, and in other regions throughout the nation, clinicians may encounter as many as 30 to 40 different cultures having multiple languages and a diversity of perspectives on health and health care.

The relationship between ethnicity and health is multifactorial and complex; one of the many approaches to develop a framework for understanding these dynamics is provided (see **Figure**).[11] Study findings have demonstrated that minority populations show patterns of disease occurrence, health care utilization, and mortality that differ from those of the majority population (that is, the nonminority white population); many factors, including social and cultural influences due to historical, political, environmental, hereditary, and economic factors, help shape these differences.[1] Of special note is the work of the National Center on Minority Health and Health Disparities, created by the National Institutes of Health for the purpose of promoting and supporting research in eliminating health disparities.[1,11]

The key point is to be willing to learn about people, to be open to cultural differences, and to respect each individual. Experts in cross-cultural education have noted that a patient-centered approach incorporating skills and attitudes that may be applicable across ethnic boundaries is the focus, rather than a mastery of "facts" about different ethnic groups.[12] Clinicians can create a more comfortable environment for a patient of another culture by acknowledging the impact of culture and cultural differences on physical and mental health. Researchers have reported that ethnic minorities rate the quality of interpersonal care by physicians and within the health care system in general more negatively than do whites.[13] Studies have found that being treated with dignity and being involved in decisions are independently associated with positive outcomes.[14] Furthermore, not only is patient involvement in decision making about treatment options an important part of respecting patient autonomy, but showing respect to patients as individuals by treating them with dignity (that is, recognizing the inherent value in each person) is essential.[14]

Effective Approaches to Treatment and Follow-Up Care

Once a diagnosis of clinical depression has been made, the treatment plan begins with educating people with depression and their families about the illness and available treatment options. Studies have found that when clinicians treat depression aggressively with multiple modalities, a desirable response can be achieved about 70% of the time.[15]

Patience and persistence are required on the part of the patient and the physician, understanding that the process of achieving optimal response may take several adjustments over time. Cognitive behavioral therapy works well in some individuals but not across all cultures and interpersonal therapy seems to be culturally transportable, as effective in Uganda as in New York City. Psychotherapy can work as well as can pharmacotherapy (including treatment with selective serotonin reuptake inhibitors), with the combination of both pharmacotherapy and psychotherapy leading to better outcomes for some patients than does either one alone.[16] Various nonpharmacologic approaches, such as electroconvulsive therapy and vagus nerve stimulation, as well as emerging studies on the usefulness of

TABLE. RECOMMENDATIONS FOR ADDRESSING BARRIERS TO THE DETECTION AND TREATMENT OF DEPRESSION[17]

Improving Diagnosis

- Assess stigma toward mental health problems for patients suspected to have depression
- Inquire about patient's experience of somatic symptoms and their relationship to depression, life stressors, and social conflicts
- Maintain a respectful, open stance in understanding patient's style of coping with depressive symptoms, including use of spirituality
- Evaluate the presence of comorbid mental health problems, such as alcohol abuse, that require different treatment approaches

Providing Effective Management

- Determine the patient's preferences for psychotherapy and pharmacotherapy and provide treatment referrals for counseling if appropriate and as resources permit
- Educate patients about antidepressant medications, their onset of action, and side effects
- At each visit after initiation of depression management, check for regular adherence to pharmacotherapy or to referred psychotherapy
- Assist patients who cannot maintain regular visits for depression care to find strategies that can overcome social or financial barriers

transcranial magnetic stimulation, may also be appropriate treatment options for some patients with certain types of depression.[18]

For many ethnic minorities, family is important; many individuals develop their identity and their beliefs from their family. Often the support from a patient's family can encourage the person with depression to seek help and follow the recommended treatment plan. For example, I sometimes encounter the patient who states, "I'm a little slowed down, but I'm not much different than in the past." However, a loved one close to this person will comment, "What do you mean? You have been in bed for a week." Such a reality check can be helpful to foster candid conversations in the primary care setting.

These relationships, the support of peers, and other factors can be extremely important in addressing barriers to the detection and treatment of depression in minorities (see **Table** on page 7).[17] On the other hand, some people with clinical depression are part of dysfunctional families, which may indicate that family therapy is necessary to achieve positive long-term results. Clinicians will find it useful to consider the families and their perspective, as well as their role in terms of either supporting individuals so that their depression can be lifted or ensuring that they are not intruders working against treatment goals.

Follow-up care is important for individuals with clinical depression; some people with this illness will probably require lifelong monitoring. The key point in follow-up care is to help prevent future depressive episodes. That is why it is important for clinicians, people with clinical depression, and their loved ones to recognize the recurrence of symptoms of depression on an ongoing basis. For many people with clinical depression, psychotherapy as well as pharmacologic therapy is useful to prevent future episodes of depression.

Now that clinicians have treatment options available that work, they will find it rewarding to see their patients with clinical depression respond to treatment. In my work with these patients, I have found enormous satisfaction when I see individuals who are relieved of their depression begin to solve some of the crises and problems in their life. People are then empowered to manage their lives and handle their problems, which helps prevent the situation from becoming worse.

Conclusion

Detecting and treating clinical depression in people who belong to racial/ethnic minority groups requires a better understanding of cultural differences and their impact on health outcomes. Deficits in recognizing depression in minority populations may be related to language and communication differences, health literacy barriers, and other cultural factors. Clinicians can adopt patient-centered strategies that use the concept of cultural flexibility (that is, the ability to show versatility in their interactions with patients of diverse backgrounds and treatment preferences) in the primary care setting. Psychotherapy and pharmacologic treatment options, alone or in combination, can be effective in helping people with clinical depression achieve better outcomes. Whenever possible, the involvement of family and loved ones can be useful to provide support to the individual with depression. The key to follow-up care is to prevent future depressive episodes.

Applying a culturally flexible approach that shows respect to patients as individuals by treating them with dignity and encouraging their participation in decision making about their health care may be an important factor in reducing health disparities among people of diverse cultures.

Dr Lawson has disclosed that he has received clinical grants from AstraZeneca, the National Institute of Mental Health, and Pfizer Inc., and is a consultant to AstraZeneca and Pfizer.

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Resources in the SPOTLIGHT

BIPOLAR DISORDERS RESOURCES

Depression and Bipolar Support Alliance (DBSA)

The Depression and Bipolar Support Alliance (DBSA) is the leading patient-directed national organization focusing on the most prevalent mental illnesses. The organization fosters an environment of understanding about the impact and management of these life-threatening illnesses by providing up-to-date, scientifically-based tools and information written in language the general public can understand. DBSA supports research to promote more timely diagnosis, develop more effective and tolerable treatments, and discover a cure.

http://www.dbsalliance.org/

NARSAD: National Alliance for Research on Schizophrenia and Affective Disorders

NARSAD supports scientific research to find better treatments and ultimately prevent severe mental illnesses. NARSAD is leading the fight against mental illness by funding innovative scientific research on the causes, treatment, and prevention of a range of mental disorders, including schizophrenia, depression, bipolar disorder, anxiety, eating disorders, autism, ADD/ADHD, and other adult and childhood disorders. NARSAD continues to support the researchers as they use their findings to develop the next generation of diagnostics and treatments for these conditions. With enough effort, NARSAD expects scientists someday to discover preventions and cures for these devastating illnesses.

http://www.narsad.org/index.html

International Society for Bipolar Disorders

The society aims to become the internationally recognized forum to foster ongoing international collaboration on education and research with an objective to advance the treatment of all aspects of bipolar disorders, resulting in improvements in outcomes/quality of life for those with bipolar disorder and their significant others. The society is open to the entire spectrum of mental health care professionals including basic and clinical researchers, psychiatrists, pharmacologists, psychologists, social workers, students, trainees, and interested lay groups and individuals.

http://www.isbd.org

MINORITY HEALTH RESOURCES

National Center on Minority Health and Health Disparities

Created by the National Institutes of Health for the purpose of promoting and supporting research in eliminating health disparities, the National Center on Minority Health and Health Disparities (NCMHD) promotes minority health and leads, coordinates, supports, and assesses the NIH effort to reduce and ultimately eliminate health disparities. The NCMHD works independently and in partnership with the NIH institutes and centers and with other federal agencies and grassroots organizations in minority and other medically underserved communities.

http://ncmhd.nih.gov/

US Department of Health and Human Services Office of Minority Health (OMH)

The mission of this organization is to improve and protect the health of racial and ethnic minority populations through the development of health policies and programs that will eliminate health disparities. The group advises the secretary of the US Department of Health and Human Services and the Office of Public Health and Science (OPHS) on public health program activities affecting American Indians and Alaska Natives, Asian Americans, Blacks/African Americans, Hispanics/Latinos, Native Hawaiians, and other Pacific Islanders.

http://www.omhrc.gov/

PRACTICAL BITS

Quick and Practical Diagnostic Tools

DIGFAST

Mnemonic for Clinicians to Help Cue Screening Questions Relating to Symptoms of Bipolar Disorder

In general, for a diagnosis of mania, a patient must have experienced either euphoria with three DIGFAST symptoms or irritability with four of these symptoms:

Distractibility
poorly focused, multitasking

Insomnia
decreased need for sleep

Grandiosity
inflated self-esteem

Flight of ideas
complaints of racing thoughts

Activities
increased goal-directed activities

Speech
pressured or more talkative

Thoughtlessness
risk-taking behaviors
(sexual, financial, travel, driving)

Source: Muzina DJ et al. *Clevelend Clinic J Med.* 2007;74:89-109.

WHIPLASHED

Mnemonic for Bipolar Depression Diagnosis

The following features are associated with bipolar illness:

Worse or wired when taking antidepressants

Hypomania, hyperthymic temperament or mood swings in history

Irritable, hostile, or mixed features

Psychomotor retardation

Loaded family history: mood swings, bipolar, affective illness

Abrupt onset and/or termination of depressive bouts or episodes <3 months

Seasonal or postpartum depression

Hyperphagia and hypersomnia

Early age of onset

Delusions, hallucinations, other psychotic features

Source: Ketter TA. Available at: http://www.medscape.com/viewprogram/7436.

David L. Dunner, MD, FACPsych

Clinical Case

Female Patient With Typical SAD Presentations: Two Scenarios

Background

The patient is a 30-year-old woman who has lived in Portland, Oregon, for 5 years. She was raised in Florida and had no history of mood disorder until 3 years ago. In the past 3 years she has noted feeling "blue" in the winter, with symptoms beginning in October and remitting in March. She contacts her primary care physician in December because she is oversleeping and missing work.

Diagnosis/Intervention

Scenario 1

On her mood disorder checklist, she presents with depressed mood, decreased interest in usual activities, oversleeping (normal for her is 8 hours, but she has been sleeping 10 hours), 5-pound weight gain since November, fatigue, and difficulty concentrating. She denies suicidal thoughts and has never had treatment for depression. Similar, but not as severe, symptomatology occurred in the previous 2 years in the winter.

Vital signs, physical examination, mental status examination, and laboratory testing (including thyroid and complete blood count) are all normal.

A diagnosis of major depressive disorder: recurrent, currently of moderate severity, with seasonal pattern, is made. Treatment is begun with a dawn simulator and fluoxetine 10 mg to be increased to 20 mg after 1 week. The plan is to treat her until symptoms of depression remit, then discontinue the dawn simulator but continue the fluoxetine on an indefinite basis. If the patient experiences a return of depressive symptoms the following year, resuming treatment with the dawn simulator while continuing the fluoxetine would be prescribed.

Scenario 2

Patient 2 is the same patient described above, who on careful interview describes feeling "better than usual" for a 2-week period in the fall prior to the onset of her depression. During this 2-week period she was more productive than usual, required less sleep than usual, and was more talkative and outgoing.

A diagnosis of bipolar II disorder, currently moderately depressed, with seasonal pattern is made. Treatment for this diagnosis included a dawn simulator and treatment with lamotrigine 25 mg with titration upwards per the manufacturer's recommendations to 200 mg daily. The plan is to continue treatment until symptoms remit and then discontinue the dawn simulator while continuing the lamotrigine. If she has a return of depressive symptoms the following year, the dawn simulator should be restarted. If she notices brisk hypomanic symptoms the next fall, consideration should be given to either adding lithium carbonate treatment or switching her to lithium carbonate maintenance treatment from lamotrigine.

Dr Dunner has disclosed that he has received grant support from, is on the advisory board of, and/or on the speaker's bureau of Bristol-Myers Squibb Company, Corcept Therapeutics, Cyberonics, Inc., Cypress Bioscience Inc., Eli Lilly and Company, Forest Laboratories, Inc., GlaxoSmithKline, Healthcare Technology Systems, Janssen, L.P., Novartis Pharmaceuticals Corporation, Organon, Otsuka America Pharmaceuticals, Pfizer Inc., Roche Diagnostics, Shire Pharmaceuticals Group plc, Somerset Pharmaceuticals, Inc., and Wyeth Pharmaceuticals.

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Seasonal Affective Disorder

In 1984, Rosenthal and coworkers[1] described Seasonal Affective Disorder (SAD), reporting on individuals who showed recurrent episodes of depression occurring around the same time each year, usually in the winter. The concept was endorsed by the psychiatric classification system in *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* (1994) as a "course modifier" and given the name "... with seasonal pattern."

In the northern hemisphere, most patients with SAD experience winter depression. Furthermore, the characteristic symptom profiles of such subjects often include hypersomnia rather than insomnia and hyperphagia/weight gain rather than anorexia/weight loss.[2] Because subjects with SAD have "reverse vegetative symptoms," the severity of their depression can be underrated by rating scales such as the Hamilton Depression Rating Scale. The Inventory of Depressive Symptoms (IDS) and its brief self-rated version, Quick Inventory of Depressive Symptoms (QIDS), are excellent scales to measure depression in SAD subjects as these scales include measurement of hypersomnia and hyperphagia.

A high percentage of individuals with SAD also meet the DSM descriptor "…with atypical features." Additionally many individuals with SAD have a bipolar disorder, often bipolar II, and experience brief hypomanic periods in the fall, before the onset of their depression, or in the spring, when their depression ends. Morning bright light therapy, either administered with a light box or a dawn simulator, has been found to be effective in the treatment of the depressive episode. By definition, subjects with SAD have recurrent major depressive episodes and should be offered maintenance pharmacotherapy (an antidepressant if they have recurrent major depressive disorder; lithium or lamotrigine if they have bipolar II) to reduce the likelihood of future depressive episodes.

The prevalence of SAD is latitude sensitive and is more likely to occur in the North than in the South and in the western edge of time zones than in the eastern edge. Geographic and climate conditions also affect the occurrence of SAD; areas such as Seattle have a high prevalence because sunrise in the winter is delayed compared to other areas.

One clinical tip on eliciting a history of hypomania in a depressed patient is to inquire about a mood change just prior to or after a depressive episode and to use the terms "better than normal," "up mood," and "increased energy and productivity." Sometimes patients will deny they have highs, but admit that their spouses or significant others recognize they are behaving differently than usual just prior to or just after a depressive episode. Some, but not all, bipolar patients have a positive family history of bipolar disorder in first or second degree relatives and this fact can be helpful in determining the diagnosis.

Clinical Cases

42-Year-Old Puerto Rican Woman

Background

N.I. is a 42-year-old married, Puerto Rican woman who initially was accompanied by her husband. Both are fluent in English, and N.I.'s husband wanted to participate in the interview. N.I. admits to having brief periods of feeling down but had never experienced the kinds of feelings she was now experiencing.

Presentation and History

N.I. complains of feeling very depressed with a range of neurovegetative symptoms, including decreased sleep, decreased appetite, poor concentration, decreased libido, and anaerobia. These symptoms are very new to her. Her symptoms had existed for approximately 6 months prior to presentation and, in that time, she experienced increasing levels of dysfunction, unchanging social isolation, diminished work performance, and relationship difficulties. When asked about the reason for the delay in seeking treatment, she reluctantly admits to feelings of shame and inadequacy in needing help. She feels that she had always been able to manage her life and saw this as a failure. In addition, she does not feel that medications are appropriate.

N.I. describes multiple psychosocial stressors, which she feels contributes to her depression. Those stressors include having the responsibility for her immediate and extended family. All of her family members look to her for emotional and practical support, and she often feels overwhelmed; yet she feels she has no recourse other than to continue in her role as the family caretaker.

58-Year-Old African American Woman

S.E. is a 58-year-old divorced African American woman who was referred by her primary care physician. S.E. has multiple chronic medical problems and has become increasingly depressed over time.

Background and History

She describes feeling chronically depressed for most of her adult life even prior to her current presentation. She attributes her depression largely to having experienced significant abuse in her relationship with her former partner with little support from her extended family. She decided to seek help for her depression after symptoms associated with her depression became much worse and with the encouragement of her primary care physician.

Despite S.E.'s complaint of feeling chronically depressed, she reports having had very limited interaction with a behavioral health specialist. She has always had concerns about "sharing her business" with other people. As such, she always talked to her primary care physician. S.E.'s symptoms include a sense of hopelessness, sleep difficulties, and lack of interest. S.E. emphasized that it was the increasing lack of interest that led to her decision to seek help because she had always been able to maintain an interest in activities despite being chronically depressed.

Dr Johnson has nothing to disclose.

Discussion of Both Cases

These cases represent common clinical presentations among all patients and complicating perceptions regarding depression for some ethnic minorities. In the case of N. I., she has signs and symptoms consistent with unipolar major depression. Her symptoms were of a relatively brief duration, include a range of classic neurovegetative symptoms such as decreased sleep and appetite, and have resulted in a significant functional decline.

S.E. has a much more chronic depression with a probable superimposed major depression. She has a limited range of symptoms that appear to have worsened resulting in a change in her usual level of interest. Both patients have limited focus on their depression.

In both cases, there are complicating perceptions common to some ethnic minorities that require particular attention. For example, both of these patients were initially very concerned about using antidepressants as a means of treatment. Overall, both Latino and African American patients are much less likely to take antidepressant medications than are their white counterparts (Miranda J, Cooper LA. *J Gen Intern Med*. 2004;19:120-126). The reasons are varied; however, African Americans in particular are less likely to find antidepressant medications acceptable for treating depression, less likely to believe antidepressant medications are effective, and are more likely to believe that antidepressant medications are addictive than whites (Cooper LA, Gonzalez JJ, Gall JJ. *Med Care*. 2003;41:479-489). Increasing evidence also exists that ethnic minorities might prefer counseling to medications. Concerns about confidentiality are particularly important as are other forms of support such as through their faith communities.

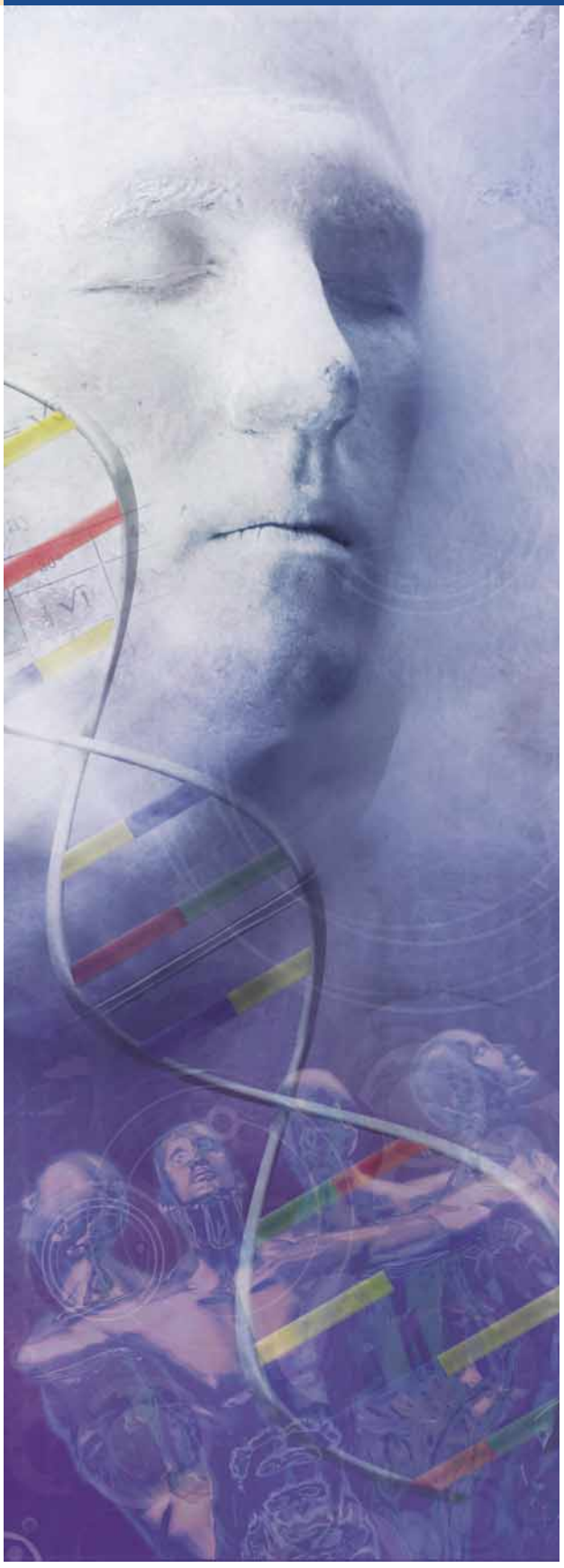
Interventions

The interventions recommended were multifactorial and consistent with current guidelines for depression. Both women were started on a selective serotonin reuptake inhibitor with supportive psychotherapy recommended as an adjunct to the treatment.

N.I. struggled with the notion of "needing" medication and talking to someone about her problem. Much of the initial intervention included very careful education regarding depression as a medical model and education regarding the benefits and limitations of medications. N.I. was strongly encouraged to participate in either group or individual therapy. She identified time constraints as the reason for not being open to therapy but was willing to talk to her psychiatrist. N.I. ultimately was started on a trial of citalopram with a starting dosage of 20 mg per day that was increased 4 months to 40 mg per day. She did not engage in either group or individual therapy but began attending church more frequently.

S.E. also found it difficult to cope with the notion of an antidepressant trial, but felt compelled to get some relief of her symptoms. She readily acknowledged that her coping strategies for managing her depression were no longer effective. She began a trial of escitalpram oxalate immediately with an initial dosage of 10 mg with an increase to 20 mg after 2 months. S.E. was also referred to a women's cognitive behavioral group. She had considerable predictable concern about a group setting in light of her feelings about "sharing her business." She did attend and found the group of other women very supportive and the focus of the group useful.

Clinical Approaches to Recognizing and Managing Bipolar Disorder



Andrew J. Cutler, MD

> **Bipolar disorder is a lifelong illness, associated with such negative factors as increased suicidal behavior, increased health care use and costs, decreased work productivity, lower quality of life, and decreased life span.**

Clinicians face serious challenges in recognizing, diagnosing, and treating bipolar disorder in people who seek care in the primary care setting. Misdiagnosis or delayed diagnosis of bipolar disorder often occurs because it can masquerade as other illnesses.[1] Since people with bipolar disorder usually present with depressive symptoms far more frequently than manic symptoms in the primary care setting, they often receive a diagnosis of major depressive disorder.[2] However, when treated with antidepressant monotherapy, individuals with bipolar disorder are unlikely to respond adequately. Unfortunately, many of these patients with bipolar disorder are incorrectly perceived as having unipolar major depression because of lack of awareness about the full spectrum of bipolar disorder manifestations (**Table 1**).[1]

Anyone with symptoms of depression should be screened for bipolar disorder.[3] Particular attention is warranted for those patients who do not respond to treatment with an antidepressant or who experience an unusual response, such as (1) an initial response to an antidepressant which then fades, (2) a partial response, or (3) actual worsening of the patient's symptoms. This article provides practical insights in identifying bipolar disorder in clinical practice.

The Need for Careful Screening

Bipolar disorder is a lifelong illness, associated with such negative factors as increased suicidal behavior, increased health care use and costs, decreased work productivity, lower quality of life, and decreased life span.[4]

Studies have found that many patients have experienced symptoms of bipolar disorder for more than 10 years before receiving an accurate diagnosis, with women more likely than men to be misdiagnosed.[5,6] Furthermore, bipolar disorder is a complicated illness with highly variable progressions among individuals. Yet, the criteria for a major depressive episode are identical for major depressive disorder and bipolar disorder in the depressed phase.[6,7] A history of hypomanic or manic symptoms is the major difference between bipolar disorder and unipolar major depression (**Table 2** on page 14).[2,7]

Detecting Signs of Bipolar Disorder

Although no single factor will clinch the diagnosis of bipolar disorder, clinicians need to seriously consider the possibility of bipolar disorder if any of the following items—and especially if more than one of them—applies to a particular individual:

- **Find out if patients have had their first episode of depression before 25 years of age.** Studies have found that people with bipolar disorder are more likely than people with unipolar depression to have their first mood episode—usually depression—at an earlier age, typically before age 25.[2,6]
- **Look for a family history of bipolar disorder or manic episodes.** Ask patients the question, "Was anyone in your family erratic or had mood/energy swings?" or "Was anyone in your family like you?" Ask about any family history of alcohol or other substance abuse and attempted or completed suicide. Ask about any family members who are very creative, artistic, or famous because bipolar disorder is associated with creativity and genius in some cases.[8]
- **Rather than ask patients about mood swings, ask if they experience energy swings.** When people become manic, they have more energy, and when they become depressed, they have less energy.
- **Be on the lookout for hypersomnia and hyperphagia.** Compared to people with unipolar depression who are more likely to have insomnia and decreased appetite, people with bipolar disorder may experience atypical depression with increased sleep and appetite.[9]
- **Ask about the frequency of depressive episodes or any kind of pattern or cyclicity of depression.** Research studies have found that the higher the number of episodes of depression individuals have experienced in their lifetime, the higher the likelihood of bipolar disorder.[10,11]
- **Ask about frequent career changes, swings in productivity or underachievement, and erratic relationships within a person's own history.** Such experiences in people who seem very intelligent and high functioning in some ways may reveal that they also experience moments when they behave uncharacteristically and find themselves in trouble, including interactions with the police. A history of chaotic psychosocial events and development, multiple jobs, multiple marriages, multiple geographic relocations, bankruptcies, and overall unpredictability of behavior may suggest bipolar disorder rather than unipolar illness.[6]
- **Initiate candid conversations about alcohol and substance abuse, including tobacco.** Substance use disorders are common in people with bipolar disorder.[12] Alcohol and other substances—including marijuana, cocaine, and tobacco—are often used by some people with bipolar disorder as a means to self-medicate their symptoms. When individuals are in the depressed phase, they may use a stimulating compound to help them feel better; when they are in a manic phase, they may use marijuana for a calming effect. However, these substances are an inefficient way of obtaining symptom relief because they are usually short-acting, difficult to titrate, and toxic to the brain. The consequences of substance abuse in people with bipolar disorder are often enormous; these patients in general have much worse outcomes and are harder to treat.[1]
- **Look for any signs of attention deficit hyperactivity disorder (ADHD).** Bipolar disorder and ADHD can be comorbid. Severely disturbed behavior in ADHD may suggest bipolar disorder.[1] If it is possible that a patient has a dual diagnosis of ADHD and bipolar disorder, the prudent course of action is to treat the bipolar disorder first before initiating therapy with a stimulant to address the ADHD symptoms.[13] Once the bipolar disorder is treated, ADHD medications can be very helpful with minimal risk of inducing mania.
- **Look for any signs of anxiety disorders.** Up to 70% of patients with bipolar disorder will also meet criteria for an anxiety disorder.[1] A person with bipolar disorder can be impulsive and sometimes uses poor judgment that leads to difficult situations. All of the anxiety disorders—including posttraumatic stress disorder, generalized anxiety, obsessive-compulsive disorder, panic disorder, and social phobia—are high on the list of potential comorbidities with bipolar disorder.

TABLE 1. CLINICAL CHARACTERISTICS OF BIPOLAR VERSUS UNIPOLAR DEPRESSION[1]

Episode characteristics of bipolar depression

- More motor slowing
- More atypical or reversed neurovegetative features: severe slowing, rejection sensitivity, hypersomnia, increased appetite and/or weight
- Mixed (depressive) episodes: three or more manic symptoms during a depressive mood
- Poor response, or loss of initial response, to antidepressive agents

Course characteristics of bipolar depression

- More relatives with affective, especially, bipolar disorder
- Earlier onset
- More frequent episodes
- Susceptibility to behavioral activation or mood lability during antidepressant or other pharmacological treatment

Symptoms of the depressive phase of bipolar disorder include persistent feelings of sadness, anxiety, guilt, anger, isolation, and/or hopelessness; disturbances in sleep and appetite; fatigue and loss of interest in usually enjoyed activities; problems concentrating; loneliness, self-loathing, apathy or indifference; depersonalization; loss of interest in sexual activity; shyness or social anxiety; irritability; chronic pain (with or without a known cause); lack of motivation; and morbid/suicidal ideation.[14] Symptoms of the manic phase of bipolar disorder —a distinct period of an elevated, expansive, or irritable mood state—may include increased energy, activity, and restlessness; excessively euphoric mood; extreme irritability; racing thoughts and talking very fast, jumping from one idea to another; distractibility; little need for sleep; unrealistic beliefs in one's abilities; poor judgment; spending sprees; a lasting period of behavior that is different from usual; increased sexual drive; substance abuse; provocative, intrusive, or aggressive behavior; and denial that anything is wrong.[14]

The bottom line: There is no substitute for a curious clinician. Various tools, including the 15-item Mood Disorder Questionnaire[15] and such mnemonics as DIGFAST (See Practical Bits, page 9)[6,16] or WHIPLASHED (See Practical Bits, page 9),[17] may be useful to clinicians in the primary care setting to identify bipolar disorder.

Making a Diagnosis and Determining a Treatment Plan

Gathering data is the first step in making a clinical assessment of the patient. Bipolar disorder involves repeated episodes of mania and depression and is categorized by various types, according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders-IV* (*DSM-IV*).[18] Bipolar I is characterized by manic or mixed episodes that are so severe that they can involve psychosis, hospitalization, or catastrophes such as incarceration or bankruptcy. Bipolar II is characterized by hypomanic episodes—a milder form of mania that is either shorter in duration (ie, less than 1 week) or has less amplitude—and usually presents with depressive symptoms in the primary care setting. People with unspecified bipolar disorder (also known as not otherwise specified) experience some bipolar characteristics but do not meet the full *DSM-IV* criteria for bipolar disorder. For example, I have seen patients who tell me they experience 1 or 2 days of manic symptoms (not 1 week), which does not fully meet the *DSM-IV* criteria. When looking at strict definitions of bipolar disorder applied in various epidemiology studies, the reported lifetime prevalence rates are approximately 1% (range 0.0% to 2.4%) for bipolar I and 2% (range 0.3% to 3.0%) for bipolar II.[19] When a broader spectrum anaylsis for bipolar disorder is used, prevalence rates of more than 6% have been reported.[20]

People with bipolar disorder can lead healthy and productive lives when the illness is effectively treated.[14] Pharmacologic treatments approved by the US Food and Drug Administration for adults with bipolar disorder include nine agents for acute mania (lithium, chlorpromazine, divalproex, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, and carbamazepine), four agents for maintenance therapy (lithium, lamotrigine, olanzapine, and aripiprazole), and only two agents for acute bipolar depression (olanzapine-fluoxetine combination and quetiapine).[21-23]

Although clinicians have more treatment options than ever before for patients with bipolar disorder, the problem is that there are not nearly enough treatment options to address all aspects of this illness for all patients.

Furthermore, pharmacologic therapies alone are never adequate for people with bipolar disorder. The best outcomes are achieved with the combination of medication and psychosocial interventions, including psychotherapy and counseling. Similar to diabetes management in which insulin and/or an oral glycemic agent is the bedrock of treatment to stabilize the physiologic process, education about the illness—including the role of lifestyle changes, diet, exercise, and stress management—and the involvement of family members to help identify signs of relapse are important components of a comprehensive care plan for people with bipolar disorder.

Paying attention to stress management and the sleep-wake cycle is critical; avoiding work that is scheduled for night shifts is a good idea for patients with bipolar disorder because studies have found that the ability to increase the regularity of social rhythms during acute treatment is associated with reduced likelihood of recurrence during the maintenance phase.[24]

TABLE 2. SUGGESTED QUESTIONS FOR UNCOVERING HYPOMANIA[2,7]

1. Do you have days of energy or ideas that come and go abruptly?
2. On those days of energy, are you productive? Creative? Do you feel unconquerable? Convinced of your self-worth, talents, abilities? Positive about the future? Talkative? Distinctly more social? Irritable?
3. On those days of energy, do your thoughts feel as if they are racing? Is your mind "crowded" with thoughts?
4. At night during this period of energy, do you need less sleep? Continue to be productive? Have ideas or make plans for the future?
5. How many consecutive days does this period of increased energy and change in mood last?
6. Do others notice the change in your mood or energy level?
7. During these "up" times, do you do things that you later regret? Make plans you find impossible to follow through with? Take on tasks that you later suddenly lose interest in or find you are without the energy or desire to complete?
8. Are you particularly more depressed or lethargic immediately before or immediately folowing these periods of energy? Does it feel like you "crash"? Does your body seem as if it is made of lead? Do you need excessive sleep?

Managing Ongoing Care

Similar to the nature of diabetes or cardiovascular disease, bipolar disorder is a chronic illness that must be carefully managed throughout a person's life.[14] Although longitudinal studies have found that the course of illness tends to worsen over time, early intervention can improve long-term outcomes.[1]

Establishing a nonjudgmental therapeutic relationship is critical, enabling the patient with bipolar disorder to share data that helps the clinician better understand and manage this illness. Sometimes working with patients with bipolar disorder is frustrating; they invariably will feel better and stop the medicines and engage in behavior—financial, sexual, and self-medicating with substances—as a consequence of impaired judgment and cognition. The key is to better understand the unique triggers for a particular person. With respect to the use of pharmacologic therapies, it is important to identify the least tolerated side effects that will influence a patient's willingness to follow through with treatment recommendations (for example, sedating versus nonsedating agents, agents with weight gain risk, and once-a-day dosing versus taking medications two or three times a day), as well as the patient's access to care, health insurance coverage, financial resources, and the involvement of family to provide emotional support and encouragement. In my clinical experience, I often encourage patients with bipolar disorder to keep a diary so they can keep track of their symptoms and their medication effects. When a new medication is prescribed, the message is communicated that the medication is on trial, not the patient.

Finding the regimen that works best for a particular individual with bipolar disorder requires patience and persistence. The majority of people with bipolar disorder will progress to therapy with more than one medication in order to try to maximize response. Using appropriate doses of a medication before trying a new medication is prudent, as well as selecting a medication that has a synergistic mechanism. No one medication appears to be completely adequate for all phases of the illness because the illness changes over time.

Furthermore, treating bipolar disorder is not as simple as setting it and forgetting it. For example, when patients with bipolar disorder are in a manic episode, they are usually hypermetabolic and require higher doses of medication or they break down medication more rapidly. When they are in the depressed phase, their metabolism is slower, and they often do not tolerate a certain medication as well. So in treating a manic phase, a clinician will use a higher dose; when the patient comes out of the manic phase, the dose is lowered.

The goal in the treatment of bipolar disorder is to achieve remission, not simply generate a response. Response focuses on a decrease in symptoms, but remission seeks to restore normal function as much as possible.

Conclusion

Greater awareness of the bipolar spectrum and its presentation in primary care can enable clinicians and their patients to benefit from advances in managing bipolar disorder.

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Adults With ADHD Need to Know Treatment Options

Carl C. Bell, MD

In their best-selling book "Driven to Distraction," Dr. Edward M. Hallowell and Dr. John J. Ratey gave voice to what thousands of inattentive, impulsive, restless adults had thought to themselves for years: "I have a problem." And their problem had a familiar name—attention-deficit/hyperactivity disorder.

The authors were not the first to consider the possibility of ADD in adults, but Driven to Distraction (New York: Pantheon Books; 1994) was among the first to popularize for a lay audience the idea that attention-deficit disorder (ADD) with or without hyperactivity is frequently a lifelong condition associated with a broad spectrum of negative consequences.

Multiple studies have shown that adults with ADD or ADHD typically have moderate to extreme difficulties in functioning at work, home, or school. Additionally, people who struggle with the disorder are more likely to "self-medicate" with alcohol or drugs and to have higher rates of substance abuse problems. They also are significantly more likely to suffer from depression and anxiety, to be fired from jobs, and to get divorced, compared with adults without the disorders.

In a longitudinal study in Sweden that followed a sample of children with ADHD into adulthood, a blinded assessment of psychiatric status showed that 49% of the adults who had been diagnosed with the disorder as children continued to have marked symptoms of the condition at age 22, and 58% met the criteria for having a poor outcome—which included drug or alcohol misuse, living off a disability pension or welfare benefits, major personality disorder, chronic severe psychiatric disorder, or conviction for a criminal offense (*J. Am. Acad. Child Adolesc. Psychiatry* 2000;39:1424-31).

Even seemingly successful adults with ADHD, which occurs at every level of intelligence, do worse occupationally than their peers without the condition. In one controlled study of functional impairments associated with adult ADHD, those adults with a self-reported ADHD diagnosis were significantly less likely to have graduated high school, obtained a college degree, or be currently employed than age- and gender-matched adults in the community without ADHD. Also, they were significantly less satisfied with their family, social, and professional lives (*J. Clin. Psychiatry* 2006;67:524-40).

Given current prevalence estimates, the number of adults at risk for such outcomes is substantial. The results of a screen for adult ADHD in the United States based on a probability subsample of 3,199 respondents between the ages of 18 and 44 in the National Comorbidity Survey Replication showed an estimated adult ADHD prevalence of 4.4% (*Am. J Psychiatry* 2006;163:716-23).

Similarly, the recent World Health Organization World Mental Survey Initiative, which screened more than 11,000 adults between the ages of 18 and 44 from North and South America, Europe, and the Middle East, showed an estimated prevalence of adult ADHD of 3.4%, ranging from 1.2% to 7.3%. (*Br. J. Psychiatry* 2007;190:402-9).

In both studies, ADHD was highly comorbid with other DSM-IV disorders and was associated with considerable role disability.

"Several recent studies suggest that adults with ADHD might be better served through combination treatment with medication and behavioral therapy."

Some experts suggest the published prevalence numbers underestimate the true burden of adult ADHD, and argue that the *DSM-IV* diagnostic criterion that symptoms be present before age 7 is too stringent and does not take into account individuals with later onset of the condition. "The age-of-onset criterion for ADHD in *DSM-IV* is based on clinical wisdom and on the belief that ADHD is a childhood-onset disorder," said Stephen V. Faraone, Ph.D., of the State University of New York, Syracuse.

In fact, Dr. Faraone and his colleagues recently demonstrated that individuals with a later onset of symptoms experience similar short- and longer-term outcomes as those with onset before age 7. The investigators compared 127 adults with full ADHD who met all of the *DSM-IV* criteria for childhood-onset ADHD with 79 subjects with late-onset ADHD who met all of the criteria except age of onset (approximately 80% of the individuals in the latter group were aged 7-12 at diagnosis). They determined that both groups had similar patterns of psychiatric comorbidity, functional impairment, and familial transmission (*Am. J. Psychiatry* 2006; 163:1720-9).

Regardless of age of onset, most adults with ADHD do not receive treatment for the condition, despite evidence supporting the efficacy of pharmacologic and behavioral interventions. In the aforementioned prevalence studies, about 10% of those respondents with adult ADHD reported receiving treatment for it, and when treatment did occur, the most common reason for seeking it was a comorbid disorder, not ADHD.

These findings suggest that adult ADHD is not well recognized and is undertreated in the community, according to Dr. Anthony Rostain, director of the Adult Developmental Disorders Unit of the University of Pennsylvania, Philadelphia. They also underscore the need for more careful screening, particularly in

adult patients receiving treatment for depression, anxiety, and substance abuse, he said.

When adults with ADHD do seek help, those with psychiatric comorbidity are significantly more likely to receive either behavioral therapy or combined behavioral and ADHD-specific pharmacotherapy than those individuals without psychiatric comorbidity, according to a 2006 study at the University of Nebraska, Omaha, that examined medication and behavioral treatment of adult ADHD in U.S. ambulatory care between 1996-2003.

In the absence of psychiatric comorbidity, adults being treated for ADHD are significantly more likely to receive pharmacotherapy alone, wrote Jayashri Sankaranarayanan, Ph.D., and her colleagues (*Curr. Med. Res. Opin.* 2006; 22:1475-91).

Several recent studies have suggest that these patients might be better served through combination treatment with medication and behavioral therapy.

At the University of Pennsylvania, for example, Dr. Rostain and colleagues examined the clinical outcomes of 43 adult patients in the Adult ADHD Treatment and Research Program who were prescribed combination therapy consisting of treatment with mixed salts of amphetamine and participation in 16 individual cognitive-behavioral therapy (CBT) sessions that were each 50 minutes long. The CBT comprised psychoeducation about ADHD, patient-centered conceptualizations of patients' associated difficulties, coping strategies, behavior modification techniques, and the identification of supportive resources.

Significant improvements were observed in all clinical measures of ADHD symptom severity and overall functioning, independent of any demographic or clinical variables, according to the authors (*J. Atten. Disord.* 2006;10:150-9).

In a Massachusetts General Hospital study, Dr. Steven A. Safren and his colleagues demonstrated that medication plus ADHD-focused CBT, initiated after medication stabilization, produces greater symptom reduction than medication alone (*Behav. Res. Ther.* 2005;43: 831-42). "Most individuals treated with medication continue to have evidence [of] at least some residual symptoms and functional impairments, which are often amenable to a structured, cognitive-behavioral treatment approach," Dr. Safren said.

The data on adult ADHD are still limited, compared with childhood ADHD, but researchers and clinicians have begun addressing, in earnest, an important question: What happens when the wiggly, distracted, rambunctious kids with ADHD grow up? Ideally, the answer should be that they are offered the help they need.

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

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Perspective

The legitimacy of attention-deficit/hyperactivity disorder as a diagnosis in adults as well as in children often has been questioned in the media. Some critics argue that the symptoms—distractibility, impulsiveness, and difficulty with task completion, for example—are normal variants of human behavior. Others, fueled by antipsychiatry venom, claim that the diagnosis is the marketing brainchild of greedy drug companies.

Clearly, these critics have not practiced psychiatry in the real world. They have not seen hundreds of children, adolescents, and adults struggle daily with issues of concentration, attention, and hyperactivity. They have neither read nor understood medical/psychiatric history, in which pediatricians in the 1950s and 1960s were diagnosing "mild mental retardation" and "minimal brain dysfunction" in patients with symptoms consistent with current criteria for attention-deficit disorder (ADD) and attention-deficit/hyperactivity disorder (ADHD).

The simple reality is that the brain develops like every other organ of the body, and as a result is subject to subtle physical and biochemical imperfections that might impair its function. In fact, to presuppose that there are no functional impairments of such a delicate organ as the brain is rather ignorant.

In pushing their own agendas, these critics are attempting to take away from the public the choice of whether or not to receive treatment for the brain impairments that are negatively affecting their lives. Who are they to do that?

The fact is, most adult patients with ADD or ADHD voluntarily seek a diagnostic assessment because of their struggles and, with informed consent, they might agree to try medication as part of the solution. They also have the freedom to refuse a trial of medication and may instead opt for behavioral intervention—or they may choose to do nothing.

That many adult ADHD patients opt for a "pill-first" or "pill-only" course of treatment is less a function of drug-company coercion than of human nature. It's just plain old easier to take a pill than to change established behaviors. You find the same basic consideration in patients with hypertension and diabetes, for whom medication is perceived as a more appealing option than engaging in a complete diet and exercise makeover.

We may encourage patients to try behavioral interventions, but our job is to present them with all of the possible treatment options. Their job is to choose those that best meet their needs.

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.

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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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Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules PV 5904 AMP

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

*Cymbalta 60 mg/day vs placebo ($P \leq .05$) by MMRM for major depressive disorder (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 within the first few months of treatment and when changing 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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