Recognizing and Treating the Patient with Somatic Manifestations of Depression

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Depressed patients often present to their family physicians with physical complaints that mimic other medical diseases rather than the classic symptoms of sadness, hopelessness, or loss of pleasure in usual activities. These somatic presentations of depression can include gastrointestinal disturbances, complaints of chronic pain, fatigue, and/or an extensive history of unexplained medical illness. Depression and other psychiatric disorders occuring in the somatic patient can often be identified through the use of a routine and noninvasive questionnaire administered at the initial physician encounter. Regardless of its presentation, however, major depression should be treated vigorously, with full therapeutic doses of antidepressants administered for at least 6 weeks to determine response, and followed by at least 6 months to ensure full remission utilizing antidepressants whose side-effect profile may help ameliorate the patient's somatic complaints while avoiding those that might exacerbate them. Effectively diagnosing and treating the somatic patient's depression will improve his or her quality of life and may reduce their current excessive use of healthcare resources.

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The majority of all psychiatric care begins not with a psychiatrist but with the primary care physician. For this reason, the practice of primary care medicine has been described as America's hidden mental health network.[1] Depression and anxiety are among the most common psychiatric disorders seen by primary care physicians[2-4] but recognizing psychiatric illness in a busy clinical practice remains a challenge.[5,6]

One factor that plays a significant role in the diagnosis of depression is somatization. Patients often experience, conceptualize, and communicate mental states and personal distress as bodily complaints and medical symptoms.[5,7] Depression is especially prevalent among patients with unexplained physical symptoms.[8] These patients can be extraordinarily difficult to diagnose and treat, typically are high users of healthcare resources,[7,9,10] and have significant functional impairment comparable to patients with major chronic illness.[11]

The stigma of psychiatric illness among both patients and physicians sets the stage for somatization. Patients may be unwilling to discuss emotional distress with their family physician or they may feel that physical symptoms are the only legitimate complaints. In addition, some patients may not accept a psychiatric diagnosis. They view their emotional distress as a consequence rather than a cause of the physical symptoms.[12] Finally, some physicians may deliberately misdiagnose depression in order to avoid stigmatizing a patient or to ensure full reimbursement from third-party payers.[13]

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DEFINITION

Primary care physicians should become familiar with the concept of somatization and be able to identify this trait.[14,15] Physicians should generally be able to differentiate it from full-blown somatization disorder, which has its own unique diagnostic criteria as described in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).[16]

Depressed individuals often present with common somatic complaints typically involving headache, gastrointestinal (GI) disturbances, or unexplained pain. These symptoms usually appear only during the depressive episode and have no known medical cause. In contrast, persons with somatization disorder have significant physical complaints throughout their lives regardless of their

TABLE 1

Comparison of Psychiatric Disorders in a General Adult Population and in High Utilizers of Medical Care

Psychiatric Diagnosis	Prevalence of Psychiatric Diagnoses Over an Individual's Lifetime (%)	
	General Population*	High Utilizer†
Major depression	17.1	68.1
Dysthymia	6.4	31.9
Panic disorder	3.5	21.8
Generalized anxiety disorder	5.1	40.3
Alcohol abuse	9.4	24.3

*Based on data from Zung WW[21]; Kessler, McGonagle, Zhao, et al.[24]
†High utilizers are outpatients in the top 10% of the number of outpatient visits to a primary care physician. Based on data from Katon et al.[7]

mood state. Their symptoms usually begin before age 30 and cause substantial social and functional impairment. By definition, patients with somatization disorder have a complex of pseudoneurological symptoms, sexual symptoms, at least two GI symptoms, and four pain symptoms.[16]

EPIDEMIOLOGY

The practice of primary care is the clearinghouse for psychiatric disorders. It has been estimated that 77% of all mental health visits in the United States occur in a primary care physician's office.[1] Unfortunately, a majority of patients who eventually receive a psychiatric diagnosis present with somatic complaints. In contrast, less than 20% of these patients complain of psychological symptoms or distress.[17]

The prevalence of major depression among primary care patients has been estimated at 5% to 10% but at least two to three times more patients have depressive symptoms that do not satisfy DSM-IV diagnostic criteria.[2,18] Thus, the true prevalence of depression in primary care is likely much higher than previously thought. Data gathered by Zung and associates demonstrate that depressed and anxious patients present to primary care doctors at a high frequency.[19-21] Therefore, family physicians are not only in an excellent position to screen for depressive disorders, they are the only physicians in a position to do so.

Depression and other mood disorders account for $43.7 billion in direct (ie, treatment costs) and indirect (ie, lost productivity, absenteeism, suicides) costs.[22] In addition, depression is associated with excessive use of healthcare resources. The annual healthcare costs for depressed primary care patients ($4,246, $P<.001$) are nearly double those for nondepressed controls ($2,371).[23] When compared with a general adult population, high utilizers of primary care services had markedly higher prevalence rates of depression, panic disorder, and generalized anxiety disorder (GAD) over the course of an entire lifetime (Table 1).[7,24] Of these, major depression was the most prevalent psychiatric disorder reported in high-utilizer patients.

COMMON SOMATIC PRESENTATIONS

In the somatic primary care patient, depression can be difficult to recognize because it can present as a number of different physical complaints (Table 2).[5,25-28] In patients whose condition is ultimately diagnosed as a mood disorder, the number of symptoms rather than the specific type of symptom may be associated with an increased likelihood of psychiatric disorder.[27] Anxiety features also are common in patients with functional somatic symptoms and are suggestive of a diagnosis of depression in primary care patients.[26] Depression should be considered in

TABLE 2

Depression Presents with a Number of Different Physical Complaints

Consider screening patients with the following symptoms:

- Fatigue (including chronic fatigue)
- Dizziness
- Headache
- Sleep complaints
- Shortness of breath
- Chronic pain (fibromyalgia, back pain, etc)
- Weight and appetite disturbances
- Atypical neurologic symptoms (ie, dizziness, numbness)
- Fibromyalgia
- Palpitations
- Abdominal complaints (pain, cramping, heartburn, diarrhea, bloating)
- Any somatic complaint that defies diagnosis
- Toxic megachart (new patient with a history of multiple negative workups/patient with multiple chronic diseases)
- Menstrual complaints (ie, cycle irregularity, PMS)

patients who present with one or more medically unexplainable symptoms listed in Table 2.

In one retrospective chart review in a solo physician, family practice setting, the prevalence and time course of somatic symptoms in 101 depressed patients were compared with 101 age- and sex-matched controls.[26] Among depressed patients, the number of office visits, unexplained pain (eg, headache, backache, and pelvic pain) or functional complaints (eg, dizziness, flatulence, and fatigue), symptoms of anxiety, and hospitalization rates (largely for GI, radiologic, and myographic studies) significantly exceeded those of controls from 18 months before to 6 months after depression was diagnosed. However, rates of reported pain, functional complaints, anxiety, and hospitalization declined upon diagnosis of depression and approached control levels 12 to 18 months later. These findings illustrate the high prevalence of somatic symptoms and healthcare utilization in depressed patients and the subsequent decline upon diagnosis and treatment of depression.

TABLE 3

Potential Consequences of Unrecognized Depression in Somatic Patients

- Unnecessary diagnostic workups for somatic complaints
- Frustration and anger toward physician and healthcare system
- Expensive and often chronic drug regimens for somatic complaints without proven medical basis
- Increased nonpsychiatric hospitalization and surgical procedures
- Decreased social and occupational functioning and quality of life
- Delayed diagnosis of psychiatric disorders possibly resulting in increased need for intensive and prolonged therapy

CONSEQUENCES OF UNRECOGNIZED DEPRESSION

There is no question that primary care physicians underdiagnose depression. Although earlier data suggested that underrecognized depression was a major public health issue,[6] newer research suggests that unrecognized depression in primary care patients probably is milder (ie, lower Hamilton Anxiety and Depression Scales scores), less likely to be associated with comorbidity, and more likely to be associated with a higher degree of functioning.[29] Evolving research also suggests that intervention for depressed patients may not always change outcome. In one study of distressed high users of medical care, psychiatric consultation increased antidepressant drug use and enhanced patient compliance but did not improve functional state or reduce hospital admissions.[30] This is a controversial area and one that requires further study.

Nevertheless, through careful evaluation and diagnosis, primary care physicians can stop the cycle of unnecessary testing, reduce the patient's psychological distress and frustration, reduce or eliminate the costs of long-term drug treatment for somatic complaints and surgery, and have a positive effect on the patient's quality of life by relieving somatic complaints (Table 3). We also know that the chances of recovery from major depressive illness decline the longer that a patient is ill and untreated.[31] There is a strong clinical impression held by many physicians that early diagnosis and aggressive treatment of depression results in better outcomes, although clinical data to support this conviction are lacking. This author believes that an aggressive approach to the diagnosis and treatment of psychiatric illness in primary care patients will have significant positive impact on patient outcome and cost-effective healthcare delivery.

Somatic patients consume a large proportion of medical resources, including unnecessary diagnostic workups, drug therapy, hospitalization, and rehabilitation for substance abuse. This relationship was demonstrated in a survey of two large primary care clinics.[7] Of 767 patients surveyed who were identified as high utilizers of health care, 51% were defined as distressed by depression/anxiety rating scales or by physician judgment. Over the course of 1 year, each patient in the distressed group made, on average, 15 phone calls to the clinic, 15 medical visits, and reported 1 self-initiated request for a specialty referral. Patients were screened with the SCL-90-R anxiety, depression, and somatization scales. Among those who met the study criteria and completed the study, 127 served as controls and 119 received psychiatric intervention. Diagnostic testing of the psychiatric intervention group demonstrated that 40% had either major depression or dysthymia, 22% had GAD, and 20% had somatization disorder. In addition, 68% and 32% had histories of major depression or dysthymia, respectively, at one time in their lives.

The economic consequences of somatization are illustrated by the extent of healthcare resources utilized by patients with abdominal complaints. Between 13% and 52% of all referrals to gastroenterologists come from primary care patients with

medically unexplained GI symptoms.[32] As many as 50% to 70% of referrals to gastroenterologists reveal no significant pathology.[33]

Irritable bowel syndrome (IBS) is one of the most common presentations in family practice, accounting for 40% to 70% of referrals to a gastroenterologist.[34] In a general population survey of 18,571 adults, patients with IBS were significantly ($P<.0001$) more likely than those without IBS to have had major depression (13.4% vs 3.8%), agoraphobia (17.8% vs 5.1%), or panic disorder (5.2% vs 1.0%) over the course of their lifetime.[32] The estimated annual cost for hospitalization and physician care for IBS is approximately $1 billion.[35] Psychiatric disorders, including depression and anxiety, are also common among patients with esophageal complaints (84%)[36] and nonulcer dyspepsia (87%).[37]

DIAGNOSIS

There is a complex relationship between chronicity of symptoms, intensity of somatic complaints, depressive features, and underlying medical conditions.[38] Therefore, underlying causes of both physical and depressive symptoms reported by the somatic patient should be evaluated because treatment may relieve some or all of the somatic complaints.[3,11] Diseases affecting the organ system(s) implicated by the patient's symptoms must be ruled out or treated (eg, gastric pain caused by peptic ulcer disease). Many medical conditions (eg, endocrine disease, cardiovascular disorders, neurological disease, cancer, pain, chronic infection, inflammatory bowel disease, connective tissue disease, and nutritional disorders) can cause depressive symptoms in combination with various somatic symptoms. Drugs such as antihypertensive agents, antiparkinsonism agents, alcohol, cocaine, and sedatives and neuroleptics have been associated with depression.[39] Nonprescription, over-the-counter medications, and health food products also should be identified. Conducting a thorough case history is the most important diagnostic tool for identifying iatrogenic sources of depression.

It is worthwhile to work up somatic complaints. The cost of diagnostic tests can be justified if they are not repeated unnecessarily and are followed through until the underlying source is found. A simple procedure that avoids unnecessary and costly duplication of tests is to examine the patient's previous medical records. One sign common to somatizers is a thick chart—a "toxic megachart"—that results from numerous workups. Such workups often will address the current symptoms as well as past complaints that implicate one or more organ systems. This finding not only allows for cost reduction through workup modification but also can be viewed as a diagnostic clue for somatization.

Follow-up by phone should be avoided when diagnostic testing has been initiated. When patients are telephoned that "the tests are normal," they fear that their doctor will conclude "It's all in my head" and often decide not to return. If the patient suffers long enough, he or she may seek care from another doctor or, if the symptoms resolve, return later with symptoms involving yet another organ system, triggering another fruitless workup. To avoid this negative, cost-inefficient cycle, test results should be reviewed at scheduled follow-up visits. This will also decrease the tendency for a prolonged misdiagnosis to occur and minimize the associated negative health and financial consequences. Follow-up alerts the primary care physician to a potential connection between somatic complaints and depression (Figure 1)[40] or other psychiatric illness and prompts the physician to look beyond the somatic complaints and focus on the psychiatric root of the problem. If appropriate, patients should be told at the outset of a diagnostic evaluation that a psychiatric disorder may be the cause of their symptoms. Such an approach will validate their symptoms and, hopefully, make an eventual psychiatric diagnosis more acceptable. Throughout the diagnostic evaluation, clinicians must continually assure the patient that their relationship will continue until all symptoms are resolved.

Patients who present with common somatic features (Table 2), multiple risk factors for depression (eg, family history of depression, significant life stresses), or with symptoms of mood disturbance should be considered candidates for psychiatric screening. A number of tools are available and should be selected based on accuracy, sensitivity, and specificity for psychiatric disorders (Table 4).[17,41-51] The instrument should be easy and quick to use and not overly intrusive to the doctor-patient relationship. Selection of a diagnostic tool may be influenced by the resources required to administer it. Most are physician- or staff-administered whereas the Zung scales or the PRIME-MD (PQ) can be self-administered by the patient.[49,50] It is advantageous to evaluate both anxiety and depression when testing patients for psychiatric illness because most patients

will have a mixture of both. This is especially true in primary care, where as many as 90% of patients have mixed symptomatology.[52] Most instruments emphasize sensitivity (eg, Zung, Beck, and Hamilton scales) and therefore only assist in detecting the presence (and severity) of anxiety or depression rather than making a specific diagnosis. In contrast, others, such as the Prime MD Diagnostic Kit, may be preferred by clinicians because they not only determine the presence of such disorders but lead the physician to a specific diagnosis.[46] Although some do not consider these tools to be as time efficient as self-administered tests (eg, Zung scales), some physicians prefer them because they assess comorbidity and attempt to provide a specific diagnosis.

Most of the above tools can be obtained from various sources at little to no cost. For example, the Zung anxiety and depressive scales can be obtained from Bristol-Myers Squibb Pharmaceuticals and Dista Pharmaceuticals. The Prime MD Diagnostic Kit is provided by Pfizer Pharmaceuticals. The Inventory for Depressive Symptomatology (IDS) can be obtained at no cost from the author. Some physicians are now using personal computers to diagnose patients' conditions and are including computers in the exam room. One example of a computer-based tool is the Symptom Driven Diagnostic System for Primary Care (SDDS-PC).[53] Because depression is known to be a chronic recurring disease,[54] more emphasis will be placed on using tools with longitudinal tracking capabilities (eg, the ability to detect relapse and recurrence).

Primary care physicians should become familiar with the tools and instruments that are available (although not entirely interchangeable) and select those that best suit their practice needs. These tools

TABLE 4

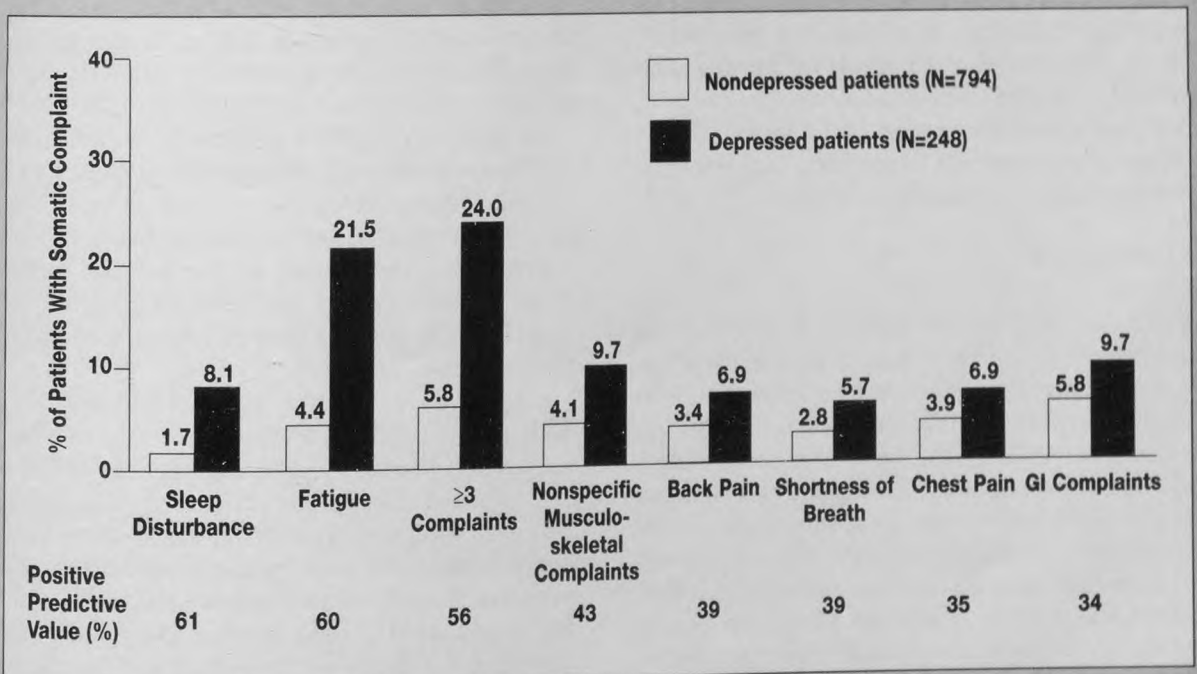
Time-Efficient Psychiatric Testing Instruments

- Hamilton Anxiety (HAMA) and Depression (HAMD) Scales
- Beck Depression Inventory (BDI)
- Zung Anxiety and Depressive Self-Assessment Scales
- Prime MD Diagnostic Kit
- Goldberg Screen for Anxiety and Depressive Disorders
- Symptom Driven Diagnostic System (SDDS-PC)
- Geriatric Depressive Scale
- Inventory for Depressive Symptomatology (IDS)

Table based on data from: Goldberg et al[17];Goldberg and Bridges[41]; Hamilton[42]; Hamilton[43]; Olfson et al[44]; Rush et al [45]; Spitzer et al[46]; Zimmerman and Lish[47]; Zimmerman and Lish[48]; Zung[49]; and Zung[50]

FIGURE

Presenting physical complaints in primary care patients who were found to be depressed or not depressed. Positive predictive value defined as percentage of patients with depression. Based on data from Gerber, Barrett, Barrett, et al.[40]



should be part of the initial workup of the somatic patient, with the results from all diagnostic tests reviewed at a scheduled follow-up visit. However, when a patient is in acute distress or where there is a strong suspicion of a psychiatric illness with a suicidal component (eg, major depressive disorder and panic disorder), testing should be administered, interpreted, and acted on at the time of the initial visit.

Once depression has been detected, the next step is to arrive at a specific psychiatric diagnosis. The size and seemingly complex lists of criteria in the DSM-IV[16] have been the most intimidating aspect of psychiatry for many primary care physicians. However, diagnosing depression is easier than diagnosing other medical disorders because the list of possible diagnoses for a given set of symptoms is mercifully short. This rule holds true for somatic patients with underlying psychiatric disease. It is likely that more than 95% of the anxiety and depressive illnesses presenting in the primary care setting arise from one or more of the following: major depressive disorder, panic disorder, obsessive-compulsive disorder, adjustment disorder with depressed or anxious mood, bipolar disorder, GAD, and subsyndromal depression. Therefore, psychiatric diagnostic proficiency in a primary care setting is dependent on a working knowledge of half a dozen common syndromes. Any primary care physician should feel comfortable in mastering these diagnoses, while the more complicated cases can be referred to a psychiatrist. And, as newer psychotropic agents are proving to be extremely safe and efficacious across the spectrum of common mood disorders, it can be argued that the practice of psychiatry at the primary care level has never been more realistically achievable.

TREATMENT

Three basic steps are necessary once depression is identified as the source of somatic complaints. First, the connection between somatic complaints and the underlying psychiatric disorder must be clearly and consistently reinforced throughout the acute evaluation and treatment phase. This reassures the patient that the physician's concerns about psychiatric illness are not a tangent irrelevant to the suffering and concerns that brought him or her to the office. Second, the somatic symptoms should be treated acutely to provide immediate temporary relief. Although the importance of recognizing the underlying psychiatric disorder has been stressed, the concerns that brought the patient to the physician should not be forgotten. If the patient perceives that his or her suffering has been ignored, he or she will look for help elsewhere. Compliance with the therapeutic regimen and, thus, treatment success will greatly be enhanced if the family physician employs a compassionate approach to relieving the acute suffering. Third, the antidepressant chosen should not aggravate the patient's somatic symptoms. In full therapeutic doses, the available antidepressants are considered equally effective. Therefore, selection of therapy can be based on safety and tolerability profiles, and ease of use.

GUIDELINES FOR TREATMENT

In general, depression in a somatic patient should be treated just as in a patient with classic depressive symptoms. Treatment should be given for at least 6 weeks to determine response; patients who have a partial response at that time may need longer treatment. Once the depressive episode is resolved, the patient can be treated for 6 months to ensure full remission and reduce the risk of relapse. Patients with two or more episodes of depression or initial episodes that were associated with suicidal tendencies or severe impairment of work, home, or social function should be considered candidates for long-term maintenance therapy at the dose that provided the initial response for at least 1 year.[54,55] Recurrences of depression that occur several years apart can be treated as initial episodes. However, patients who experience frequent recurrences of depression may require long-term (ie, ≤5 years) antidepressant treatment. Other treatment strategies for patients unresponsive to antidepressant monotherapy (eg, switching between different classes of antidepressants, combination antidepressant therapy, augmentation therapy [eg, lithium, thyroid hormone]) are beyond the scope of this paper and are reviewed elsewhere.[39,56,57]

TRICYCLIC ANTIDEPRESSANTS

Unquestionably, the tricyclic antidepressants (TCAs) are effective for the treatment of depression.[56] However, a number of features relegate them to second-line status for most primary care patients. To minimize side effects (see below), the lowest effective dose should be used and because patients vary greatly in the degree of absorption and metabolism of TCAs, doses often must be slowly titrated upward.

This process may necessitate multiple visits to the physician's office to evaluate efficacy, blood levels (of nortriptyline, imipramine, desipramine), and/or tolerability. The TCAs cause a broad spectrum of adverse effects, including anticholinergic effects (eg, dry mouth, constipation, blurred vision, urinary retention, impaired cognition), antihistaminergic effects (eg, sedation, weight gain), serotonergic effects (eg, sexual dysfunction), and in overdose, direct cardiotoxic effects similar to those with quinidine antiarrhythmics (Table 5).[58-61] Unfortunately, in a patient population focused on somatic complaints, even minor, nuisance side effects may limit compliance with a prescribed drug regimen. For example, depressed patients frequently present with what they feel is an alarming and incapacitating amount of fatigue. Prescribing a drug that will increase sluggishness and sedation will not promote compliance in this instance.

The side-effect profile of the TCAs is highly undesirable for most patients and although tolerance to some of these effects may develop, there are better alternatives for the primary care depressed patient. In fact, patients who have been treated with a TCA in the past may be reluctant to begin another course of therapy for fear of intolerable side effects. However, there are exceptions for which TCA therapy may be preferred as initial therapy (Table 6).[39,56] Many somatic complaints may be partially or completely ameliorated by TCAs because of the wide range of receptors affected by these drugs. For example, the antihistaminergic effects of TCAs may be used to clinical advantage in patients with comorbid neurotic dermatitis or with abdominal complaints related to acid production.[39] Tricyclic antidepressants that

TABLE 5

Antidepressant Medications for Patients with Depressive Disorder

Antidepressant	Usual Starting Dosages (mg/d)	Usual Maintenance Dosages (mg/d)	Sedation	Anticholinergic Effects	Orthostatic Hypotension	Activation
Selective serotonin reuptake inhibitors						
Fluoxetine (Prozac)	20	20	0	0	0	++
Sertraline (Zoloft)	50	100-150	0	0	0	0
Paroxetine (Paxil)	20	20	0	0/+	0	0
Tertiary amines						
Amitriptyline (Elavil, Endep)	75	75-300	+++	+++	+++	0
Imipramine (Janimine, Tofranil)	75	75-300	++	++	++	0
Doxepin (Adapin, Sinequan)	75	75-300	+++	++	+++	0
Secondary amines						
Nortriptyline (Aventyl, Pamelor)	40	40-200	++	+	+	0
Desipramine (Norpramin, Pertofrane)	75	75-300	+	+	+	0
Monoamine oxidase inhibitors						
Phenelzine (Nardil)	30	30-60	+	0	+++	0
Tranylcypromine (Parnate)	20	20-30	0	0	+++	0
Second-generation agents						
Trazodone (Desyrel)	50	50-400	+++	0	++	0
Bupropion (Wellbutrin)	200	300-450	0	0	0	++
Venlafaxine (Effexor)	150	150-375	0	0	0	0
Nefazodone (Serzone)	200	300-600	++	0	+	0

+ = minimal; ++ = moderate; +++ = severe

Table based on data from: Abramowicz[58]; Holliday and Benfield[59]; Leonard[60]; and Schatzberg.[61]

TABLE 6

Using Side Effects of Antidepressants to Minimize Somatic Complaints

Presenting Complaint	Possible Antidepressant Selection*
Anxiety, agitation	Nefazodone, paroxetine, trazodone
Chronic pain, headache	Amitriptyline, doxepin, trazodone, SSRI, venlafaxine
Constipation	Bupropion, nortriptyline, sertraline, trazodone
Dermatitis, pruritus	Amitriptyline, doxepin, trimipramine
Diarrhea, IBS	Amitriptyline, doxepin, paroxetine, trimipramine
Hypersomnia, sedation	Bupropion, desipramine, MAOI, SSRI, venlafaxine
Insomnia	Amitriptyline, bupropion, doxepin, imipramine, nefazodone, nortriptyline, trazodone
Psychomotor slowing	Bupropion
Sexual dysfunction	Bupropion, nefazodone
Weight gain	Bupropion
Ulcer disease	Doxepin, trimipramine

* Selections are in alphabetical order and are not ranked by effectiveness. The selection of therapy always must be individualized and guided by underlying medical conditions or concurrent drug therapy.
IBS denotes irritable bowel syndrome; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor.
Based on data from Charney et al[59] and Potter et al[66]

increase norepinephrine levels may be more efficacious in treating somatic syndromes relating to chronic pain and migraine headache.[37] Because IBS is one of the most common complaints of somatic patients with underlying psychiatric illness, patients who have predominant cramping and diarrhea may benefit from the anticholinergic properties of TCAs.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) are used infrequently in primary care for the treatment of depression because of a distinctive side-effect profile. Hypertensive crisis caused by interactions with tyramine-containing foods or sympathomimetic drugs, the serotonin syndrome (ie, diaphoresis, restlessness, myoclonus, altered mental status), orthostatic hypotension, and an extensive drug interaction profile are important safety concerns with MAOIs. These drugs are best reserved for patients with atypical, refractory, or bipolar depression.[56,62,63]

Unlike phenelzine and tranylcypromine, which are irreversible and nonselective inhibitors of monamine oxidase (MAO), moclobemide is a new, reversible, and selective inhibitor of this enzyme that is being investigated in the United States, but is not yet marketed. In clinical trials, moclobemide has been shown to be effective and well tolerated.[64] Further experience with this agent is needed in order to determine its place in the family practice setting.

Selective Serotonin Reuptake Inhibitors

The superior adverse-effect and tolerability profiles of the selective serotonin reuptake inhibitors (SSRIs) have made them preferred agents for the treatment of depression.[65] In the United States, three SSRIs (fluoxetine, paroxetine, and sertraline) are indicated for the treatment of depression; another (fluvoxamine) is approved only for obsessive-compulsive disorder but has been used in Europe as an antidepressant for years. Unlike the TCAs, the SSRIs do not cause the broad spectrum of side effects that result from anticholinergic, antihistaminergic, and α-adrenergic properties. Suicide is always a risk with depressed patients, and the SSRIs are significantly safer than TCAs or MAOIs in overdose situations.[65] In general, the side-effect profile of the SSRIs is described as nausea, headache, sleep disturbance, and sexual dysfunction.[65,66] It is worthwhile to advise patients that nausea and other adverse effects of SSRIs are prominent at the beginning of treatment but frequently resolve after 1 to 2 weeks.[67]

In addition to recognized class effects, individual SSRIs are associated with a discriminating side-effect profile. Fluoxetine frequently causes patients to be anxious, jittery, restless, and nervous on initiation of treatment, a situation encountered less commonly with sertraline and rarely with paroxetine (Table 5).[58-61,68] This syndrome, known as activation, can be minimized by a 2-week course of concomitant alprazolam therapy (0.5 to 4 mg per day). After 2 weeks, the alprazolam dose should be tapered down by 0.5 mg per week.[69] To avoid this potentially compliance-impairing situation, alternate SSRIs or nefazodone should be considered for patients who present with symptoms of anxiety (Table 6). Paroxetine can cause constipation and somnolence because of its mild anticholinergic properties, which may explain the calming effect that often occurs during therapy. Loose stools or diarrhea has been associated with sertraline therapy in some patients.[70,71] An awareness of these potential side effects would suggest that patients with GI com-

plaints, such as irritable bowel-related diarrhea and cramps, should avoid therapy with sertraline and may fare better on paroxetine (Table 6).

The SSRIs differ in their pharmacokinetic profiles, which may have clinical implications when switching from one antidepressant to another. These agents interfere with the metabolism of other antidepressants and the continued presence of an SSRI with an active metabolite or a long elimination half-life (eg, fluoxetine) may complicate the course of patients who are switched to other antidepressants.[72-74]

The SSRIs inhibit several cytochrome P450 drug-metabolizing enzymes and an extensive body of literature on subsequent drug interactions is available for the interested reader.[75] The drug-interaction profile of SSRIs is relevant to primary care practitioners because many commonly used drugs are metabolized by these enzymes (eg, phenytoin, tolbutamide, carbamazepine, alprazolam, triazolam, terfenadine, astemizole, type IC antiarrhythmic agents, and antipsychotics).[76-79] Many SSRIs also inhibit the cytochrome system involved with TCA metabolism.[80-83] Unfortunately, it is not possible to predict development of a clinically significant drug interaction. Therefore, combined administration of SSRIs and drugs that are metabolized via the cytochrome P450 system or with narrow therapeutic indices should be done cautiously and with an increased level of clinical monitoring.[75]

The only serious objection raised about using SSRIs as first-line therapy relates to cost. However, recent data have reinforced the logic of using SSRIs as first-line therapy.[84-86] For example, the Boston Consulting Group examined the direct costs associated with the use of TCAs versus SSRIs.[87] The SSRIs were less costly than the TCAs because of lower physician labor costs and fewer days spent in the hospital.

Bupropion

Bupropion is devoid of anticholinergic, antihistaminergic, cardiac, or sexual side effects that commonly occur with the TCAs. However, bupropion possesses a unique adverse-effect profile that consists of nausea, visual disturbances, activation, appetite suppression, insomnia, psychotic symptoms and, rarely, seizures. In patients who have lost weight because of their depression, bupropion should not be considered first-line therapy. In contrast, patients who are experiencing psychomotor slowing or weight gain may benefit (Table 6). The activation associated with bupropion often is temporary, occurring in the first few weeks of treatment, and may be minimized by coprescribing a short course of a benzodiazepine. Treatment-emergent seizures have been observed during bupropion therapy (4 in 1000 patients).[88-90]

The risk of seizures can be reduced by restricting the total daily dose to no more than 450 mg and limiting individual doses to no more than 150 mg administered in intervals of 6 hours or more. Multiple daily dosing is required with bupropion because of its relatively short elimination half-life. Additionally, efficacy in depressed patients with comorbid anxiety disorders, including panic disorder, has not been well established. These reasons, combined with the need for multiple daily doses and dose titration, suggest that bupropion should remain as second-line therapy.

Nefazodone

Nefazodone is chemically related to trazodone but causes less sedation, orthostasis, and priapism.[89,90] It inhibits serotonin and norepinephrine uptake, but its main mode of action has been postulated to be antagonism of the 5-HT_2 receptor.[90,91] Because trazodone has been viewed by many as a comparatively weak antidepressant, there has been some concern that nefazodone may be less potent than the SSRIs. Results of recent head-to-head comparisons have failed to show any difference in efficacy between nefazodone and the SSRIs.[92,93]

Side effects of nefazodone include sedation, dizziness, asthenia, dry mouth, nausea, constipation, headache, and amblyopia.[94] These effects occur in a minority of cases, and comparisons between nefazodone and the SSRIs have not demonstrated significant differences in tolerability or in patient acceptance.[95] Perhaps more significant, however, is the consistent lack of sexual dysfunction,[95] the lack of early emergent anxiety and agitation,[95,96] and the normalization of sleep patterns[97] associated with nefazodone therapy. Such a profile suggests nefazodone may represent a viable therapeutic alternative to the SSRIs for the treatment of depression, especially in patients who experience sexual dysfunction, anxiety, and/or sleep disturbance as a component of their depression or as a consequence of SSRI therapy.[54]

Once-daily therapy is not recommended with nefazodone because of the short elimination half-lives of the parent compound and active metabolites; rather, two to three doses per day are suggested for

therapeutic response. The initial starting dose is 200 mg per day, but clinically effective doses range from 300 to 600 mg per day (Table 5).[58-61]

Like the SSRIs, nefazodone has been implicated in clinically important drug interactions involving the cytochrome P450 system. For example, initiating nefazodone or trazodone shortly after discontinuing an SSRI could lead to increased blood levels of *m*-chlorophenylpiperazine (an anxiogenic metabolite of nefazodone and trazodone that is metabolized by cytochrome P450 IID6) and subsequent flushing, tachycardia, dizziness, nausea, and feelings of nervousness.[98-100] This may be especially problematic when switching from fluoxetine, an SSRI with an extremely long elimination half-life. Nefazodone should not be used with terfenadine, astemizole, or cisapride because of the hypothetical risk of inducing ventricular arrhythmias. Nefazodone also inhibits alprazolam, triazolam, and midazolam metabolism, and combined use necessitates a reduction in the benzodiazepine dose and monitoring for enhanced sedation, impaired cognition, and hangover effects.[75]

VENLAFAXINE

Venlafaxine selectively inhibits serotonin and norepinephrine reuptake. Like nefazodone, short elimination half-lives of the parent compound and active metabolite necessitate taking two or three doses per day. Some patients treated with higher doses of venlafaxine experience severe nausea and vomiting; this can be minimized by starting with a low dose of 75 mg per day and slowly titrating upward until full therapeutic response is achieved.[101] Other dose-related adverse effects include blood pressure increases, sexual dysfunction, sweating, and somnolence. Doses of venlafaxine of 375 mg or higher have been associated with increases in systolic blood pressure (by 7.5 mm Hg), which necessitate blood pressure monitoring for patients with borderline or existing hypertension. At present, its adverse-effect profile, need for multiple daily dosing, and necessity for dose titration and blood pressure monitoring suggest that venlafaxine be considered second-line therapy. An exception would be for patients with comorbid chronic pain or migraine who might benefit from its dual mechanism of action or its lack of drug interactions with TCAs. Because of its potential broad spectrum of efficacy, a longer-acting, more tolerable formulation would significantly enhance the usefulness of venlafaxine to primary care physicians.

MIRTAZAPINE

Mirtazapine (Remeron) is a newly approved antidepressant agent that enhances transmission of norepinephrine and serotonin.[102,103] Controlled clinical studies have shown that mirtazapine is more effective than placebo[104-106] and trazodone[107] and as effective as amitriptyline.[104,106] The side-effect profile of mirtazapine appears to be characterized by sedation and weight gain,[104-106] although its blockade of 5-HT_3 and 5-HT_4 receptors and the associated decreased GI side effects and sexual dysfunction may make this drug particularly useful in depressed patients with corresponding somatic profiles.

COUNSELING AND PSYCHOTHERAPY

Psychotherapeutic counseling techniques such as cognitive and behavioral therapies can be useful adjuncts to antidepressant therapy for depressed patients or can be an effective therapeutic intervention for patients with only mild depressive symptoms who are not receiving medication. When used by primary care practitioners, these techniques may enhance initial patient compliance with the prescribed regimen.[108] Even providing simple but specific messages to the patient about the expected delay in treatment response or anticipated side effects can improve patient compliance and may link the patient and physician together in a more trusting relationship.[109]

CONCLUSIONS

Patients with multiple, unexplained somatic complaints are among the most vexing of clinical challenges. The prevalence of depression in somatic patients and the economic burden associated with unnecessary diagnostic testing, chronic symptomatic treatments, and increased office visits underscore the pressing need to recognize and treat depression in the primary care setting. With a few important exceptions, depression in a patient who presents with somatic symptoms is essentially treated as depression presenting in a more classic fashion. Full doses of antidepressants must be used for at least 6 weeks to determine response with at least 6 months of therapy thereafter to ensure full remission. Patients with multiple depressive episodes or with severe initial episodes may require long-term, even lifelong treatment.[54]

Some discriminating caveats emerge when treating somatic depressed patients. First, the connection

between the patient's underlying depression and his or her somatic complaints should be stated clearly to the patient. Second, compliance will be greatly enhanced by paying appropriate attention to the patient's somatic complaints. Continued concern for the patient should be extended even after antidepressant therapy is initiated. Third, adverse effects of the antidepressants should dictate the selection process for somatic patients. Avoiding agents that worsen somatic complaints and using antidepressants with side-effect profiles that help ameliorate physical symptoms may dramatically enhance compliance.

It has been suggested that somatic manifestations occur early in the course of depression, possibly preceding the onset of more classic depressive symptoms.[26] Longitudinal follow-up of patients with major depression has shown an indirect relationship between the length of the depressive episode and the probability of recovery.[31] Thus, in the primary care setting, a strong patient-physician relationship and early recognition of the somatic manifestations of depression should enable prompt diagnosis and intervention, which may result in an improved long-term outcome. Therefore, careful evaluation and testing of patients presenting with "high-risk" somatic presentations and/or multiple risk factors for depression should become standard practice in the primary care setting.

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DISCUSSION

Dr Richardson: We often see patients with gastrointestinal symptoms who have negative pathology. We know that these patients are depressed. What is your approach to choosing treatment in this setting?

Dr De Wester: This question raises several issues. First, when should you screen a patient with somatic symptoms? My staff screens these patients with the Zung scale so that when I see the patient, I have baseline information. I often see patients with irritable bowel symptoms. If this patient is depressed with or without symptoms of anxiety, he or she is a candidate for an antidepressant to be started immediately. If diarrhea is a predominant symptom, I use paroxetine as the SSRI of choice because it does not cause anxiety and has mild anticholinergic properties. I also address the acute symptoms by discussing the role of fiber, dietary changes, or lactose intolerance and explain that the antidepressant will help alleviate symptoms over the course of several weeks.

Dr Susman: Could you provide some practical tips for differentiating between somatic symptoms in a depressed patient and somatization associated with multiple medical illnesses? Many times we see patients with diabetes, hypertension, arthritis, and many somatic complaints. When should we start thinking about depression in this scenario?

Dr De Wester: This is an important and potentially confusing issue. We need to be sure that the symptoms are not suggestive of inadequate treatment of one of the underlying medical conditions. If I am unable to relate the symptoms to the underlying diseases and if treatment does not offer relief, I begin to suspect a mood disorder. In this case, I will use a screening tool to better assess the presence of depression and determine the need for treatment.

Dr McCoy: I agree about the importance of screening patients. When we see a particularly difficult, angry, unpleasant, irritable patient who has no obvious organic basis for disease, we really need to look one step further for underlying psychiatric morbidity.

Dr Kuzel: Another clue to hidden depression is the patient who repeatedly asks for prescriptions for H_2-receptor antagonists for abdominal pain or discomfort or for products to treat irritable bowel syndrome. We have all seen these patients who, despite the lack of diagnosis, just can't get relief from their symptoms. It is to our benefit and the benefit of our patients that we maintain a high index of suspicion for depression and stop the cycle of repetitive diagnostic testing.

TABLE 1

***Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) Criteria for a Major Depressive Episode**

At least 5 of the following symptoms are present during the same period. Either depressed mood or loss of interest or pleasure must be present. Symptoms are present most of the day, nearly daily for at least 2 weeks:

- Depressed mood (sometimes irritability in children and adolescents) most of the day, nearly every day
- Markedly diminished interest or pleasure in all or almost all activities most of the day, nearly every day
- Significant weight loss/gain or decrease or increase in appetite
- Insomnia/hypersomnia
- Psychomotor agitation/retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive inappropriate guilt
- Impaired concentration or indecisiveness
- Recurrent thoughts of death, suicidal ideation with or without a specific plan, or suicide attempt

Modified from DSM-IV, 1994, with permission.[8]

Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for major depression are used to diagnose postpartum depression (Table 1).[8]

The basis of the mother's depressive thoughts may stem from her insecurity about being able to adequately care for her infant.[9] As a result, the mother experiences intense feelings of inadequacy and inability to cope, social withdrawal, anorexia or weight gain, and loss of interest in normal activities. These symptoms may even cause indifference or anger toward the baby to a degree that may endanger the infant's health.[10] Somatic complaints related to the gastrointestinal system are a less severe manifestation of postpartum depression. As with other depressive disorders that fit the DSM-IV criteria, postpartum depression is associated with significant functional impact. With proper treatment, however, the majority of patients (approximately two thirds) recover within 1 year.[4]

Risk Factors

The acute stresses of caring for an infant, coupled with feeling alone and unsupported, predispose new mothers to develop depression. The social and psychological insecurity of coping with the new role of parenthood may explain why first-time mothers are more likely to become depressed than are women with other children.[11,12] Other variables that are consistently associated with postpartum depression include lack of social or spousal support,[13] poor communication with a significant other, and difficulties in the marital relationship.[14,15] Women with husbands who help with housework or with child-care responsibilities are less likely to become depressed than are women with partners who are less cooperative.[6] Another risk factor that has been variably implicated in the development of postpartum depression is a stressful childbirth, such as a stillbirth, an illegitimate birth, or a twin birth.[6,16,17]

POSTPARTUM PSYCHOSIS

A small number of patients (2 per 1000 deliveries) develop a depressive disorder severe enough to require hospitalization.[12,18] The clinical features of postpartum psychosis, such as mania, psychotic thoughts, severe depression, and symptoms consistent with schizophrenia or a thought disorder, are easily recognized and warrant urgent treatment.[10] The substantial risk for infanticide provides another reason for prompt and aggressive treatment. The incidence of postpartum psychosis is highest within 30 days after parturition, with the majority of cases (54%) occurring within the first 2 weeks. Hospitalization is required in most cases, and 95% of treated patients improve within 3 months.[19]

Risk Factors

Similar to other forms of psychoses that are precipitated by stressful events, childbirth increases the risk by 20 times.[4] A personal or family history of affective disorder further increases the risk for developing postpartum psychosis by 40%. Other patients who should have frequent mood assessments during the postpartum period include those who experience a perinatal death, who give birth by cesarean section, or who lack social support.[12]

IMPACT ON THE CHILD

The early experiences and emotional support provided by parents significantly influence the infant's behavior and development. Depressed women have difficulty relating to their babies, may develop negative attitudes toward their children, and are less responsive to their social signals.[20] In some cases, this may lead to physical abuse. Even after the mother recovers, the impact of maternal depression persists as the child becomes older. Children of mothers

who were depressed postnatally often have more negative impressions of their mothers,[21] are more temperamental,[22,23] and suffer more cognitive deficits[24] than do children of nondepressed mothers. Therefore, early detection and intervention are imperative so that the long-term impact on the child can be minimized.

DIAGNOSIS

Primary care physicians should familiarize themselves with the risk factors associated with postpartum depression in order to initiate early case finding. This can be accomplished by universally screening all women with one of the readily available depression screening instruments (eg, the Hamilton Anxiety and Depressive Scales, the Beck Depression Inventory, and the Zung Anxiety and Depressive Self-Assessment Scale) or by inquiring about the cardinal signs of major depression (eg, depressed mood, incapacity to experience pleasure, or diminished interest) at each visit. In addition, several specific postpartum depression scales are available, including the Postpartum Support Questionnaire and the Edinburgh Postnatal Depression Scale. Patient education about the prevalence of mood disorders in the postpartum period and their associated signs and symptoms can facilitate awareness and early detection and intervention. These discussions should be included with postpartum discharge counseling.

Differential Diagnosis

The postpartum period is associated with common physiologic and pathologic problems that can present as depressive symptoms. The diagnostic workup for postpartum depression should begin with a careful history, thorough physical examination, and lab tests that include a serum hemoglobin and TSH. Fatigue may be an indication of anemia caused by excessive blood loss during delivery or of sleep loss associated with nocturnal child care, rather than depression. Iron or folate supplementation may be all that is necessary to return the patient to normal functioning. In addition to fatigue, loss of initiative, mood changes, and weight gain may be manifestations of thyroid dysfunction, a common disorder. Transient hypothyroidism occurs in 4% to 7% of patients and peaks 4 to 6 months postpartum.[25] Conversely, thyrotoxicosis can present with symptoms suggesting panic disorder. Other problems in the differential diagnosis should include pituitary, adrenal, and other endocrine disorders, spousal abuse, infection, and other more rare difficulties associated with a major depressive disorder.[26]

Challenges in Recognition

Social and physical changes associated with postpartum adjustment can cause signs and symptoms that mimic depression. Therefore, the primary care physician must maintain a high index of suspicion when behavioral changes occur in the mother. Complaints of insomnia may be due to changing sleep patterns needed to care for the baby,[10] but insomnia as a result of depression usually presents as early-morning awakenings. Weight fluctuations suggesting depression could be due to dieting or normal weight loss that occurs postpartum. Somatic symptoms, such as generalized headache, joint or muscle pain, or digestive problems, are also common during the postpartum period. Still, it is important to determine the source of these symptoms because they may be masking an underlying depressive disorder.[27] If the origin of the symptoms remains unclear, the patient should be screened for other features of depression, such as depressed mood and anhedonia.

TREATMENT

Counseling

Expectant mothers and fathers should be counseled during the prenatal period about the symptoms of postpartum depression. This education will better prepare them for their upcoming roles and occupational changes.[28] Unrealistic expectations of the mother should be dispelled so that she does not feel guilty when she saves time for her significant other or for herself. The mother should also be taught to avoid self-blame if she is unable to meet her expanded responsibilities. If a depressive episode occurs despite these preventive measures, practitioners should validate the mother's depressive feelings and help her develop a practical approach to problems. Cognitive behavioral counseling may be the preference. The primary care physician should educate the parents about support systems, coping mechanisms, and rest. Stress reduction and family therapy may also help women cope with the emotional and physical demands of their families. In some patients, abuse or deficient or disturbed family relationships are important issues.[5]

TABLE 2

The US Food and Drug Administration Use-in-Pregnancy Ratings

Category	Interpretation
A	Controlled studies show no risk: Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
B	No evidence of risk in humans: Either animal findings show risk but human findings do not; or, if no adequate human studies have been done, animal findings are negative.
C	Risk cannot be ruled out: Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well; however, potential benefits may justify potential risk.
D	Positive evidence of risk: Investigational or postmarketing data show risk to the fetus; nevertheless, potential benefits may outweigh risks.
E	Contraindicated in pregnancy: Studies in animals or humans or investigational or postmarketing reports have shown fetal risks that clearly outweigh any possible benefit to the patient.

Based on data from the *Physicians' desk reference.*[30]

PHARMACOTHERAPY

Psychotherapy is the first-line treatment for postpartum depression; however, some patients may require the addition of medication or electroconvulsive therapy. Antidepressants should be used in conjunction with counseling and support groups in patients with vegetative signs, such as sleep and appetite changes, psychomotor agitation or retardation, or poor concentration.[29] Mothers should continue on medication for 6 to 12 months postpartum to ensure a complete recovery. The treatment goals are the same as for other depressive episodes, but considerations for the risk versus benefit ratio to the baby and the mother complicate the selection of medications. Moreover, treatment of depression may be initiated during pregnancy or be part of treatment for preexisting depression. Thus, this article also highlights important considerations for antidepressant use during pregnancy.

There are only a few reports or small studies regarding the use of antidepressants during pregnancy; thus, the risk for teratogenicity and long-term developmental problems with these agents may be appreciable. The US Food and Drug Administration (FDA) classifies medications for use during pregnancy, and to date no antidepressant has been approved as a category A agent for use during pregnancy or lactation (Table 2).[30] Nevertheless, the use of antidepressants may be warranted in patients with severe psychiatric disorders. Therefore, the decision to use pharmacotherapy in pregnancy requires careful clinical judgment based on both the physician's and the patient's understanding of the risk versus benefit ratio and may often prompt consultation with other health professionals, such as a psychiatrist or a perinatologist.

Monoamine Oxidase Inhibitors

Drawbacks that cause monoamine oxidase inhibitors (MAOIs) to be reserved for treatment-resistant cases of depression are further compounded in the pregnant patient. Ingestion of foods or drugs containing tyramine can cause an MAOI-induced hypertensive crisis that may terminate the pregnancy.[31] Side effects, such as sedation, palpitations, dizziness, insomnia, and constipation, occur frequently and may cause further impairment of the expectant mother's existing functional limitations.[32] The MAOIs are known teratogens in animals, but the numbers from prospective studies are too small to conclude whether they are human teratogens; they are category C agents (Table 3).[33]

Tricyclic Antidepressants

Despite the fact that tricyclic antidepressants (TCAs) have been available for more than 30 years and that there are more data regarding the use of these agents during pregnancy, the available information is still plagued with methodological difficulties. The majority of tricyclics are either category C or D for use in pregnancy (Table 3).[33]

Fetal abnormalities have been reported in patients taking TCAs; however, no clear associations have been demonstrated.[34-36] In contrast, TCA-induced side effects, such as dry mouth, sedation, and postural hypotension, are significantly more pronounced in pregnant women[37] and can cause withdrawal symptoms of tachypnea, tachycardia, cyanosis, irritability, and diaphoresis in the neonate.[38] Fetal withdrawal symptoms can be avoided by tapering the dose 3 weeks prior to delivery. The use of secondary amines (eg, nortriptyline, desipramine) may be preferred because of the lower incidence of anticholinergic effects.[39]

Physiologic changes that occur during pregnancy (eg, increased total body water) can cause unpredictable shifts in the plasma levels of antidepressants. It is not uncommon for doses to increase 1.5 times over baseline as the pregnancy progresses.[40]

TABLE 3

Recommended Dosing and Use-in-Pregnancy and Breast-feeding Ratings for Antidepressant Medications

Generic Name	Daily Dose (mg/day)	Half-Life (hours)*	FDA Risk Category	Effect of Drug on Nursing Infants†
Tricyclic/heterocyclic antidepressants				
Amitriptyline (Elavil, Endep)	150-300	10-22	D	Unknown but of concern
Imipramine (Tofranil)	150-300	11-25	D	Unknown but of concern
Desipramine (Norpramin)	150-300	12-76	C	Unknown but of concern
Nortriptyline (Pamelor, Aventyl)	75-150	15-93	D	NA
Clomipramine (Anafranil)	150-250	19-37	C	Compatible
Doxepin (Sinequan, Adapin)	150-300	11-23	C	Unknown but of concern
Maprotiline (Ludiomil)	140-225	21-66	B	NA
Protriptyline (Vivactil)	15-60	54-198	C	NA
Monoamine oxidase inhibitors				
Phenelzine (Nardil)	45-90	NA‡	C	—
Tranylcypromine (Parnate)	30-60	NA‡	C	—
Selective serotonin reuptake inhibitors				
Fluoxetine (Prozac)	20-60	24-96¶	B	Unknown but of concern
Fluvoxamine (Luvox)	50-300	17-22	C	Unknown but of concern
Paroxetine (Paxil)	20-50	24	C	—
Sertraline (Zoloft)	50-200	26¶	B	—
Other antidepressants				
Bupropion (Wellbutrin)	150-450	8-24¶	B	—
Trazodone (Desyrel)	200-300	4-13	C	Unknown but of concern
Venlafaxine (Effexor)	150-375	5-11	C	—
Nefazodone (Serzone)	300-600	2-4	C	—

FDA = US Food and Drug Administration; NA = not applicable; — = not available.

* Half-life of elimination is listed for parent compound.

† Based on the 1994 American Academy of Pediatrics Committee on Drugs report on the use of medications during breast-feeding.

‡ Duration of action is based on irreversible enzyme inhibition; half-life of elimination is not applicable.

¶ Elimination half-life of active metabolites of fluoxetine (4 to 16 days), sertraline (2 to 4 days), and bupropion (>3 days).

Modified from Stowe and Nemeroff, 1995, with permission.[33]

To minimize the risk for toxicity or subtherapeutic drug levels, stringent plasma-level monitoring should be instituted during pregnancy.

It is well established that breast milk concentrations of TCAs are equal to those measured in maternal serum,[7] but breast-fed infants have nearly undetectable TCA serum levels.[41,42] Nonetheless, the short- and long-term effects on the newborn's central nervous system development and behavior are still poorly understood. Until more definitive data become available, the mother should minimize her infant's drug exposure by breast-feeding immediately before the next dose and by refraining from nursing at least 4 hours from the last dose.[43] This provides time for the medication to be absorbed and distributed in the mother so that less is available to be transferred to the infant. Bottle feeding is another option that can be used to minimize drug exposure to the infant. In addition, treatment with TCAs may be complicated in new mothers concurrently prescribed oral contraceptive agents. Preliminary evidence suggests that oral contraceptives inhibit the hepatic metabolism of TCAs. Thus, when oral contraceptives are concomitantly administered, dose reductions of TCAs may be necessary.

Selective Serotonin Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRIs) have become the first-line agents for the treatment of depression because of their favorable side-effect profile, ease of use, and proven efficacy.

TABLE 4

Case Finding Approach and Treatment Recommendations for Postpartum Depression

- Universally screen all women for depression or risk factors for depression with a rating scale (eg, the Hamilton Anxiety and Depressive Scales, the Beck Depression Inventory, and the Zung Anxiety and Depressive Self-Assessment Scale) during pregnancy or during the patient history
- Facilitate early detection and treatment by educating the patient and family about the tendency for postpartum mood disorders to occur and their associated signs and symptoms
- Continue screening women for depression during well-child examinations and postnatal maternal visits
- Provide aggressive follow-up during postpartum period for patients who develop depression during pregnancy or who have risk factors for depression
- Consider risk versus benefit ratio of instituting pharmacotherapy in symptomatic patients (according to DSM-IV criteria)
- Choose antidepressants with fewer anticholinergic effects, no active metabolites, and shorter half-lives
- Treat for 6 to 12 months postpartum to assure a complete recovery

Unfortunately, more data are needed to support the safety of SSRIs during pregnancy (Table 3).[33,44] To date, only one study has prospectively studied women who were exposed to an SSRI during their first trimester. No increase in major congenital abnormalities or change in pregnancy outcome or gestational age at delivery was observed in 128 women who received a mean fluoxetine dose of 25.8 mg compared with 128 nondepressed control patients unexposed to known teratogens.[45] An evaluation of a smaller sample of age-matched cases treated with fluoxetine or TCAs compared with nondepressed controls (74 patients in each group) demonstrated that there was a higher percentage of miscarriages in patients receiving fluoxetine (12.2%) and TCAs (13.5%) when compared with control patients (6.8%). This difference was not significant. Emotional instability or other biological changes that occur with depression may have contributed to the higher rate of miscarriages reported in patients receiving antidepressants. However, further study is needed to substantiate the effect of these factors on the developing fetus.

All SSRIs are excreted in breast milk, so the feeding schedule should be adjusted based on the time that the dose is administered. A recent case report of sertraline serum and breast milk concentrations in a woman and her nursing infant describes peak breast milk concentrations occurring 1 to 9 hours after the dose.[46] Based on this information, it would be reasonable to recommend that the mother refrain from nursing during the time of peak breast milk concentrations in order to limit exposure to the infant. Another option is to prescribe SSRIs with shorter half-lives, such as paroxetine or sertraline. Paroxetine and sertraline have a half-life of approximately 24 hours, which is much shorter than the extended half-life of fluoxetine (4 to 6 days) and its pharmacologically active metabolite, norfluoxetine (4 to 16 days).[47] Choosing an agent with no active metabolites, such as paroxetine, is another measure to minimize infant drug exposure.

Breast milk concentrations were measured in a 39-year-old mother taking paroxetine; it was estimated that the weight-adjusted dose the infant would receive through breast milk would be 0.34% of the maternal dose.[48] This is similar to the value reported for fluvoxamine (0.5%)[49] and is much lower than that reported for fluoxetine (1.2% to 6.2%).[50,51] As with all antidepressants, the short- and long-term cognitive-behavioral effects on the neonate of SSRIs administered in utero and in breast-feeding mothers are unknown, and the decision to initiate therapy should be on an individual basis.

Other Antidepressants

The increased risk of seizures associated with maprotiline and bupropion deters their use during pregnancy, especially in women who are subject to eclampsia.[38] Lithium should be used cautiously because of the risk of congenital malformations, particularly cardiac abnormalities, in the fetus.[29] Because lithium concentrations are very dependent upon the patient's volume of distribution and glomerular filtration rate, the associated physiologic changes during pregnancy require that lithium levels be monitored carefully. Toxic lithium levels can also occur in the neonate because lithium freely crosses the placenta. If neonates develop lithium toxicity, it may persist for more than 7 days and present with symptoms of cyanosis, bradycardia, flaccidity, lethargy, poor suck reflex, impaired respiratory function, and nephrogenic diabetes.[52] Precautions should also be taken in breast-feeding mothers because nursing infants can achieve serum lithium concentrations that are up to 50% of maternal levels.[53,54] Because of the potential risks to the fetus and the dif-

ficulties associated with monitoring lithium during pregnancy, consultation is advised. Treatment recommendations are summarized in Table 4.

CONCLUSIONS

Because postpartum depressive disorders are common, primary care physicians should develop preventive and aggressive case-finding strategies so that the negative impact on both the mother and baby is limited. During the pregnancy period, all women should be assessed for depression or risk factors for depression. Early detection and treatment can be facilitated by educating the patient and family. After parturition, it is best to continue to screen women during well-child examinations and postnatal maternal visits. Mothers who develop depression during pregnancy or who have risk factors should receive close follow-up postpartum screening. If the woman meets DSM-IV criteria, consider the risks and benefits of instituting pharmacotherapy. For many patients, careful counseling may be sufficient. For patients in whom medication is indicated, choose antidepressants that have fewer anticholinergic effects, no active metabolites, and shorter half-lives to minimize drug exposure and side effects to the fetus. As with other depressive episodes, treatment for postpartum depression should continue for 6 to 12 months to assure a complete recovery.

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DISCUSSION

Dr De Wester: It is known that there is an increased risk in patients with a history of postpartum depression to develop it again with subsequent pregnancies. What kind of follow-up would you suggest for patients with recurrent postpartum depression?

Dr Susman: Anyone with a history of postpartum depressive disorder needs close follow-up with subsequent pregnancies, especially if they display depressive symptoms during pregnancy. I would recommend a visit be scheduled within the first week of discharge from the hospital. The frequency of follow-up visits should then be determined on an individual basis. Some patients may need weekly follow-ups. It is hoped that with frequent follow-ups, we can recognize patients who are developing a major depression and intervene early with appropriate measures.

Dr Kuzel: Does postpartum depression follow the same rates of recurrence as nonpostpartum depression or do the hormonal changes associated with pregnancy make depression in postpartum mothers different from that in the average depressed patient?

Dr Susman: There is a lack of good clinical or longitudinal studies that have addressed this issue directly. Nonetheless, there continues to be two schools of thought about the nature of postpartum depression. One group of experts regards postpartum depression to be similar to other episodes of depression and considers pregnancy to be just like any other life event that triggers a depressive episode. Others believe postpartum depression is strongly influenced by the physiologic changes, for example, hormonal changes, that occur during pregnancy and that depressive episodes experienced by new mothers are different from depressive episodes observed in other individuals. Clearly, mothers who develop postpartum depression are at an increased risk for developing depression in the future, but the magnitude of this risk is unknown.

Dr Kuzel: What do you recommend for a depressed woman whose depression is in remission with medication and who wants to get pregnant? Do you advise her to discontinue or taper medication or are there other alternatives?

Dr Susman: I think that this decision requires careful discussion with the patient about the potential harms of both discontinuing and continuing therapy. The patient's clinical history of depression also should be considered. Patients in whom I would consider continuing antidepressants are those who began therapy 2 or 3 months ago and have just recently been stabilized or patients with a number of very severe or complicated episodes. I would also consider changing the patient's medication if she is receiving an older tricyclic to either nortriptyline or an SSRI so that the anticholinergic effects on the fetus are minimized. Patients in whom I would choose to discontinue medication are those who have remained stable on medication for a year with no breakthrough episodes or who have had only one uncomplicated episode of depression. Regardless of whether the decision is to continue or discontinue medication, the patient will need to be monitored closely for changes that may jeopardize the health of the fetus.