Continuing education credit for physicians and pharmacists sponsored by The Chatham Institute

DEPRESSION

• Prevalence and economic implications
• Guidelines for treatment
• Drug-therapy review
• Pharmacoeconomics of treatment
• Adherence to therapy
• NCQA/HEDIS measures
• Social anxiety disorder

Supported by an educational grant from GlaxoSmithKline
A Tool for Formulary Decision Makers

Depression is one of the most common illnesses in the United States and a major driver of health care utilization costs. The literature is replete with studies that show that depression is managed poorly and that failure to diagnose and treat depression can lead to poor yet avoidable medical and financial outcomes. The primary goals and challenges of treating depression involve accurate diagnosis of this highly comorbid condition and improving patient compliance with therapy.

This peer-reviewed publication is a digest of up-to-date guidelines for treatment, therapeutic approaches to treatment of depression, pharmacoeconomic considerations in treatment, and a discussion of comorbid conditions. In consolidating this information, it serves as a valuable tool for formulary committees and is an important contribution to the medical literature.

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GlaxoSmithKline
DEPRESSION

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Depression

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EDUCATIONAL NEEDS ASSESSMENT

Depression is a serious public health threat and, by extension, a threat to the health of populations for which managed care organizations have responsibility. Medical and pharmacy directors and other decision makers in managed care organizations seek state-of-the-art information about evidence-based guidelines, emerging therapies, and pharmacoeconomics. This publication serves as a digest of this information for managed care decision makers, who can use it to develop treatment protocols and formulary recommendations and disseminate it to providers to improve the collective health of their populations.

The information herein also is valuable to health care providers, who must stay abreast of current treatment approaches. The success of treatment depends on the clinician’s ability to accurately diagnose patients and encourage adherence to therapy. This publication synthesizes best-practice information for clinicians.

The subject matter in this publication was selected on the basis of literature searches and faculty perception of significant issues.

EDUCATIONAL OBJECTIVES

After reading this publication, the participant should be able to:

• Illustrate the prevalence of depression, as well as the clinical and economic implications thereof.
• Describe major published treatment guidelines for depression, as well as their shortcomings as advanced therapies have reached the market.
• Identify various SSRI treatments for depression and explain their mechanisms of action.
• Understand the dynamics of pharmacoeconomic evaluation of SSRI therapy.
• Elucidate strategies for therapeutic compliance and the consequences of noncompliance.
• Discuss NCQA guidelines for depression medication management and follow-up after hospitalization for depression.

TARGET AUDIENCES

Managed health care professionals, including physicians, pharmacists, medical directors, chief medical officers, pharmacy directors, and other senior managers in managed care organizations.

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INTRODUCTION

Depression: Underdiagnosed, Undertreated, Underappreciated

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SUMMARY

Major depressive disorder is significantly underdiagnosed and undertreated, particularly in the primary care environment. Although more patients are seeking help for depression and the utilization of antidepressants is on the rise, the level of treatment is inadequate. Rectifying this will involve patients, providers, payers, employers, accrediting agencies, and even governmental entities.

Major depressive disorder in the United States is a serious, recurring, and debilitating illness. More than 16 percent of the population, or approximately 35 million American adults, will suffer from it at some point during their lives. According to the National Comorbidity Survey Replication, published last year in the Journal of the American Medical Association, 12-month prevalence rates for major depressive disorder (MDD) translate to 6.6 percent of the population, or about 14 million U.S. adults (Kessler 2003).

To illustrate the magnitude of depression, consider this: In the United States, there were 30,622 suicides in 2001; most were by people with depression. By contrast, there were 20,308 homicides the same year (CDC 2001).

Such widespread incidence and prevalence translates to a significant deterioration of quality of life, medical well being, and personal productivity for millions of Americans. From a societal perspective, depression contributes to substantial worker absenteeism and disability and erodes billions from the U.S. economy. From a health plan or employer perspective, MDD is one of the most expensive disorders that payers face.

MDD is not simply the experience of a few “blue days.” It is characterized by a severe persistent depressed mood and loss of interest or pleasure in normal activities. MDD commonly includes decreased energy, changes in sleep patterns and appetite, and feelings of guilt or hopelessness. To be classified as MDD, these symptoms must be present for at least 2 weeks, cause significant distress, and interfere with activities of daily living. If the depression is extremely severe, it may be accompanied by psychotic symptoms or by suicidal thoughts or behaviors.

From all principal perspectives — the patient, the provider, and the payer — the problem is large and growing larger. This is due, to a great extent, to the fact that MDD is significantly underdiagnosed and undertreated — particularly in the primary care environment, where the preponderance of treatment for it takes place. Readers who are responsible for reining in ever-increasing pharmacy budgets may find this statement difficult to accept. With antidepressant drug use becoming more common among insured populations, their perspective has a certain validity. For example, the medical literature documents a significant rise in the number and rate of outpatients being treated for depression over the past 25 years. In 1987, 0.73 per 100 persons were treated on an outpatient basis for depression; by 1997, that rate had increased to 2.33 per 100 persons — an increase of more than 300 percent (Olfson 2002). The same trend is documented with regard to antidepressant prescribing during office visits.
with a near doubling of such visits over approximately the same time period (Olfson 1998).

So, while it is true that more patients are seeking help for depression and that utilization of antidepressants is on the rise, the question becomes: Is it adequate? The simple answer is no. Referring to the JAMA article cited earlier, it is clear that even with increased numbers of people now receiving pharmaceutical treatment for depression, this still only represents just over half of all patients diagnosed with the disease. Beyond that, of those who are receiving treatment, less than 42 percent receive adequate treatment. In short, less than 22 percent of all persons diagnosed with depression receive adequate treatment for their disease (Kessler 2003).

COLLECTIVE RESPONSIBILITY

There are numerous and complex reasons for this unfortunate situation. Rectifying it will involve patients, providers, payers, employers, accrediting agencies, and even governmental entities. We will touch on several of these reasons in turn.

Anyone involved with any aspect of the care of depressed patients must understand the recurrent and comorbid nature of the disease. The former serves to make an accurate diagnosis of depression more likely; the latter frequently contributes to missed diagnosis or misdiagnosis. Depression often is accompanied by other mental and physical comorbidities. These commonly include anxiety, substance abuse, heart disease, hypertension, diabetes, and chronic pain resulting from other conditions. Designing an appropriate treatment plan in the presence of comorbid conditions is understandably a challenge for providers, particularly when the depression is the underlying disorder.

Stigma is still stubbornly associated with depression and other mental illnesses. This must be addressed head-on with educational campaigns aimed at providers of health care, the public, and employers. The stigma of mental illness is a barrier to good care; When patients are unwilling or unable to share their symptoms with their health care providers, an accurate diagnosis and a targeted treatment plan will remain elusive.

Another obstacle to optimal care is lack of follow-up. This can result from physician time constraints, a weak link in the system that does not automatically schedule patients for an appropriate number of follow-up visits, or ignorance on the part of providers that in-office visits or even telephone consults can increase patient compliance and improve clinical outcomes. According to numerous studies, as well as anecdotal evidence, the well-informed patient will be a more compliant partner.

This lack of adequate follow-up is seen in the primary care setting as well as the specialist’s office. It also has been the National Committee for Quality Assurance’s point of entry. NCQA is an accrediting body with a mission to measure and improve the quality of health care in America. Using process measures as a proxy for quality, NCQA has developed numerous indices to evaluate quality of care. Several of these involve depression. Two of the measures concern adherence to medication regimens during the acute (12-week) and continuation (6-month) stages of the disease, and one measures the number of follow-up visits with a primary care practitioner or mental health care provider. NCQA has established that 3 visits during the 12-week acute stage is the benchmark (1 visit must be with a prescribing practitioner). Yet, few health plans in America meet the benchmark; in 2002, across all plans reporting, only 19.2 percent of patients with a new episode of depression had at least 3 follow-up visits. Obviously, systems are not in place to guarantee that patients who are newly diagnosed with depression and prescribed medication are seen for what some would argue is a minimum necessary number of follow-up visits.

Besides lack of follow-up, dropout or noncompliance with therapy is a major documented problem. In a well-referenced study by Lin (1995), researchers found a 52 percent dropout rate by week 12 among a group of Medicaid patients who were prescribed antidepressants; only 27 percent remained on an adequate, 6-month course of therapy. Again, several causative factors can be identified. One is side effects; treatment-emergent nausea is the most common. Yet, if patients are made aware that this potential side effect is essentially gone within the first 12 weeks of therapy, compliance rates may improve.

Another causative factor in dropout can be a perceived lack of efficacy or unreasonable expectations regarding the length of time needed for the antidepressant to do its work. Again, good patient-provider communication is critical if patients are to have a realistic picture of what to expect from therapy. Unfortunately, a disconnect is evident in the respective perceptions of providers and patients about the quality of their communications. Providers assume that they have imparted more and better information about the therapeutic regimen than patients claim to have heard.

Yet another factor that may limit a patient’s compliance is the cost of antidepressant medications. Employers and other payers are wise to give serious consideration to health plans and insurance policies that provide their employees, retirees, and dependents with adequate medication coverage that makes treatment affordable. Poor clinical outcomes resulting from lack of adherence to a therapeutic regimen are avoidable, and the downstream costs of follow-up care are potentially much higher than the cost of the medication itself. The most scientifically robust, evidence-based treatment algorithm
will have little or no beneficial effect if patients cannot or do not follow their medication protocols.

So, the challenges are many and multifaceted. They involve people, organizations, policy, and process. Changing our nation’s poor performance in caring for persons with major depression begins with awareness of these problems. Awareness leads the problem-solver to seek information and answers. We hope that in the following pages, we provide a foundation for taking steps to improve both the process and the outcomes of care for the millions of Americans suffering from MDD.

WHAT’S INSIDE

Here is an overview of the contents of this publication, which has been prepared and reviewed by some of the nation’s most respected experts in the field.

In “Prevalence and Economic Effects of Depression” (page 9), Bernard Bloom, PhD, explores the economic implications of MDD for individuals, health plans, employers, and society at large. Bloom presents direct medical costs and indirect costs of depression. Indirect costs include not only disability and absenteeism, but also interactive effects, costs with other diseases, and depression’s role in unemployment.

This is followed by an examination of current clinical practice guidelines for treatment. Several national and international organizations have published evidence-based guidelines for the treatment of patients with MDD. In “Clinical Practice Guidelines for Treating Depression in Primary Care” (page 17), Christy Beaudin, PhD, and Robert Burchuk, MD, review respected, commonly utilized guidelines and discuss how they might be updated to improve clinical outcomes given health plan environments and practice limitations. Guidelines, while key to optimal treatment of patients with depression, are frequently misunderstood as prescriptive rather than descriptive, a phenomenon that contributes to their disuse.

Jeffrey Weilburg, MD, reviews the array of available modern pharmacotherapies for depression — the selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors. In “An Overview of SSRI and SNRI Therapies for Depression” (page 25), Weilburg examines their chemical structures, mechanisms of action, contraindications, side effects, salient clinical trial data, and indications for their use. Certain SSRIs have been approved for social anxiety disorder, for instance. Beginning on page 52, Ashok Raj, MD, reviews treatment plans for depressed patients; with an understanding of the scope of the disease, diagnosed and undiagnosed, we can improve HEDIS performance measures and, by extension, help patients with depression to reach remission of symptoms and, hopefully, recover fully.

REFERENCES


Prevalence and Economic Effects Of Depression

BERNARD S. BLOOM, PhD
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SUMMARY

The lifetime risk of major depression among Americans is 17 percent, with as many as 10 percent suffering from depression in any 1-year period. The author reviews the epidemiology of depression, costs of treatment and nontreatment, and its economic impact on quality of life and daily function. This review also examines ways to improve value for money spent relative to this disease.

The World Health Organization (WHO) estimates that about 340 million people worldwide suffer from an episode of major depression each year. It is the fourth leading cause of disability worldwide. In the United States, about 18 million people have had at least one episode of depression and sustain a lifetime risk of about 17 percent (NIMH 2002).

Depression has a profound impact on population health and health-system costs, individual and family quality of life, activities of daily living, and daily functioning, as well as on businesses, employers, and employees. About 15 percent of people with major depression commit suicide (Moller 2003).

Persons with depression tend to have multiple comorbidities, with substantial interactive effects relative to suffering and cost. Because of the negative connotations associated with mental health disorders, many depressed persons shun treatment, losing work days and performing inadequately on the job. These factors add up to enormous human and economic costs.

Depression is common, persistent, often associated with other chronic conditions, underrecognized, and undertreated. Conservative estimates hold that clinical depression (Kamlet 1995):

- Affects between 1 and 3 percent of the U.S. population during any 6-month period
- Has a lifetime incidence of more than 15 percent
- Affects nearly twice as many females as males
- Recurs at least once among 50 percent of persons, within 10 years of the initial episode
- Recurs a third time among 90 percent of persons with 2 previous episodes
- Has a 40 percent relapse rate within 15 weeks among persons with 3 or more lifetime episodes
- Has a relapse rate of 65 percent within the first year, if untreated, among recurrent depressives
- Is the primary psychiatric disorder suffered by at least 60 percent of suicide victims, accounting for about 16,000 deaths annually

PREVALENCE

Pincus (2001) determined that the percentage of depressed persons increases relative to the disease’s prevalence rate in the general population. Among general medical patients, particularly hospital inpatients, the 1-year prevalence rate of major depression is 2 to 3 times that found in the community population.

Globally, in 1999, one person in six was expected to suffer from major depression, with estimates that by 2020, major depression would be the second most important cause of disability worldwide (Davidson 1999).
The National Comorbidity Survey (NCS) reported that nearly half of respondents had experienced at least one psychiatric disorder (Kessler 1994); most common was major depression, with a lifetime prevalence of 17.3 percent and a 1-year prevalence of 10.3 percent. The National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) program estimated lifetime prevalence of major depression at 7 percent, and reported that about one third of major depressive patients sought no treatment. In 1999, only about 10 percent received adequate doses of antidepressive drugs for a sufficient period (Davidson 1999).

Depressed patients are 3 times more likely to fail to adhere to treatment than non-depressed patients, and most depressed persons suffer chronic or recurrent episodes. About 40 percent of depressed persons will meet diagnostic criteria for depression a year after the initial episode; 15 to 20 percent remain depressed for 2 years. About 60 percent of those who experience an episode of depression will experience a second, and risk of recurrence increases with each subsequent episode (Pincus 2001).

Quality of life and daily function

Even among people with minor depression, NCS reported that symptoms interfere substantially with daily activities in 18.1 to 52.3 percent of people, rising with increased depression severity (Davidson 1999). Wells (1999) found that depressed patients generally functioned at lower physical and mental/emotional levels than those with 11 other common chronic conditions — asthma, diabetes, hypertension, arthritis, migraines, as well as lung, neurological, heart, gastrointestinal, vision, and back problems. Those who self-reported 12-month depressive disorder had lower mental and social function than those with any of the other chronic conditions, and worse physical functionality than patients with four of those conditions.

Diagnosis and Treatment

Typically in the United States, primary care physicians diagnose and treat patients with depression and refer them to specialists. The diagnosis of depression is associated with higher primary care costs, but failure to diagnose it is associated with higher subsequent laboratory and other diagnostic costs, as primary care physicians strive to determine the cause of the patient’s symptoms.

In the general medical setting, half of depressed patients are not diagnosed correctly (Croghan 1998). Depressives’ symptoms may be attributed to physical illnesses; further, evidence suggests that physicians may alter the stated diagnosis, resulting in differing claims, medical records, and physician notes for the same patient. Callahan (2002) found that primary care physicians underdiagnose depression. As indicated in Figure 1, primary care physicians diagnosed depression in slightly more than one fourth of patients who self-reported moderate to severe depression, while making the diagnosis in fewer than 1 in 10 patients whose depression was mild. When patients’ own and primary care physicians’ diagnoses failed to match, the physicians ordered laboratory tests, increasing costs. The researchers concluded that primary care physicians were more likely to diagnose depression accurately when the patient’s symptoms were severe. Using a screening tool such as the Beck Depression Inventory probably would increase depression diagnoses, but it is unclear from this study what effect screening would have on care processes, patient outcomes, or costs.

The NIMH Collaborative Depression Study reported that only 34 percent with major depression lasting at least 1 month received antidepressive treatment for at least 4 weeks (Davidson 1999). In addition, the treatment they received was adequate in only 23 percent of cases. The investigators found a correlation between increased depression severity and increased utilization of physician services. Despite suffering recurrent episodes (mean 12.7 episodes per lifetime), only 35.3 percent of study patients sought professional help. The investigators observed that depression symptoms can be controlled effectively, but that the condition is often undiagnosed or inade-
quately treated in primary care settings due to factors relating to the patient, provider, and system.

Depression also is treated inadequately by mental health specialists; only 45 to 49 percent of patients diagnosed with depression receive adequate therapy (Davidson 1999). The reasons found for inadequate care were:

- Primary care physicians receive inadequate training in diagnosis and management of depression; need to develop the interpersonal skills necessary to understand patients with depression; and must develop the proper mindset to treat depression as an illness.
- Patients with depression need counseling because they lose initiative, often become passive, blame themselves for their problems, and quickly become noncompliant, all leading to adverse outcomes.
- Health care systems tend to perceive depression as a short-term rather than chronic and recurrent illness, and most do not encourage monitoring patients throughout the treatment regimen. Instead, they may discourage appropriate treatment and follow-up care by reducing or denying coverage.

The major difficulties in treating depression (and any mental illness) in primary care are rooted in organizational and financial arrangements. Behavioral health carve-outs and risk-based physician payment often distort primary care physician decision making as a result of the absence of real costs that physicians face when making treatment decisions (Frank 2003).

**COMORBIDITIES**

Callahan (1997) suggested that patients with depression have a greater burden of comorbid nonpsychiatric illness than people without depression. In addition, older adults with depressive symptoms have nearly twice the functional impairment as people without depression.

Figure 2 lists comorbidity rates for patients with common chronic conditions. Among diabetics, depression is associated with poor glycemic control; increased risk of complications, particularly heart disease; and higher overall health care costs. Asthmatics report decreased quality of life. Among patients recovering from myocardial infarction, the mortality rate is 3 times higher in patients with comorbid depression than for those without depression. Forty percent of high utilizers of health care have been diagnosed with depression or dysthymia. These patients were found to represent the highest decile of consumers of health care in a large HMO, responsible for 29 percent of primary care visits, 40 percent of inpatient days, and 26 percent of prescriptions (Pincus 2001).

**Economic consequences**

A multinational study in Seattle; Barcelona, Spain; Be’er Sheva, Israel; Melbourne, Australia; Porto Alegre, Brazil; and St. Petersburg, Russia, demonstrated that the economic consequences of depression are substantial in the presence of medical comorbidity compared with depression alone (Chisholm 2003). Researchers found that comorbidity increased health care costs 17 to 46 percent at five of six study sites. While they noted a strong association between depression and comorbidity, study limitations did not allow them to establish a consistent trend relative to the effect of psychiatric comorbidity on costs.

Croghan (1998) differentiated expenditures attributable to depression from those related to comorbidities that complicate depression. The investigative team reviewed patients’ records for comorbidities and total health care charges for physician and other outpatient visits, diagnostic tests, hospitalizations, and prescriptions occurring within 1 year of the index antidepressant prescription. In more than 95 percent of patients, they found an indicator for at least one nondepression diagnosis. The most frequent of these, in 94.5 percent of people, was nondepressive mental disorder; also common were ear, nose, mouth, throat, musculoskeletal system, and skin disorders. Predicted expenditures for those with at least one comorbid condition were significantly higher than for patients without comorbidity.
On average, treatment of depression alone represented about 28 percent of total charges ($2,279 of $8,037) for depressed patients with comorbidities. The most frequently occurring comorbidity — mental illnesses other than depression — accounted for approximately $1,600 of total charges. Other characteristics associated with large incremental spending included neurological disorders ($2,194), pregnancy and postpartum conditions ($1,697), and musculoskeletal conditions ($1,505). These results indicate that while treating depression is expensive, depression-related expenditures represent only about one fourth of total cost. More recently, Kupfer (2003) showed that comorbidities effectively double the cost of caring for people with depression.

Over 4 years, Unützer (1997) studied people in an HMO who were at least 65 years old. The investigators found persistent depressive symptoms to be common, and established an association between depressive symptoms and higher health care costs. Total health care costs for seniors with significant depression symptoms were about 50 percent higher than costs for those without depression. They noted that primary care physicians may be less likely to recognize depression in older patients or may believe that they would not benefit from care.

Individuals with depression who are at least 60 years old and who have a greater number of nonpsychiatric comorbid conditions visit ambulatory care centers and emergency rooms more frequently, have more hospitalizations, and have greater median total diagnostic test charges for 1 year ($583 vs. $387) than those without depression (Callahan 1997).

COSTS OF DEPRESSION

Using a human-capital approach, Greenberg (1993) estimated the annual cost of depression in the United States in 1990 at $43.7 billion (Figure 3). Estimates were based on direct costs of medical, psychiatric, and pharmacological care; mortality costs associated with depression-related suicide; and indirect costs of morbidity, such as the costs associated with lost work days and reduced productivity.

Researchers concluded that the true economic burden might not be realized, as many important cost categories have yet to be estimated. Future studies should address comorbidity costs, reduced quality of life, and patients’ and families’ out-of-pocket expenses.

Davidson (1999) also estimated total cost of major depression: nearly $44 billion in 1990. The investigators estimated that direct medical costs accounted for only $12.4 billion (28 percent of total costs), for all inpatient and outpatient services and pharmaceuticals. Early mortality costs accounted for $7.5 billion. More than half of the total cost, $24 billion, was attributed to absenteeism and reduced productivity. This study did not account for out-of-pocket expenses, excess hospitalizations, diagnostic tests, or costs associated with minor depression.

**Absenteeism and reduced productivity**

Depressive disorders pose a major occupational health challenge, with implications for productivity, competitiveness, absenteeism, insurance benefits utilization, and medical care costs. Employers — the primary health care payer in the United States — are concerned about increased health-benefit costs. They often overlook the benefits of treatment compared with continued illness and inadequate diagnosis and treatment, however. Most employers are unaware of how often depression contributes to worker disability, the extent of its indirect costs, and the availability of effective treatment options. Further, because the workers’ compensation system and courts have been slow to recognize depression as a workplace disability, employers lack incentives to encourage treatment and to implement preventive measures.

Goldberg (2001) concluded that depressed patients in the United States were at least as functionally impaired — in terms of physical, social, and role functioning — as those with medical disorders such as hypertension, diabetes, advanced coronary artery disease, back problems, angina, arthritis, breathing problems, and gastrointestinal disorders. The investigators referred to a WHO study...
indicating that depressed patients are 23 times more likely to have a social disability 1 year after diagnosis than are patients with physical disability 1 year after diagnosis.

Conti (1995) found that depression was responsible for over half of mental health diagnoses and claims paid by a major Midwestern employer. Further, depression was responsible for more disability days and 12-month recidivism than were such physical complaints as heart disease, diabetes, hypertension, and lower-back pain.

In an international study, the economic burden of untreated depression also affected the workplace (Chisholm 2003). When the cost of lost work days is included, the economic burden increases greatly. In the 3–months before baseline assessment, study participants lost an average of 3.7 workdays (range 1.5–8.0 days), at an average cost of $225 per participant. The authors acknowledged, but did not include, the economic burden of partial workdays that were lost.

In a study of 10,000 employees and dependents, Goldberg (2001) found mean annual health care expenditures for patients with depression and related illnesses to be more than 4 times that of patients with no depression claims (Figure 4). The team noted that the accepted prevalence rate of depression in the workplace — 2 percent — is probably substantially underestimated.

Detected or hidden depression in the workplace leads to reduced productivity, absenteeism, increased health care resource utilization, job dissatisfaction, substance abuse, and accidents. Kessler (1999) showed that depressed workers lost 1.5 to 3.2 days more than other workers in a 30-day period, at an average productivity loss of between $182 and $395, based on an estimated treatment cost of $402 per episode.

Employees with depression reported a mean of 5.6 hours per week of lost productive time, whereas those without depression lost 1.5 hours. Extrapolation of these data suggests that U.S. workers with depression cost employers an estimated $44 billion per year in lost productivity — $31 billion per year more than nondepressed workers — and this estimate does not include labor costs associated with short- or long-term disability.

A comparison of the effects of different common chronic conditions on work impairment in the general population showed that major depression was associated with a higher likelihood of impairment than heart disease and hypertension (Kessler 2001). In addition, Davidson (1999) noted that 72 percent of all depressed persons are in the workforce. The researchers estimate that annual cost of depression per employee is nearly $4,900 and the cost of appropriately treating persons with affective disorders would offset direct costs by nearly $4 billion.

**Work loss and disability**

People with major depression have 4.78 times greater risk of disability, while those suffering from minor depression with mood disturbance (but not major depression) are at 1.55 times greater risk than those without depression (Broadhead 1990). The investigative team concluded that depression was an important predictor for disability days during the year after diagnosis.

Druss (2000) studied the effects of heart disease, diabetes, hypertension, and back problems compared with depression, and analyzed mental health costs, medical costs, sick days, and total health and disability costs. The per-capita cost of depression was significantly more than that of hypertension or back problems, and comparable to that of diabetes or heart disease (Figure 5, page 14). The cost of treating employees with depression plus any of the other conditions was 1.7 times higher than that of treating employees with the same or other conditions who were not depressed.

In an analysis of the NCS and the Midlife Development in the United States Survey (MIDUS) data, Kessler (1999) found that depression cost businesses between 1.5 and 3.2 more short-term disability days in a 30-day pe-
period than did workers without depression. Major depression affects 1.8 to 3.6 percent of the workforce monthly. Salary-equivalent productivity loss averaged between $182 and $395. Using the estimated cost of $402 for 30 days free from depression provided by nortriptyline therapy, the research team determined that effective treatment offsets between 45 percent ($182 of $402) and 98 percent ($395 of $402) of lost productivity costs. The team concluded that because this study omitted indirect costs, and because employers bear the full brunt of lost productivity, effective treatment is cost-effective for employers, especially when other factors are considered — such as costs of short-term disability, early intervention, reduced hospitalization, and other medical care, and reduced absenteeism from work.

Rizzo (1996) estimated the economic effects of chronic illness on productivity and the mitigating effects of prescription drug therapy. The investigators estimated the effects of medications on hourly wages and work days lost, assuming average compliance. Effective drug therapy achieved a net benefit, above the cost of therapy, for employees with diabetes, heart disease, depression, and hypertension (Figure 6). The investigators concluded that benefits accrue because medications substantially lower absenteeism among chronically ill workers.

Improving the mental health status of depressed medical patients who were high medical service utilizers alters the course of functional disability (Von Korff 1992). People with severe depression reported an average of 134 disability days per year at baseline; those with moderate depression reported 77 days. For study participants whose mental health improved by the 12-month follow-up, average annual disability days fell 36 percent, from 79 to 51, for those with severe depression; for those with moderate depression, disability days declined 72 percent, from 62 to 18. Those with severe-unimproved depression were more likely to have current major depression and to be unemployed.

HEALTH CARE RESOURCE UTILIZATION

Understanding health care resource utilization is vital to understanding the total cost of depression. It starts with investigating the cost-effectiveness of pharmacotherapy but also addresses other factors affecting costs, such as the value of psychotherapy, enhanced practice at the primary care level, and improving adherence to a therapeutic regimen. Borghi (2000) calculated that among people with moderate or severe depression treated by a primary care physician, overall cost of care for those who discontinued depression treatment was about 50 percent higher than for those who remained on their medications.

Henry (1997) noted that, in light of contemporary diagnosis and treatment abilities — and considering the consequences of treatment failure, including attempted and successful suicide — the indirect costs of depression including mortality, may be 7 times as burdensome as the direct medical costs. The authors advised that physicians should focus primarily on clinical benefits when choosing an antidepressant and offered that market price is only one of many factors that influence medication choice. They also warned that, in the long run, the trend to emphasize cost-containment first may increase costs.

Pharmacotherapy vs. psychotherapy

Kamlet (1995) investigated prospectively by randomized controlled trial the cost-utility of maintenance treatment for depression. The researchers found imipramine drug therapy to be more cost-effective than either interpersonal psychotherapy (IPT-M) or placebo, improving expected quality adjusted life years (QALYs) and reducing direct medical cost. Compared with placebo, neither IPT-M nor combination therapy reduced direct medical costs, but did improve QALYs.

Kamlet’s team determined a 0.0025 base case value to
the probability of suicide associated with a major depressive episode. Using a $2.1 billion estimate of the direct cost of depression in the United States in 1980 and a 2 percent, 6-month prevalence rate, they estimated $250 in direct per capita costs in 1980 dollars, or $500 in 1991 dollars, with a range of $200 to $1,500. To generate empirical results, the researchers used Monte Carlo analysis for a baseline 40-year-old woman.

IPT-M and IPT-M+placebo increased expected QALYs from 9.6 in the placebo group to more than 14, while drug and combination therapy increased QALYs to between 15 and 22, depending on the magnitude of the estimated impact of adverse side effects. IPT-M increased lifetime direct costs by $13,000 (62 percent), which offsets the savings from a reduced number of future depressive episodes and their associated costs. The cost of resulting health improvements was less than $5,000 per QALY for both IPT-M and imipramine, well below the $50,000 per QALY typically cited in the literature as the threshold to determine if an intervention represents sufficient value for use of health care resources.

Lave (1998) compared pharmacotherapy and psychotherapy in a randomized controlled prospective trial of depressed persons. The researchers found that tricyclic antidepressant therapy yielded slightly better quality-of-life outcomes at a slightly lower cost compared with psychotherapy. Both resulted in better outcomes than usual care, at a higher cost and with no meaningful cost offsets.

Enhanced primary care
Pyne (2003) compared usual primary care for depression with enhanced intervention. Intervention enhancement consisted of educating physicians, nurses, and office staff coordinators to assess, educate, and monitor depressed patients during their acute depressive episode and during the following year. The investigators assessed the incremental effect of the intervention, defined as enhanced care minus usual care, on costs and QALYs. The mean incremental cost-effectiveness ratio (CER) was $15,463 per QALY. The team concluded that enhancement was cost-effective compared with usual primary care interventions and according to commonly accepted cost-effectiveness thresholds.

IMPLICATIONS FOR PAYERS
Depression can be treated effectively, but providing effective therapy will likely increase up-front costs associated with educating primary care physicians and staff to understand depression, screen effectively for it, provide effective pharmacotherapy and psychiatric support, and monitor adherence. Nevertheless, effective treatment, according to available evidence, will reduce overall societal costs, particularly in terms of increased productivity, reduced disability, fewer suicides, and better quality of life for depressed persons and their families.

Callahan and colleagues added that primary care physicians and mental health specialists should address organic and psychiatric illnesses simultaneously to control health care costs and improve outcomes for depression patients (Callahan 1997). In particular, primary care physicians need better treatment options and more effective educational models for complex patients, and older adults need better access to mental health services.

MCOs could care for depressed patients more efficiently by examining frequently occurring patient characteristics that generally predict higher costs (Croghan 1998). Applying intensive services, in a collaborative model earlier in the course of illness, would increase initial costs modestly but also should improve outcomes, therefore making a strong cost-effectiveness argument.

Treating depressed persons with appropriate care modalities and regimens, including non-pharmacological elements, is cost-effective (Davidson 1999). Introducing a collaborative approach to major depression would increase response rates from 43.8 percent — with usual primary care — to 74.4 percent, when a primary care physician and psychiatrist treat the patient together.

CONCLUSION
Depression is costly to treat effectively, but leaving it untreated is
EPIDEMIOLOGY AND ECONOMICS

Even more costly. Increased treatment nearly always increases costs for every diagnosis. Most research on the majority of diseases ultimately finds that early savings evaporate over the long term when tested in the real world. Improving patient health nearly always has up-front costs. The conservative view would assume that improved health would cost more but that the benefit to individuals and society may outweigh those concerns. Thus, the issue is not whether treatment will improve health outcomes and reduce expenditures, but whether treatment and its benefits are worth the cost — the cost-effectiveness question from the societal perspective.

Effective treatment starts with improving the mindset and perceptions of primary care physicians regarding depression, continues with effective treatment using antidepressants and psychiatric therapy in a coordinated effort, and leads to effective patient education, self-care, and monitoring for adherence with established protocols.

Simply allowing the existing system of variable diagnoses, care, and follow-up to continue will mean that benefits are being foregone and resources wasted. The problem is guaranteed to grow larger; already, in the United States alone, between 1.8 and 3.6 percent of workers suffer from major depression, between 17 and 21 percent of the workforce experiences short-term disability in any year, and between 37 and 48 percent suffer short-term disability during their lifetimes.

If these estimates of disease burden are reasonably accurate, direct and indirect expenditures for depression will rise quickly and dramatically; low levels of benefit for people with the disease, their families, employers, and society will continue, however, if inadequate treatment and follow-up by the health care system and patient adherence to therapy are not corrected.

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Clinical Practice Guidelines for Treating Depression in Primary Care

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**SUMMARY**

Clinical practice guidelines for depression offer the best available treatment options as evidenced by randomized controlled clinical studies. Although the use of evidence-based guidelines has been shown to improve treatment success, there are few data to suggest the extent to which they are used or their effect on treatment outcomes. Keeping guidelines current and increasing the probability of use in daily clinical practice are critical.

Practice guidelines for treating depression in primary care have been available for a decade. Practitioners may think of them as prescriptive, whereas their originators and organized medicine intend them to offer guidance on clinical practice supported by research and consistent with community standards. Guidelines are not designed for dogmatic application. However, using them can improve detection and treatment of depression, reduce suicide risk, promote the prevention of relapse, and reduce treatment costs. It has been demonstrated that patients have higher treatment rates for depression and better outcomes when treated in primary care practices that use evidence-based strategies (Wells 2000).

Clinical practice guidelines represent the best science underlying the art and science of healing. As with practice guidelines for any disease, those for depression are based upon clinical evidence and refereed by peers to ensure practical applicability and consistency before being released. The clinical evidence used in guideline development is authoritative medical literature with randomized controlled clinical studies as the standard.

Depression guidelines for primary care practitioners are limited, with some simply listing medications without reference to psychotherapy for milder cases. More widely available guidelines are those generated by professional societies, organized delivery systems, and health plans. Most depression guidelines used by clinicians and health care organizations are based solely or in part on the guideline issued by the American Psychiatric Association (APA 2000).

Health care organizations use practice guidelines to achieve improved treatment processes and outcomes.

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DIAGNOSIS AND TREATMENT

Their focus is on patient demographics, service needs, and available resources, so self-generated guidelines may differ from those issued by national medical societies. If a health plan chooses to develop its own depression guidelines rather than adopt those of professional societies, the guidelines should be based on a combination of the recommendations of professional societies, a review of the literature, scientific and expert presentations by clinicians skilled in treating the disorder, and standards of care in the community. Any organization embarking on this undertaking should emphasize:

- Symptom assessment
- Suicide risk assessment and reassessment
- Medication options (if, when, how, how long to treat)
- Selection of modalities between drug options, psychotherapy, and electroconvulsive therapy
- Monitoring adherence to medications and general treatment plan
- Visit intervals
- Knowing when/how to switch or terminate treatment
- Clarifying maintenance treatment, if any

CONSIDERATIONS FOR DEPRESSION GUIDELINES IN PRIMARY CARE

Fifteen years ago, depression was a diagnosis less commonly treated in primary care and more typically referred to behavioral health specialists for treatment. With the advent of selective serotonin reuptake inhibitors (SSRIs) in the late 1980s, treatment of depression was adopted more readily in the primary care setting — to the point that the significant majority of antidepressant prescriptions now are provided by nonpsychiatrists.

Studies on the inadequate treatment of depression led the U.S. Department of Health and Human Services to establish an Office of the Forum for Quality and Effectiveness in Health Care. As part of this effort, the Agency for Health Care Policy and Research (AHCPR) — today known as the Agency for Healthcare Research and Quality (AHRQ) — issued guidelines for depression in primary care in 1993 (these guidelines are no longer considered current by AHRQ).

While AHRQ-sanctioned practice guidelines are available online through its National Guidelines Clearinghouse, there is currently no guideline available for the treatment of depression. One AHRQ criterion for a guideline is that it must be no more than five years old. This suggests that the APA depression guideline must be reviewed by 2005. Maintaining or updating guidelines is expensive, because organizations that issue them perform much of the rigorous review of current research. They call on their constituents to ensure that the guidelines are consistent with current community standards of practice and known developments in scientifically based research.

Available guidelines

Depression guidelines have been disseminated by health care organizations and professional associations. Many have commonalities in assessment and treatment strategies but diverge in the comprehensiveness of considering treatment strategies in a medical or primary care setting where the treating clinician is not a behavioral health specialist.

In 1993 and again in 2000, the APA issued its Practice Guideline for the Treatment of Patients with Major Depressive Disorder. The APA guideline often is viewed as the gold standard and is now updated on a fixed 5-year cycle or, if needed, on the basis of important new clinical information and research on the brain, human behavior, and therapies. The flow chart in Figure 1 depicts APA recommendations for choosing treatment modalities for major depressive disorder.

The APA protocol suggests treatment options during each phase of therapy, including starting and maintenance doses of antidepressant medications. It also provides guidance for the clinician regarding when it is appropriate to consider termination of therapy.

The most commonly distributed guidelines on depression for primary care physicians are derived from or rely heavily on the APA guideline, but are condensed and may incorporate factors relevant to local delivery system concerns or needs of special populations. Five guidelines presented below exemplify the different approaches to guideline development: health care organization, community collaboration, statewide initiative, professional association, and international development.

Health care organization

Brigham and Women’s Hospital

Depression: A Guide to Diagnosis and Treatment

Brigham and Women’s Hospital developed a depression guideline “to assist the primary care physician in identifying patients in need of treatment and how to optimally treat them” (Brigham and Women’s Hospital 2004). The guideline offers recommendations for treating women with depression and is based on depression research and the APA’s 2000 guideline. The Brigham and Women’s guideline neither prescribes nor mandates treatment options, but provides the primary care physician with an algorithm for assessment and treatment planning intended to meet the needs of the individual woman. Within the guideline, the following are addressed:

- Medical impact of depression
- Medical conditions associated with depression
- Medications associated with depression
- Psychiatric disorders associated with depression

3 The entire APA guideline can be found online: [www.psych.org/psych_pract/treatg/pg/Depression2e.book.cfm](http://www.psych.org/psych_pract/treatg/pg/Depression2e.book.cfm).
Life situations associated with depression

Diagnostic strategy and treatment

Commonly used antidepressants

Depressive disorders unique to women

The Depression Management Algorithm offers the primary care physician a system driven by alarms related to presentation of symptoms where treatment options include emergency treatment, a referral to psychiatry, a referral for substance abuse treatment, or an assessment for medical comorbidities (Figure 2, page 20).

Community collaboration

Health Care Guideline:
Major Depression in Adults for Mental Health Providers

In Minnesota, where large group practices are common, 30 medical groups adopted a single set of guidelines. One objective of the Institute for Clinical Systems Improvement (ICSI), a collaboration of health care organizations, is to accelerate implementation of best clinical practices. An ICSI effort is underway to improve depression treatment. Its goals include improving diagnosis and assessment by using rating scales, such as the Hamilton Rating Scale for Depression, and increasing adherence to therapy and maintenance of treatment via follow-up contacts by health care providers and their staffs (ICSI 2003). The ICSI guideline is summarized in Table 1, page 21.

Statewide guideline
Colorado Major Depression Disorder in Adults Diagnosis and Treatment Guidelines

Universal adoption of a statewide guideline may provide advantages, such as a single point of reference for all clinicians and creation of a natural environment in which to conduct impact research. In Colorado, health care

** FIGURE 1 APA recommendations for choice of treatment modality

**#1 Should a specific effective psychotherapy be provided?

- Mild to moderate depression: preferred as solo treatment or in combination
- Moderate to severe depression: in combination with medication or electroconvulsive therapy (ECT) if psychosocial issues are important and/or if preferred

**#2 Should medication be provided?

- Mild depression: if preferred as solo treatment
- Moderate to severe depression: with or without a specific effective psychotherapy unless ECT is planned
- Psychotic depression: combination of antipsychotic medication and antidepressant medication, or ECT

**#3 Should medication and a specific effective psychotherapy both be provided?

- Mild depression:
  - If preferred as combination treatment
  - History of partial response to single modality
  - Poor compliance
- Moderate to severe depression:
  - Prominent psychosocial issues
  - Interpersonal problems
  - Personality disorder
  - Poor compliance

**#4 Should ECT be provided?

- Chronic, moderate to severe depression: with or without a specific effective psychotherapy. If patient prefers.
- Severe depression and any of the following:
  - Psychotic features
  - Patient prefers
  - Previous preferential response, need of rapid antidepressant response, intolerance of medication

Go to other treatment considerations

SOURCE: APA 2000
providers and plans agreed 3 years ago on a single set of criteria to guide the treatment of depression. The Colorado Clinical Guidelines Collaborative developed its Major Depression in Adults Diagnosis and Treatment Guidelines. Notably, the brevity of the Colorado guidelines addresses the low success rate in diagnosis and initial treatment of depression. The short-form guidelines (Figure 3, page 22) provide a thumbnail description of an appropriate treatment plan by graphically depicting a timeline with intervals for follow-up visits; a physician can use this tool to direct the future schedule for patient appointments during different treatment phases — acute, continuation, and maintenance, if indicated. It also includes a classification scheme for antidepressants, depicting dosages, potential adverse effects, and contraindications for certain medications.

**Professional association**

**American College of Physicians (ACP)**

*Pharmacological Treatment of Acute Major Depression and Dysthymia*

The ACP develops its evidence-based practice guidelines using a rigorous development process. The ACP guidelines are produced through scientific policy staff, a steering committee (Clinical Efficacy Assessment Subcommittee), and in collaboration with scientists. ACP released two publications to support its depression guidelines:

- Clinical Guideline Part 1: Pharmacological Treatment of Acute Major Depression and Dysthymia (Snow 2000)

**International development**

*Clinical Practice Guidelines for the Treatment of Depressive Disorders*

The Canadian Network for Mood and Anxiety Treatments, in collaboration with the Canadian Psychiatric Association, developed a guideline that outlines strategies for treatment of depressive disorders. Published as a supplement to the *Canadian Journal of Psychiatry*, the guideline was a national initiative and a collaborative effort among providers with input from international experts (CPA/CANMAT 2001). The guideline offers a description of prevalence and health burden, principles of management, psychotherapy, comorbidities, medication, and biologic treatments. Notably, the guideline reports on the needs of special populations for which there may be fewer evidence-based treatment recommendations in the literature.

**USE/DISUSE OF GUIDELINES**

Barriers to using guidelines are numerous, and range from the philosophical to the most mundane practical considerations — including how to locate the guidelines when they are needed (Table 2, page 23). Most medical

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**FIGURE 2**

**Depression management algorithm**

*Brigham and Women’s Physician Hospital Organization*

**Major risk factors for recurrent depression**

The presence of any of the following should direct the primary care physician to consider, strongly, maintenance use of antidepressants and/or consider a consultation with a psychiatrist:

1. Family history of recurrent depression
2. Family history of bipolar disorder
3. Personal history of recurrence within 1 year after discontinuing effective treatment
4. Onset of major depressive episode before age 20
5. Severe, sudden, or life-threatening depressive episode (e.g., suicide attempt)
practitioners still use paper — not digital — records, and with the literature they see daily, paper proliferates.

Those physicians who perceive guidelines as infringing on their autonomy may negatively influence the use of guidelines. Some remain skeptical about outcomes research and evidence-based medicine in general, especially more seasoned clinicians; these practitioners are often unwilling to abandon practice traditions and office culture (Diamond 1998). But even if a practitioner wishes to use guidelines, there may be issues surrounding patient care (e.g., setting, funding) that make it impossible to implement the guideline’s recommendations (TAC 2001).

The reason for issuing the guidelines must be explained to physicians, along with the expected benefits of using them. A clear rationale for the guidelines helps dispel fears about lack of autonomy. Further, new guidelines

### TABLE 1 ICSI Guideline for Depression, Major, in Adults in Primary Care

**Scope and target population:** adults >18 years

**Clinical highlights for individual clinicians**

1. A reasonable way to evaluate whether a system is successfully functioning in its diagnosis, treatment plan, and follow-up of major depression is to consider:
   - How well the diagnosis is documented
   - How well the treatment team engages and educates patients/families
   - Whether the system documents ongoing patient contact
   - Whether the system measures/documents outcomes

2. Presentations for major depression include:
   - Multiple somatic complaints, weight gain/loss, mild dementia
   - Multiple (>5/year) medical visits; more than one organ system affected with absence of physical findings
   - Fatigue
   - Work or relationship dysfunction/changes in interpersonal relationships
   - Sleep disturbances

3. Effective treatment for some patients presenting with a major depressive disorder may differ significantly from other depressed patients. When assessing a patient, consider asking about manic or hypomanic episodes.

4. If the patient is not experiencing a significant reduction of symptoms after 4–6 weeks of treatment, other treatment strategies should be considered.

5. The key objectives of treatment are:
   - To achieve remission of symptoms in the acute treatment phase for major depression
   - To reduce patient relapse and reduction of symptoms
   - To return to previous level of occupational and psychosocial function
   - Antidepressant medications and/or referral for psychotherapy are recommended as treatment for major depression without coexisting medical conditions, substance abuse, or other specific psychiatric comorbidities. Physical activity and tailored patient education are also useful tools in easing symptoms of major depression.

6. When antidepressant therapy is prescribed, medication adherence and completion is critical. The patient should be advised of the following:
   - Most people need to be on medication at least 6 months.
   - It may take 2–6 weeks before improvement is seen.
   - Take the medication as prescribed, even after the patient starts feeling better.
   - Do not stop taking the medication without calling your provider. Side effects can be managed by changes in the dose or dosage schedule.

**Priority aims and suggested measures for health care systems**

1. Increase the use of DSM-IV TR criteria in the detection and diagnosis of major depression in primary care.

2. Increase the functional status of patients with major depression (e.g., Hamilton [HAM-D] scores).

3. Increase the percentage of patients with major depression who stay on antidepressants for clinically appropriate periods.

4. Improve the adherence and maintenance of appropriate treatments for patients diagnosed with major depression by having follow-up contacts with a health care professional.

5. Increase the assessment for major depression of primary care patients with more than 5 visits in the past year with problems in more than one organ system.

**Additional background**

Depression is a treatable cause of pain, suffering, disability, and death, yet primary care providers detect depression in only one third to one half of their patients with major depression. Anxiety disorders (panic disorder and generalized anxiety disorder) are associated with diminished well being, increased substance abuse, increased medical care utilization, and suicide attempts at rates often exceeding other psychiatric problems including major depression. This guideline stresses early suspicion of the two-question screen, depression, and a “positive diagnosis,” by asking simple key interview questions.
should be geared toward specific populations and health care settings. There are important differences among guidelines and approaches for different age groups. Well-designed guidelines offer both an in-depth version for educational purposes for the clinician and a shorter, quick-reference version for use in the office. Clinicians do not have time to pore over lengthy guidelines.

Overproliferation of guidelines is a problem. While a practitioner in an integrated health system probably has two sets of guidelines, a primary care physician in a group practice may be expected to use different sets of guidelines from all the health plans with which he or she contracts. Sensory and information overload may become analogous to too many brands on a shelf, which makes intelligent product selection difficult.

Guidelines can be integrated into quality improvement (QI) programs and activities. In fact, the National Committee for Quality Assurance requires that MCOs adopt behavioral health guidelines and has an established framework for integrating practice guidelines into QI management and improvement (see Table 3). Recent research suggests that QI programs targeting depression can make a difference in outcomes (Sherman 2004, Wells 2004).

Guideline development and implementation can be a significant component of a QI program where an organization targets prevalent or higher-risk diagnoses or disorders with the goal of improving treatment process or outcomes. As an example, the Minnesota effort marries guidelines with QI and focuses on building a relationship with providers to deploy guidelines and produce improved process and/or outcomes.

**OPPORTUNITIES AND CONSIDERATIONS**

Despite the development of the second-generation SSRIs and serotonin norepinephrine reuptake inhibitors, as well as such nonmedical therapies as problem-solving psychotherapy, treatment practices still lag new findings from clinical studies. A number of studies document inadequate care of depression (NIMH 1999). National initiatives in managed care have been undertaken to improve depression treatment. AHRQ, through its Patient Outcomes Research Team on depression, found that only one fourth of patients with depression received appropriate care in a primary care setting. This was attributed in part to the fact that primary care patients often resist psychiatric labeling; further,
primary care physicians may lack depth of training in psychiatric disorders and may face barriers to referring their severely depressed patients to specialty mental health services (AHRQ 2003).

Can the lack of effective depression care in the United States be remedied by guideline adherence? This is unknown; further research is necessary to determine the extent to which treatment quality initiatives and treatment guidelines improve patient care in any setting. It is still unknown whether the pioneering depression treatment guidelines of the 1990s have influenced depression treatment by the average primary care physician. Several areas of opportunity exist for improving care for patients with depression. These address systemic issues and practical considerations, in addition to clinical best practices.

**Systems issues.** In 2001, President Bush established the President’s New Freedom Commission on Mental Health to provide a road map for improving mental health services within the budgets of existing funding streams. Two years later, the commission reported that the treatment of mental health in the United States was in alarming disarray, partially because of the fragmentation of the mental health service delivery system. The report stated that many outdated and ineffective treatments were still being used, and that there was a lag between state-of-the-art treatment options and actual clinical practice.

One New Freedom recommendation notes: “The workforce will be trained to use the most advanced tools for diagnosis and treatments… translating research into practice.” This would be accomplished by circulating evidence-based protocols beyond the mental health subspecialties into the general health care setting and into

### Table 2: Barriers to guideline implementation

<table>
<thead>
<tr>
<th>Practice level</th>
<th>System level</th>
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<tbody>
<tr>
<td>• Primary care physician time pressures</td>
<td>• Insurance coverage not available for recommended therapy</td>
</tr>
<tr>
<td>• Difficulty locating the guidelines in the office</td>
<td>• Organizational fragmentation in the health care system</td>
</tr>
<tr>
<td>• Lack of time/resources for implementing the practice recommendations</td>
<td>• Guidelines not well-integrated into the health care system</td>
</tr>
<tr>
<td>• Patient comorbidities that make generalized guidelines risky to follow</td>
<td>• Lack of timely dissemination of guidelines to practitioners</td>
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### Table 3: NCQA framework for quality improvement

As part of its quality improvement program, an organization utilizes clinical practice guidelines to help practitioners and members make decisions about appropriate health care for specific clinical circumstances. Key elements of practice guidelines and quality improvement include:

<table>
<thead>
<tr>
<th>Element</th>
<th>Explanation</th>
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<tr>
<td>The organization adopts clinical practice guidelines for acute, chronic, and behavioral health care, relevant to its population.</td>
<td>Guidelines that the organization adopts and promotes to practitioners to improve health care and reduce unnecessary variations in care. There must be evidence that the organization has adopted at least three clinical practice guidelines for the treatment of acute, chronic, and behavioral health conditions.</td>
</tr>
<tr>
<td>The organization establishes a clinical basis for its guidelines by:</td>
<td>Evidence-based guidelines are clinical practice guidelines known to be effective in improving health outcomes. Effectiveness of guidelines is determined by scientific evidence or, in the absence of scientific evidence, professional standards or, in the absence of professional standards, expert opinion. The organization must adopt guidelines from recognized sources or involve board-certified practitioners from appropriate specialties in the development or adoption of its own clinical practice guidelines that are not from recognized sources.</td>
</tr>
<tr>
<td>• Using evidence-based clinical practice guidelines</td>
<td>Routinely measuring specific aspects of care addressed in the clinical practice guidelines determines whether the organization and its practitioners follow the guidelines. It is preferable to measure more aspects of performance. If the organization chooses to use only two measures to assess performance, the measures must relate to important aspects of the guideline most likely to affect care. Because clinical practice guidelines describe the process of care, the intent of this standard is to measure at least two important clinical process elements that relate directly to the clinical guideline.</td>
</tr>
<tr>
<td>• Using an appropriate body for approval</td>
<td></td>
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<tr>
<td>The organization annually measures performance against at least three clinical practice guidelines, one of which relates to behavioral health.</td>
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schools. To accomplish this, the commission encouraged technology-based educational and information access (New Freedom 2003).

Increasing the recovery rate. This is a foremost opportunity for improvement. Guidelines can create such opportunities by improving symptom recognition, including proactive screening questions, providing for coordination between behavioral health and medical practitioners, and reducing the complexity of managing other conditions and illnesses that accompany depression.

Flexibility. Good guidelines take into account the wishes of the patient for treatment choices and cover all forms of therapy, including pharmacotherapy and psychotherapy. Table 4 lists characteristics of effective guidelines.

The process of developing guidelines involves many steps, checks, and balances. There is typically a 3 to 5 year lag between guidelines revisions by professional associations. For guidelines to be effective, there must be a feedback mechanism in place so “practice-based evidence” of treatment efficacy can be documented and incorporated into updated guidelines as new evidence.

CONCLUSION

Clinical practice guidelines that are evidence-based, rather than anecdotal or consensus-based, can advance success in the diagnosis and treatment of depression in the primary care setting. Several well-documented and carefully developed guidelines exist; these documents serve to assist clinicians with the art and science of healing. A guideline’s recommendations should be considered in conjunction with a patient’s progress in recovery.

Treatment guidelines are not mandates. In and of themselves, they cannot cure depression or prevent recurrences. Psychiatric disorders such as depression can be, by nature, chronic diseases. As with many other diseases addressed by the primary care practitioner, early detection, intervention, and treatment prevent relapse and hospitalization, and reduce emotional and financial burdens to the individual and society. As guidelines are updated, consideration should be given to both treatment advances and practical considerations that will encourage their use.

REFERENCES


Diamond F. You can drag physicians to guidelines but you can’t make them comply (mostly). Manag Care. 1998;7(9):14–22.


Depressive episodes may be precipitated by stressful events and relieved by psychotherapy. Yet major depressive disorder (MDD) and related mood disorders are serious medical illnesses that have a significant negative impact on morbidity, mortality, role function, and quality of life (Druss 2000). Even mild depressive symptoms can affect employee productivity and health care costs significantly.

MDD has a genetic basis and presents with remarkable similarity and frequency across cultures. Criteria for diagnosing MDD are provided in Figure 1 on page 26.

In addition to MDD, mood disorders outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (APA 2000) include dysthymic and bipolar disorders, and mood disorders caused by a general medical condition or substance abuse. In DSM-IV-TR, premenstrual dysphoric disorder (PMDD) was listed among depressive disorders not otherwise specified, but a consensus panel has determined that PMDD is a distinct clinical entity. The U.S. Food and Drug Administration subsequently embraced the concept, and agents have been marketed for the treatment of PMDD.

Dysthymia, sometimes called “minor depression,” is a chronic mild to moderate form of depression that persists for at least 2 years (1 year in adolescents and children). Those patients with dysthymia are at risk of developing MDD; treatment for dysthymia is nearly identical to that for MDD.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are used widely to treat mood and anxiety disorders. Indications, pharmacologic characteristics, and dosing and administration are outlined. Because more patients receive SSRIs in general medical versus psychiatric settings, this chapter includes information relevant to both.

An Overview of SSRI and SNRI Therapies for Depression

JEFFREY B. WEILBURG, MD
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SUMMARY

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are used widely to treat mood and anxiety disorders. Indications, pharmacologic characteristics, and dosing and administration are outlined. Because more patients receive SSRIs in general medical versus psychiatric settings, this chapter includes information relevant to both.

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dosing and continuation of therapy for at least 6 to 12 months. For patients who relapse following drug discontinuation, or who have had prior episodes of depression or anxiety, extended periods of treatment are recommended. For those with multiple episodes, maintenance therapy is the standard of care (Fava 1994).

**SSRI/SNRI OVERVIEW**

**Mechanism of action**

The precise mechanism of action of SSRIs and SNRIs remains undetermined but may be associated with alterations in gene expression that produce sustained changes in the function of selected brain cells. Simply increasing or reducing brain levels of serotonin is probably insufficient to produce an antidepressant response. Newer agents have been developed, following the recognition that balancing levels of serotonergic, noradrenergic, and other neurotransmitter activity may be required.

**Efficacy, effectiveness, and cost considerations**

Prospective, randomized, controlled trials help to establish the efficacy of antidepressants in reducing depression symptom severity based on a standardized rating scale. For treatment of anxiety and mood disorders, SSRIs and SNRIs appear no more efficacious than older agents, such as tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors (Williams 2000). SSRIs and SNRIs are used much more widely, however, in part because they are associated with lower rates of adverse events (MacGillivray 2003) and better tolerated.

Although efficacy of these drugs has been demonstrated in randomized controlled trials, these studies are limited in their number of subjects and in their follow-up duration, which is generally shorter than the length of time antidepressants would be used in routine clinical settings. Also, participants in psychiatric studies may differ from typical patients in primary care settings. Thus, it may be difficult to apply such findings to primary care settings, where most antidepressants are prescribed.

Effectiveness is measured retrospectively based on processes of care (e.g., guideline adherence) and clinical outcomes achieved under naturalistic conditions and across populations. SSRIs are most effective when used for sufficient periods and at sufficient doses to achieve and sustain full symptom remission. If used appropriately, SSRIs generally are regarded as more effective than TCAs and MAO inhibitors. SSRIs appear to be more effective than TCAs for treating depression in women (Yonkers 2003) and have demonstrated effectiveness as first-line therapy for postpartum depression (Wisner 2002).

Cost considerations are important in formulary development but can be counterproductive if given more...
importance than effectiveness of a drug. For example, health care costs associated with 6 months of treatment with fluoxetine or a much less costly TCA (imipramine or desipramine) were equivalent as demonstrated in a randomized controlled trial. The higher cost of fluoxetine was offset by reduced spending for outpatient visits and inpatient services (Simon 1996). Therefore, even though older agents are relatively inexpensive, SSRIs may be more cost-effective (Weilburg 2003, Singletary 1997).

**AGENTS FOR DEPRESSIVE DISORDERS**

**Initiation of treatment**

No single SSRI or SNRI has demonstrated clear superiority. Despite the apparent similarity between these antidepressants, patients often will respond to one agent but not another. As a result, there are no well-defined guidelines for selecting the optimal agent for initial treatment of depressive disorders. Various treatment algorithms are based, at least partly, on cost. Likewise, many drug benefit plans offer three tiers, with generics on the first tier for no copayment or a minimal copayment. Such a structure tends to steer patients and clinicians toward TCAs and, more recently, toward generic SSRIs. In clinical practice, physicians may choose to begin therapy with agents marketed for the treatment of anxiety and mood disorders for those patients with a combination of symptoms. They also may start with agents that have been useful for other family members with depression.

Although the practice is controversial, some physicians choose agents based on the anticipated side-effect profile. Thus, they will use agents less likely to produce anxiety or insomnia for patients who complain of these symptoms, and more “activating” agents, such as fluoxetine, for those patients who are anergic. Some evidence suggests that sustained-release formulations may produce less nausea than their immediate-release formulations (Devane 2003). Nausea, a relatively common medication side effect, may be associated with premature discontinuation, which may support making sustained-release agents available for treatment initiation.

**Treatment continuation**

Many patients cannot tolerate side effects associated with an initial antidepressant or may fail to respond to it. Given that the goal of therapy is achieving remission, such patients should be switched to other agents. This is well illustrated by an open-label, naturalistic, 9-month trial in which 573 depressed adults were randomly assigned to begin treatment with fluoxetine, paroxetine, or sertraline (Kroenke 2001). The decision to initiate treatment was based on a primary care physician’s judgment that a patient had clinical depression warranting treatment (as opposed to meeting criteria for a diagnosis). If a patient did not respond adequately or tolerate the initial SSRI, the primary care physician was free to switch to a different SSRI or an antidepressant from another class. After 1 month, 13 percent of patients switched to another antidepressant; after 3 months, 23 percent; 6 months, 32 percent; and 9 months, 40 percent. The initial SSRI the patient received at randomization made no difference with respect to discontinuation or switching, and each SSRI had a similar side-effect profile. The percentage of patients who remained on their initial SSRI for the entire 9 months and scored 40 or higher on the 36-item Short-Form Mental Component Summary was 37 percent in the fluoxetine group, 34 percent in the parox...
etine group, and 37 percent in the sertraline group. At the end of the study, 26 percent of the population met the criteria for MDD, compared with 74 percent at baseline and 32 percent at 3 months.

Most patients require therapy of several weeks’ duration to exhibit a full response. At least 8 weeks of treatment should be allowed to elapse before nonresponse to fluoxetine is declared (Quitkin 2003). The American College of Physicians–American Society of Internal Medicine reports that patients who have responded poorly or not at all after 6 weeks of treatment with an adequate dose of an antidepressant are unlikely to benefit from continued treatment at that dose.

Recurrences are common in some forms of unipolar depression, necessitating a continuation or maintenance phase of therapy. Although patients who feel better may have difficulty adhering to continuation therapy, it is important for them to do so because high rates of relapse are observed upon drug discontinuation during maintenance therapy. Patients at relatively higher risk for relapse and recurrence are those with a recurrent course of depression, double depression (cycle between MDD and dysthymic disorder), long duration of the index episode (e.g., >2 years), and residual depressive symptoms (Fava 1994).

The optimal dose for maintenance therapy in depression is the same dose that led to remission of the depressive symptoms (Frank 1993). In a double-blind study of patients whose depression was stabilized with paroxetine 40 mg, the recurrence rate was 51 percent among those who were randomly assigned to paroxetine 20 mg compared with 23 percent among those who continued on paroxetine 40 mg (Franchini 1998). The guidelines of the American College of Physicians–American Society of Internal Medicine for the pharmacologic treatment of acute major depression and dysthymia recommend continuing drug treatment at the same dose for at least 4 months after recovery or improvement (Snow 2000).

Relapse and recurrence occur despite antidepressant treatment in 10 to 30 percent of patients (Fava 1994). To minimize the risk of relapse, depressed patients who achieve symptom remittance must continue therapy for a substantial period of time — a minimum of 4 to 6 months. It has been shown, for example, that at least an additional 26 weeks of fluoxetine treatment is necessary to reduce the risk of relapse following an initial 12-week course of fluoxetine (Reimherr 1998). Depending on the number of recurrences, lifelong prophylactic therapy may be warranted (Montgomery 1996).

Patients who experience a relapse or recurrence during antidepressant treatment may respond to an increase in dose. In a small study (N=18), depressed patients who had recovered on fluoxetine 20 mg and then relapsed were treated with fluoxetine 40 mg, with 67 percent showing a full response and 17 percent showing a partial response (Fava 1995). During follow-up for a mean of 4.7 months, 11 of the 18 patients maintained response. In a larger trial (N=501), patients who responded to fluoxetine 20 mg were randomized to fluoxetine 20 mg daily, fluoxetine 90 mg weekly, or placebo during a 25-week continuation phase (Schmidt 2002). Patients who relapsed during the continuation phase were offered a resumption of fluoxetine 20 mg daily if they had been on placebo, fluoxetine 40 mg daily if they had been on 20 mg daily, and fluoxetine 90 mg twice weekly if they had been on 90 mg once weekly. A total of 57 percent of the 40 mg group and 72 percent of the 90 mg twice-weekly group responded to the dose increase; 35 percent of patients either failed to respond or relapsed after the dose increase.

Switching to another agent also can be an option to treat relapsed or recurrent depression and may result in reduced drug costs, fewer drug-drug interactions, improved adherence, and greater convenience for the patient, as opposed to adding another agent (Marangell 2001). When a patient is switched to another SSRI, it is preferable to base the dose of the new SSRI on that of the original one, instead of subjecting the patient to a washout period that may induce discontinuation effects.

Persistence of symptoms after the end of a depressive episode points to a patient at increased risk for another episode of depression progressing from the residual symptoms (Nierenberg 2003). Long-term drug therapy is recommended for patients at high risk of relapse or recurrence. Augmenting pharmacotherapy with psychotherapy also is effective in reducing the risk of new episodes of depression, as is psychotherapy alone.

Nonadherence to the drug regimen — anything less than 80 to 85 percent of the prescribed medication — should be suspected whenever relapse occurs during the continuation phase of therapy for patients who had achieved full remission (Thase 2003).

**AGENTS FOR ANXIETY DISORDERS**

**General anxiety disorder**

For patients with GAD, SSRIs and SNRIs are supplanting benzodiazepines as first-line treatment (Sramek 2002). GAD is commonly comorbid with depression, and an SSRI often can be effective for both disorders, sparing the patient the need to take a second drug.

**Obsessive-compulsive disorder**

In the treatment of OCD, a combination of drug and cognitive-behavioral therapies (CBT) is the most effective strategy for restoring social functioning, even if complete remission of symptoms is rarely achieved (Jenike 2004). Drug therapy should be initiated before CBT is
added. An SSRI appears to be a better choice than a TCA for initial therapy, but efficacy within the SSRI class seems to be similar. A trial of 10 to 12 weeks (longer than might be employed for MDD) may be necessary, at a higher dose than for MDD. If a patient fails two or three consecutive SSRIs, a trial of clomipramine is warranted.

**Panic disorder**

For treatment of panic disorder with or without agoraphobia, SSRIs have been identified by an international consensus group as the drugs of first choice, used for 12 to 24 months and discontinued over the course of 4 to 6 months (Ballenger 1998). A 10-year longitudinal study

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**TABLE 2 Selected pharmacologic properties of SSRIs and SNRIs**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>% protein-bound</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (hours)</th>
<th>Half-life</th>
<th>Linear pharmacokinetics</th>
<th>Major metabolic pathways; excretion</th>
<th>Possible drug-drug interactions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>80</td>
<td>3–4</td>
<td>35 hours</td>
<td>Yes</td>
<td>3A4, 2C19; renal clearance, 20%</td>
<td>MAO inhibitors</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>56</td>
<td>5</td>
<td>27–32 hours</td>
<td>Yes</td>
<td>3A4, 2C19; renal clearance, 7%</td>
<td>MAO inhibitors</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>94</td>
<td>6–8</td>
<td>1–3 days after acute administration; 4–6 days after chronic administration</td>
<td>No</td>
<td>2D6; primarily urine</td>
<td>MAO inhibitors benzodiazepines NSAIDs/Aspirin thioridazine phenytoin carbamazepine warfarin</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>77</td>
<td>2–8</td>
<td>15 hours</td>
<td>No</td>
<td>Oxidative demethylation and deamination; urine, 94%</td>
<td>MAO inhibitors tacrine metoprolol propranolol</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>95</td>
<td>5.2</td>
<td>20 hours</td>
<td>No</td>
<td>2D6; urine, 64%</td>
<td>MAO inhibitors NSAIDs/Aspirin warfarin tryptophan thioridazine</td>
</tr>
<tr>
<td>Paroxetine (controlled release)</td>
<td>95</td>
<td>6–10</td>
<td>15–20 hours</td>
<td>No</td>
<td>2D6; urine, 64%</td>
<td>MAO inhibitors NSAIDs/Aspirin warfarin tryptophan thioridazine</td>
</tr>
<tr>
<td>Sertraline</td>
<td>98</td>
<td>6–8</td>
<td>26 hours</td>
<td>Yes</td>
<td>3A3/4; urine, 40–45%</td>
<td>MAO inhibitors warfarin</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>27</td>
<td>2</td>
<td>5 hours</td>
<td>Yes</td>
<td>2D6; urine, 87%</td>
<td>MAO inhibitors</td>
</tr>
<tr>
<td>Venlafaxine (extended release)</td>
<td>27</td>
<td>5.5</td>
<td>5 hours</td>
<td>Yes</td>
<td>2D6; urine, 87%</td>
<td>MAO inhibitors</td>
</tr>
</tbody>
</table>

*This listing is not inclusive. Consult product labeling for details.
MAO inhibitor=monoamine oxidase inhibitor; NSAID=nonsteroidal antiinflammatory drug; T<sub>max</sub>=time to maximum (peak) concentration.

SOURCE: MANUFACTURERS’ PACKAGE INSERTS
suggests that SSRIs may be no more effective for panic disorder than common benzodiazepines (Bruce 2003). Still, the SSRIs deserve consideration on the basis of greater safety and tolerability, minimal potential for abuse, and comorbidity with other disorders for which they have been shown to be efficacious (Zamorski 2002). Patients with panic disorder tend to need SSRI dosages that are higher than for other conditions. The starting dose, however, is usually half the dose for depression.

**Posttraumatic stress disorder**

On the basis of their safety and tolerability, SSRIs also are first-line drugs for management of PTSD (Yehuda 2002). If there is no response after an 8-week trial of an SSRI, a consensus group recommends that treatment be switched to venlafaxine or nefazodone. The nefazodone label cautions about liver toxicity, and recommends discontinuance if serum AST or serum ALT reaches 3 times normal.

**Social anxiety disorder**

Paroxetine, sertraline, venlafaxine, and high-potency benzodiazepines are medications of choice among those indicated. Developing an effective treatment plan depends on making a diagnostic distinction between generalized SAD and nongeneralized SAD, as therapeutic options tend to differ (see article by Raj, page 52).

**CHARACTERISTICS OF SPECIFIC SSRIs/SNRIs**

Information about metabolism may be helpful for determining which drug might be more appropriate for patients taking concomitant drugs that may interact with the same metabolic pathways. Table 2 (page 29) lists selected pharmacologic properties of SSRIs and SNRIs; table 3 (page 31) lists their dosing schedules. Concurrent use of SSRIs/SNRIs and MAO inhibitors is contraindicated, but the recommended washout interval between agents varies.

**Fluoxetine**

Fluoxetine (Prozac, Sarafem) was introduced in the United States in 1987. Except for having different trade names and capsule colors, Prozac and Sarafem are identical. Fluoxetine is available as a tablet, capsule (Pulvule), or oral solution for daily use, or as a delayed-release 90 mg capsule for weekly use.

Both fluoxetine and its active metabolite norfluoxetine have extremely long elimination half-lives, persisting in the body for many weeks after discontinuation. Fluoxetine therefore tapers naturally. There should be at least 5 weeks between discontinuation of fluoxetine and initiation of an MAO inhibitor or thioridazine, however.

In clinical trials, the most commonly reported side effects of fluoxetine were nausea (22 percent of subjects given fluoxetine vs. 9 percent of subjects given placebo) and insomnia (19 vs. 10 percent, with fluoxetine and placebo, respectively).2

**Sertraline**

Sertraline (Zoloft) was the second SSRI to enter the U.S. market, earning FDA approval in 1991. It is available as coated tablets or oral concentrate. The concentrate is 12 percent alcohol, so it should not be given to patients using disulfiram (Antabuse).

Sertraline should not be used in combination with an MAO inhibitor, and at least 14 days should elapse between MAO inhibitor discontinuation and sertraline initiation, or vice versa.

As with fluoxetine, nausea was the most frequently reported adverse effect of sertraline (25 vs. 11 percent, with sertraline and placebo, respectively). Insomnia was the next most commonly reported side effect (21 vs. 11 percent, with sertraline and placebo, respectively).

**Paroxetine**

Paroxetine (Paxil) first became available in 1992, and a controlled-release version (Paxil CR) was approved in 1999. The tablets of controlled-release paroxetine contain a polymeric matrix that degrades at a controlled rate over the course of 4 to 5 hours. These tablets also have an enteric coating that delays drug release until the tablet has left the stomach.

Because of the 2D6 metabolism, paroxetine should not be used in combination with thioridazine, which also is metabolized by 2D6. Concurrent use of paroxetine could result in elevated plasma levels of thioridazine, which is associated with an apparently dose-related increase in the QTc interval.

Paroxetine should not be used in combination with an MAO inhibitor. Paroxetine treatment should not be initiated within 14 days of discontinuing an MAO inhibitor, and at least 2 weeks should elapse between discontinuation of paroxetine and initiation of an MAO inhibitor.

When paroxetine treatment is discontinued, the dose should be reduced gradually to reduce the risk of discontinuation symptoms.

The most common side effect of immediate-release paroxetine was nausea (26 vs. 9 percent, with paroxetine and placebo, respectively). Ejaculation disorder (26 vs. 1 percent, with paroxetine and placebo, respectively) was most commonly reported by subjects taking controlled-release paroxetine.

**Venlafaxine**

Venlafaxine (Effexor) was the first SNRI to become

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2 The treatment-emergent side effects reported herein are based on placebo-controlled trials cited on manufacturers’ package inserts. Comparisons shown are versus placebo.
available in the United States, receiving FDA approval in 1993. Extended-release venlafaxine (Effexor XR) was approved in 1997. Release of drug by the extended-release product is controlled by diffusion through the coating membrane and is not pH-dependent.

At least 14 days should pass between discontinuation of an MAO inhibitor and initiation of venlafaxine, and an interval of at least 7 days should separate venlafaxine discontinuation and MAO inhibitor initiation.

In clinical trials, a mean increase in pulse rate of 3 beats per minute was observed among patients receiving venlafaxine, versus no change among patients receiving placebo. In addition, a dose-related increase in diastolic blood pressure was observed. For all doses, the overall mean increases ranged from 0.7 to 2.5 mm Hg, versus decreases of 0.9 to 3.8 mm Hg for placebo. At dosages less

### Table 3

**Dosing and administration of SSRIs and SNRIs**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Products available</th>
<th>Initial dose</th>
<th>Therapeutic dose</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Tablets (10, 20, 40 mg)</td>
<td>MDD: 20 mg</td>
<td>MDD: 40 mg</td>
<td>Once daily, morning or evening, with or without food</td>
</tr>
<tr>
<td></td>
<td>Oral solution (10 mg/5 mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Tablets (5, 10, 20 mg)</td>
<td>MDD: 10 mg</td>
<td>MDD: 10 mg</td>
<td>Once daily, morning or evening, with or without food</td>
</tr>
<tr>
<td></td>
<td>Oral solution (5 mg/5 mL)</td>
<td>GAD: 10 mg</td>
<td>GAD: 10 mg</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Tablets (10 mg)</td>
<td>MDD: 20 mg</td>
<td>MDD: 20–80 mg</td>
<td>Initially, once daily in morning, with or without food</td>
</tr>
<tr>
<td></td>
<td>Capsules (10, 20, 40 mg)</td>
<td>Bulimia: 60 mg</td>
<td>Bulimia: 60 mg</td>
<td>&gt;20 mg, once daily in morning or twice daily (morning and noon)</td>
</tr>
<tr>
<td></td>
<td>Oral solution (20 mg/5 mL)</td>
<td>OCD: 20 mg</td>
<td>OCD: 20–60 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delayed-release capsules (90 mg)</td>
<td>Panic: 10 mg</td>
<td>Panic: 20–60 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMDD: 20 mg</td>
<td>PMDD: 20 mg</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Tablets (25, 50, 100 mg)</td>
<td>OCD: 50 mg</td>
<td>OCD: 50–200 mg</td>
<td>Initially, single dose, at bedtime; &gt;100 mg, divided dose, with larger portion given at bedtime</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Scored tablets (10, 20 mg)</td>
<td>MDD: 20 mg</td>
<td>MDD: 20–50 mg</td>
<td>Single dose, preferably the morning, with or without food</td>
</tr>
<tr>
<td></td>
<td>Tablets (30, 40 mg)</td>
<td>GAD: 20 mg</td>
<td>GAD: 20–60 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral suspension (10 mg/5 mL)</td>
<td>Panic: 10 mg</td>
<td>Panic: 10–60 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTSD: 20 mg</td>
<td>PTSD: 20–40 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAD: 20 mg</td>
<td>SAD: 20 mg</td>
<td></td>
</tr>
<tr>
<td>Paroxetine (controlled release)</td>
<td>Coated tablets (12.5, 25.0, 37.5 mg)</td>
<td>MDD: 25.0 mg</td>
<td>MDD: 25.0—62.5 mg</td>
<td>Single dose, preferably the morning, with or without food</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panic: 12.5 mg</td>
<td>Panic: 12.5–75.0 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMDD: 12.5 mg</td>
<td>PMDD: 12.5–25.0 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAD: 12.5 mg</td>
<td>SAD: 12.5–37.5 mg</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Scored tablets (25, 50, 100 mg)</td>
<td>MDD: 50 mg</td>
<td>50–200 mg</td>
<td>Once daily, morning or evening, with or without food</td>
</tr>
<tr>
<td></td>
<td>Coated tablets (25, 50, 100 mg)</td>
<td>OCD: 50 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral concentration (20 mg/mL)</td>
<td>Panic: 25 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTSD: 25 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAD: 25 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Tablets (25.0, 37.5, 50.0, 75.0, 100.0 mg)</td>
<td>MDD: 75 mg</td>
<td>75–375 mg</td>
<td>Two or three divided doses, with food</td>
</tr>
<tr>
<td>Venlafaxine (extended release)</td>
<td>Capsules (37.5, 75.0 mg)</td>
<td>MDD: 75 mg</td>
<td>MDD: 75–375 mg</td>
<td>Single dose, with food, morning or evening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAD: 37.5–75.0 mg</td>
<td>GAD: 37.5–75.0 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OCD: 37.5–75.0 mg</td>
<td>OCD: 75–225 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMDD: 37.5–75.0 mg</td>
<td>PMDD: 75–225 mg</td>
<td></td>
</tr>
</tbody>
</table>

GAD = generalized anxiety disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder.

SOURCE: MANUFACTURERS’ PACKAGE INSERTS
than 100 mg a day, the incidence of a sustained elevation in supine diastolic blood pressure was 3 percent (placebo, 2 percent); 101 to 200 mg a day, 5 percent; 201 to 300 mg a day, 7 percent; more than 300 mg a day, 13 percent. Regular monitoring of blood pressure thus is advised for patients receiving venlafaxine.

When venlafaxine is discontinued, if patients have received more than 1 week of treatment, the dose should be tapered to reduce the risk of discontinuation symptoms. If the treatment period exceeds 6 weeks, the dose should be tapered gradually over the course of 2 weeks.

Nausea was the most prevalent adverse effect of both the immediate- and extended-release forms of venlafaxine (37 vs. 11 percent and 31 vs. 12 percent, with venlafaxine and placebo, respectively).

### Fluvoxamine

Fluvoxamine (Luvox) was the first SSRI to receive an indication for OCD. Although it lacks an FDA-approved indication for MDD, fluvoxamine often is used to treat depression, much as other SSRIs commonly are used without regard to their official indications.

Unlike other SSRIs, which may be given as a single dose, it is advised that fluvoxamine doses exceeding 100 mg be given in two divided doses, with the larger dose (if applicable) being given at bedtime.

Two weeks should be allowed to elapse between the discontinuation of an MAO inhibitor and the initiation of fluvoxamine, and vice versa.

The most commonly reported adverse effects with fluvoxamine were nausea (40 vs. 14 percent, with fluvoxamine and placebo, respectively) and somnolence (22 vs. 8 percent with fluvoxamine and placebo, respectively).

### Citalopram

Citalopram (Celexa) is a racemic mixture, containing the R- and S-enantiomers in equal proportion. The S-enantiomer is responsible for most of citalopram’s inhibition of serotonin reuptake.3

MAO inhibitors should not be administered with citalopram or escitalopram, and at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of citalopram or escitalopram therapy, and vice versa.

The most common side effects of citalopram are nausea (21 vs. 14 percent, with citalopram and placebo, respectively) and dry mouth (20 vs. 14 percent, with citalopram and placebo, respectively).

### Escitalopram

Escitalopram (Lexapro) was the last SSRI to receive FDA approval, in 2002. As its generic name suggests, escitalopram consists entirely of the therapeutically active S-enantiomer of citalopram. One consequence of isolating the active isomer is that escitalopram is more potent than citalopram, with 10 mg of escitalopram being the equivalent of about 40 mg of citalopram. Escitalopram 10 mg has been shown to be as efficacious as citalopram 40 mg in the treatment of MDD (Burke 2002). In another study, a greater percentage of moderately to severely depressed patients responded to treatment with escitalopram than did those receiving citalopram (P=.021) (Lepola 2003). Escitalopram, along with citalopram, has been shown to be efficacious in the treatment of panic disorder (Stahl 2003), but neither agent has yet received such an indication.

Escitalopram offers a side-effect profile that is similar to citalopram (Lepola 2003, Burke 2002).

In fixed-dose trials, the incidence rate of some adverse events increased in a dose-related fashion. For example, insomnia was reported in 7 percent of patients receiving escitalopram 10 mg but 14 percent of those receiving escitalopram 20 mg; diarrhea, 6 and 14 percent; dry mouth, 4 and 9 percent; somnolence, 4 and 9 percent; dizziness, 4 and 7 percent, respectively.

### SUMMARY

The SSRIs and SNRIs are used commonly for treating mood and anxiety disorders. They are effective when used properly; proper use entails providing a patient with an adequate dose for an adequate period of time before deciding that an agent is ineffective. No evidence favors one SSRI or SNRI over another as initial therapy for a given anxiety or mood disorder. Physicians and patients should be free to begin treatment with any SSRI or SNRI deemed appropriate and to switch to another SSRI or SNRI whenever necessary.

### REFERENCES


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3 Enantiomers, or stereoisomers, are mirror images of molecules with the same molecular formula. R (from the Latin rectus) indicates the right-handed version, S (from the Latin sinister), the left. Because they have different spatial configurations, R- and S-enantiomers may have very different pharmacologic properties.


Pharmacoeconomic Evaluation Of Antidepressant Therapies
MATTHEW W. SARNES, PHARMD,1 AND LAURA E. FRANKUM, PHARMD2
Applied Health Outcomes

SUMMARY
With today’s emphasis in the managed care environment on evidentiary literature, new antidepressants must provide economic evidence of their value compared with previously available agents. Various pharmacoeconomic models have shown newer antidepressant agents to be cost-effective relative to older agents. The authors review methodologies and published results.

Since its inception in the early 1980s, pharmacoeconomics as an industry and a science has evolved and flourished. Pharmacoeconomics traditionally focused solely on evaluating the economic impact of pharmaceutical products to the health care system; however, it has matured into a discipline that compares the clinical and economic outcomes associated with various pharmacotherapies against the inherent costs of providing those therapies. The goal of these types of assessments is to determine if the value derived from a pharmaceutical agent justifies its acquisition and administration costs and the costs that are associated with potential side effects. In addition, pharmacoeconomic analyses provide health care decision makers with data to help them determine the value of a pharmaceutical agent versus another.

Drug-acquisition costs and the vast number of drug products that are associated with depression have made antidepressant pharmacoeconomic data paramount to formulary committees. Pharmacoeconomic literature regarding depression management during the past 2 decades has focused primarily on three questions: Are neurotransmitter receptor-specific antidepressants cost-effective alternatives to older agents? Are there differences in clinical and economic outcomes between newer antidepressants? Does compliance with guidelines regarding recommended length of antidepressant therapy translate into beneficial economic outcomes?

Five distinct methodologies (randomized clinical trials, prospective naturalistic inquiries, meta-analyses, decision analytic models, and retrospective database analyses) have been employed to answer these questions. Each of these study designs has a role in the assessment process. In fact, several studies using various methodologies typically are needed at different points during a pharmaceutical product’s life cycle to assess its value. Herein, each methodology will be described, inherent strengths and weakness will be considered, and relevant examples from the literature will be presented.

RANDOMIZED CLINICAL TRIALS
Randomized clinical trials (RCTs) with an economic component often are considered the gold standard of pharmacoeconomic analyses by clinicians. Random as-
Assignment of interventions to samples of demographically similar populations inherently controls for known and unknown confounding variables. In addition, patient and investigator blinding in these studies minimizes potential biases. Conclusions from RCTs may provide the strongest evidence for causality, as temporality is certain and internal validity is maximized. Nevertheless, internal validity often is achieved at the expense of external validity (ability to generalize to a broader population), an inherent limitation of RCTs (Frank 2001). In addition, RCTs are, by design, time and resource-consuming, thus restricting their usage.

Data from RCTs assessing the economic impact of antidepressant comparators generally are limited, and review articles have reported that the available data lack conclusive evidence (Skaer 2000). Hosak (2000) conducted a prospective, open, intent-to-treat trial assessing the cost and efficacy of antidepressants in the Czech Republic. This analysis was a continuation of an RCT assessing the efficacy and tolerability of amitriptyline, citalopram, and fluoxetine in hospitalized patients. In this analysis, clinical and economic endpoints for patients following hospital discharge were collected via questionnaires. The questionnaires were sent to outpatient psychiatrists, who reported utilization of psychotropic medications, outpatient visits, and rehospitalizations. At the conclusion of the study, the investigators found no significant differences in efficacy, defined as the number of hospitalization-free days, between the treatment groups. In addition, while drug-acquisition costs were higher for the selective serotonin reuptake inhibitors (SSRIs), total medical costs were not significantly different between the three treatment arms (Table 1). The authors concluded that there is no advantage in restricting the use of SSRIs, based on their comparable cost and superior safety and tolerability profile.

In addition to assessing pharmacoeconomic differences between newer and older antidepressant therapies, RCT designs have been used to evaluate clinical and economic differences between SSRIs. Boyer (1998) conducted a double-blind, randomized trial of 231 patients initiating antidepressant therapy with sertraline and fluoxetine within primary care clinics in France. Outcomes were assessed at 4 and 6 months, using the Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impressions (CGI) severity scores for clinical outcomes, and the Functional Status Questionnaire (FSQ) for quality-of-life measures. Direct costs, from a third-party payer perspective, were determined from medical-service use. Indirect costs, from the societal perspective, were determined from work absence and productivity loss. Significant clinical and quality-of-life improvements were observed in both groups compared to baseline, but there were no between-group differences. Fluoxetine patients utilized more medical resources and incurred more costs from the societal and third-party payer perspectives (Table 2); the statistical significance of cost difference was not reported, however. The validity of this trial was questioned subsequently, as antidepressant therapy costs were not considered and two patients from the sertraline group who attempted suicide were excluded (Frank 2001).

### PROSPECTIVE NATURALISTIC INQUIRIES

As mentioned previously, RCTs apply strict inclusion and exclusion criteria to their sample population to best determine a causal relationship between a pharmaceutical intervention and the outcomes of interest. Demonstration of such a causal relationship establishes the efficacy of the studied pharmaceutical interventions. While RCT designs are a necessary first step in determining the value of an intervention, patients in RCTs often have little comorbidity, are not taking medications that could influence outcomes.

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Fluoxetine</th>
<th>Sertraline</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean decrease in MADRS score</td>
<td>17.9</td>
<td>17.9</td>
<td>NS</td>
</tr>
<tr>
<td>Third party payer costs*</td>
<td>$585</td>
<td>$585</td>
<td>NR</td>
</tr>
<tr>
<td>Societal costs*</td>
<td>$1,551</td>
<td>$1,551</td>
<td>NR</td>
</tr>
</tbody>
</table>

MADRS=Montgomery-Asberg Depression Rating Scale; NS=not significant; NR=not reported.

*Originally reported in French francs but converted here to nearest whole U.S. dollar. At the time of the study, 1.00 FF=U.S. $0.1993.

SOURCE: BOYER 1998
COST-EFFECTIVENESS

Meta-analyses when there are many small studies regarding a parallel designed trials. This technique is particularly used to investigate some of these hypotheses by quantitatively not designed to investigate. Meta-analyses provide a way to analyze additional related hypotheses that the original trial was not designed to answer a specific research question or set of research questions. Often, the results or trends observed in these trials can be used to generate new hypotheses or to modify existing hypotheses. Meta-analyses provide a way to investigate some of these hypotheses by quantitatively and systematically aggregating results from several similarly designed trials. This technique is particularly useful when there are many small studies regarding a particular topic or when the results of the available studies are heterogeneous.

The most rigorous method of conducting a meta-analysis is to aggregate the raw data from the individual trials of interest, but these data sets typically are difficult to obtain. Therefore, investigators most often use data available from published literature. These data may be subject to publication bias, as results are published selectively; therefore, conclusions drawn from these types of meta-analysis must be thoroughly evaluated. In addition, the results of meta-analyses are limited by the level of external validity provided by the studies employed in the meta-analysis.

To our knowledge, meta-analyses assessing economic endpoints in depression have not been conducted in the area of depression. It is likely that this is due to the limited amount of pharmacoeconomic RCT and prospective naturalistic inquiry data available to generate such an analysis. Nonetheless, meta-analyses have been conducted regarding clinical outcomes, particularly with respect to discontinuation rates due to adverse events. Four meta-analyses have concluded that significantly fewer patients discontinue SSRIs resulting from adverse events as compared with placebo or TCA (Montgomery 1994, 1995; Anderson 1995). These results have been used to fuel the debate about selection of a cost-effective antidepressant pharmacotherapy. Arguably, lower discontinuation rates due to adverse events observed with SSRIs should translate to a cost benefit; the validity of the results ascertained in the aforementioned analyses has been questioned, however (Gallo 1999, Hotopf 1996, Freemantle 2000).

DECISION ANALYTIC MODELS

Because economic data often are not collected in clinical trials, decision analytic models provide a technique to estimate the cost impact of the clinical outcomes associated with new antidepressant therapies. In addition, modeling may be used to estimate and compare the cost-effectiveness of two or more antidepressants that have not been studied in a head-to-head clinical trial or evaluated in a naturalistic setting. These models are constructed by populating decision trees or mathematically based computer simulators (e.g., Markov models) with event data from clinical trials and real-world cost data. An advantage of this design is that it allows researchers to simulate different treatment patterns (e.g., switching therapies, dose titration), identify cost and outcome drivers, and extrapolate data to time frames that are not practical in clinical trials. When evaluating a decision analytic model, it is important for the user to determine whether the construct, assumptions, and time frame are relevant to their environment.
The construct of a model typically depends on which perspective is taken when developing the model. The societal perspective is the most inclusive one and attempts to assess all costs (both direct and indirect) associated with an intervention or disease state. Models that include only direct health care costs or only indirect health care costs, however, such as productivity losses, may be more useful in assessing outcomes from the standpoint of the insurance payer or employer.

Once it is determined that the construct is relevant to the user’s health care environment, it is essential to evaluate the validity of the inputs and critical assumptions used in the model. The impact of the uncertainty of any of the inputs in models can be assessed for robustness using a sensitivity analysis, which accompanies most decision analytic models. Finally, the user must assess whether the time frame is appropriate for the disease state, treatment pattern, and the environment to which results are extrapolated.

Several decision analytic model analyses have been conducted with an objective of determining if the higher drug-acquisition costs of SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) compared with TCAs are offset by their superior tolerability profile (Frank 2001). The majority of these models have used the payer perspective to test this hypothesis; a couple of models have also taken a societal or semisocietal perspective by including indirect costs, however. Regardless of the perspective, most of these modeling exercises have concluded that SSRIs and/or SNRIs are a more cost-effective alternative than TCAs. Building on this body of evidence, the Canadian Coordinating Office for Health Technology considered possible sequences of antidepressant therapies, a technique allowed by modeling. Researchers determined that initiation of therapy with an SSRI and subsequently switching to a TCA in the event of intolerance or poor response is a more cost-effective sequence than the reversed sequence or a TCA alone, indicating that the use of SSRIs as first-line agents is warranted (CCOHTA 1997).

Modeling also has been used to evaluate the effect of increasing the length of antidepressant therapy, consistent with national guidelines. In a decision analysis conducted by Nuijten (2001), patients were initiated on SSRI therapy and subsequently went into remission (while remaining on an SSRI, switching to a TCA, or discontinuing antidepressant therapy), were switched to a TCA, or were hospitalized for severe depression. Outcome probabilities were derived from the literature. Clinical endpoints were time without depression (TWD) from the third-party payer perspective and quality-adjusted life years (QALYs) from the societal perspective. The economic endpoints were direct medical costs and costs resulting from lost productivity, which was based on number of lost working days. At 9 months, patients who went into remission and discontinued antidepressant therapy had substantially more TWD and no increase in the number of QALYs. In addition, this group incurred fewer costs and hence dominated (less costly and more effective) all other treatment patterns. When maintenance treatment with antidepressant therapy was continued for 21 months, costs decreased, TWD increased, and QALYs did not change. Therefore, continuation of therapy extending beyond 9 months to a minimum of 21 months, in accordance with guidelines, was determined to be cost effective (Table 3).

The results described in Table 3 stem from decision analytic models designed to simulate head-to-head comparisons between antidepressant therapies in a naturalistic setting. Although the structured process and flexibility make decision analytic modeling a valuable tool for estimating the cost-effectiveness of various therapies, their representation of actual clinical practice is only as good as the assumptions and inputs used to populate the

| TABLE 3 | Cost, efficacy, and quality-of-life outcomes at 9 and 21 months |
|----------|
| **Months without depression** |
| **QALYs** |
| **Direct costs** | **Lost productivity** | **Total costs** | **QALYs** |
| **9 months** | | | |
| Termination group* | $474 | $909 | $1,383 | 7.78 | 0.61 |
| Prolongation group† | $1,276 | $304 | $1,580 | 8.72 | 0.60 |
| **21 months** | | | | |
| Termination group | $4,681 | $4,282 | $8,963 | 14.92 | 1.31 |
| Prolongation group | $3,831 | $1,512 | $5,343 | 17.09 | 1.31 |

QALYs=quality-adjusted life years. *Termination group: patients who went into remission and discontinued pharmacologic therapy. †Prolongation group: patients who went into remission and continued with their index selective serotonin reuptake inhibitor.

SOURCE: NUIJTEN 2001

model. Because most clinical inputs used in these cost-effectiveness models are based on clinical trial data, a significant role has emerged for retrospective database analysis to assess the economic effect of antidepressants in a real-world environment.

RETROSPECTIVE DATABASE ANALYSES

In an effort to overcome the external validity quandary of the aforementioned study designs, retrospective database analyses draw upon population-based information obtained from large claims databases (federal, state, or private insurers) to provide real-world data. This study design affords large sample sizes, the targeting of a highly specific population, and the capture of both resource utilization and patient characteristics. Although this method provides valuable information regarding utilization in a naturalistic setting, it does not offer the validity and bias protection afforded by RCTs. Despite its nonexperimental design and limited internal validity, retrospective database analyses offer insight into actual clinical practice and its associated resource utilization and cost.

Several retrospective database analyses have established that patients treated with SSRIs are more likely to be treated at an appropriate dose and duration than those treated with TCAs. It was hypothesized that inappropriate doses and durations of therapy lead to poorer clinical outcomes with an economic impact. McCombs (1990) identified and quantified the economic consequences of subtherapeutic treatment in a retrospective database analysis. Patients who were not treated with a TCA at a minimum therapeutic dose for 6 months or more incurred an additional $1,000 per patient in the first year of depression treatment as compared with those patients treated at the clinically recommended dose and duration. In addition, a series of retrospective database analyses in network-model HMOs have established that patients prescribed an SSRI, irrespective of dose, incur significantly fewer health care expenditures relative to those prescribed a TCA ($5,143 vs. $7,858). Similar results were seen in a recent study conducted by Eaddy (2004), which used an analysis comparable to Thompson’s to determine if the relationship between length of therapy and health care expenditures is similar in the current managed care environment. As with Thompson’s findings, patients changing or augmenting antidepressant pharmacotherapy incurred the highest total medical costs ($7,858). The lowest total medical costs were incurred by patients remaining on therapy for at least 90 days ($5,143) (Figure 1).

COST-EFFECTIVENESS

Evidence-based guidelines recommend pharmacotherapy lasting a minimum of 90 days for acute management of depression and extension to a minimum of 180 days for continuation therapy to achieve optimal outcomes (APA 2000). Thompson (1996) assessed the economic consequences of compliance with these recommendations in a retrospective database analysis of patients initiating therapy for depression with an SSRI. This analysis classified patients into one of five patterns of antidepressant-use cohorts: 1) early discontinuation, 2) switching/augmentation, 3) upward titration, 4) partial compliance, and 5) 3-month use (Figure 1). Patients who switched therapies or augmented their pharmacotherapy with another agent incurred the highest total medical costs ($7,590). The lowest costs were observed in patients continuing their use of antidepressant therapy for a minimum of 3 months ($3,393). Similar results were seen in a recent study conducted by Eaddy (2004), which used an analysis comparable to Thompson’s to determine if the relationship between length of therapy and health care expenditures is similar in the current managed care environment. As with Thompson’s findings, patients changing or augmenting antidepressant pharmacotherapy incurred the highest total medical costs ($7,858). The lowest total medical costs were incurred by patients remaining on therapy for at least 90 days ($5,143) (Figure 1).

While the substantial economic implications of switching antidepressant pharmacotherapies have been defined, clinical predictors of switching agents also have been assessed in retrospective database analyses. Sclar (1998) showed that patients initiating therapy with a TCA were 3 to 4 times more likely to switch agents compared with patients initiating therapy with an SSRI. As

expected, patients in the TCA cohort accrued higher health care expenditures than patients in the SSRI cohort. Russell (1999) conducted a similar analysis comparing three SSRIs: fluoxetine, immediate-release paroxetine, and sertraline. Patients beginning therapy with fluoxetine were the least likely to switch antidepressant agents ($P=.001$) compared with patients initiating immediate-release paroxetine or sertraline therapy. In contrast to previous results, total health care expenditures did not differ significantly between the groups even though the rate of switching within the treatment groups differed.

As evidenced by Thompson (1996) and Eaddy (2004), increasing length of antidepressant therapy to a duration consistent with national clinical guidelines translates to a reduction in total health care expenditures. With that premise in mind, researchers investigated whether there were differences in length of therapy based on the individual antidepressant that was prescribed for new antidepressant cases (APA 2000, Thompson 1996, Eaddy 2004). Russell (1999) and Crown (2001) compared the durations of therapy for patients initiating therapy with sertraline, immediate-release paroxetine, and fluoxetine and examined the costs incurred by patients in each group. In both analyses, patients initiated on fluoxetine were more likely to achieve treatment durations consistent with recommendations (Russell $P<.001$; Crown $P<.05$) as compared with patients initiated on sertraline or immediate-release paroxetine. Significant differences in costs were not observed between patients in the three groups. In a similar analysis, Polsky (2002) determined that patients initiated on therapy with fluoxetine experienced an interruption in treatment (defined as a 30-day lapse in prescriptions) significantly later than patients initiated on sertraline or immediate-release paroxetine. Interruption of therapy was not shown to be related to health care costs.

Eaddy (2003) expanded on these analyses by using survival analysis to compare the time to discontinuation for each of the available SSRIs on the market at the time of their analysis. Patients who received one of the immediate-release SSRIs or controlled-release paroxetine between April 1, 2002, and Dec. 31, 2002, were identified in a large commercial managed care database. Patients were required to have 6 months of enrollment data before their index date, defined as the date of the first SSRI prescription, without evidence of antidepressant therapy. Only patients experiencing new therapy with SSRIs were included in the study.

All prescriptions were given a starting date (when the prescription was filled) and ending date (corresponding to the starting date of the prescription plus the number of days for which medication was supplied). Patients were deemed to have discontinued therapy when more than 15 days elapsed between prescriptions. A patient’s time to discontinuation was calculated from the index date to the ending date of the last prescription prior to the 15-day gap. Patients receiving controlled-release paroxetine were less likely to discontinue therapy when compared with those receiving each immediate-release SSRI ($P<.0001$). Patients who received fluoxetine were least likely of all those receiving immediate-release SSRIs to discontinue therapy, while patients receiving immediate-release paroxetine were most likely to discontinue.

Building on these findings, Sheehan (2004) investigated the economic consequences associated with early discontinuation by comparing patients on immediate-release paroxetine with patients receiving controlled-release paroxetine. A total of 3,500 patients initiating therapy with paroxetine immediate- or controlled-release were included in this analysis and stratified into two groups, those with and without a diagnosis for an approved indication for their study agent. After controlling for age, gender, mental health diagnoses, presence of mental health specialty care, and Charlson comorbidity scores, the risk of early treatment discontinuation was assessed. Controlled-release paroxetine reduced the risk of
early treatment discontinuation by 40 percent in the indication-specific analysis (Figure 2, page 39) and by 35 percent in the analysis independent of indication.

An examination of expenditures in this analysis revealed that patients initiating therapy with paroxetine immediate-release incurred significantly higher costs than those initiating therapy with paroxetine controlled-release (Table 4) in both the indication-specific and non-indication analyses. Antidepressant-related pharmacy expenditures were higher in the controlled-release paroxetine cohort; differences in medical costs offset this increase by $59 to $109, however.

Discontinuation of antidepressant pharmacotherapy before the recommended length of therapy has been shown to be associated with an increased risk of relapse or recurrence in several retrospective database analyses (Sood 2000, Melfi 1998, Croghan 1998). In addition, patients remaining on their index SSRI for at least 120 days at a consistent dose were shown to be least likely to experience a relapse or recurrence relative to other pattern of use groups (Claxton 2000).

CONCLUSIONS

Five pharmacoeconomic study designs have been presented, inherent strengths and weaknesses considered, and depression-specific examples have been provided. Overall, three general conclusions may be drawn from the results presented herein:

- RCTs and prospective naturalistic inquiries have shown newer and older antidepressant agents to be approximately equal in terms of efficacy. A series of decision analytic models have employed these clinical data and shown newer agents (SSRIs and SNRIs) to be cost-effective relative to older agents.
- Cost-effectiveness data regarding the individual newer antidepressants are limited and not as clear. Nonetheless, there is a growing body of literature defining the clinical and economic differences between these agents.
- Multiple retrospective database analyses have shown an economic benefit associated with adherence to clinical guidelines regarding the length of antidepressant therapy.

As evidence-based medicine evolves, the importance of pharmacoeconomic data increases. The prudent practitioner will strive to understand pharmacoeconomic methodologies, each study design’s role in the pharmaceutical product’s life cycle, and the relevant literature relating to the specific area of practice. The knowledge gained through the study of pharmacoeconomics is pivotal in formulary decision making.

REFERENCES


Nonadherence with antidepressant medications is a well-documented factor in treatment failure. This article uses the literature to build a collaborative counseling model to increase antidepressant adherence. Studies may be warranted to determine whether specific antidepressants, when used as part of a collaborative strategy, can improve long-term adherence rates.

Nonadherence can be defined as deviating from a prescribed course of treatment and can include not filling a prescription, premature discontinuance of a regimen, dosing errors, and/or self-initiated changes. Up to 20 percent of patients do not fill an initial prescription (Burns 1992). Estimates of noncompliance for all medical conditions range from 20 to 80 percent of the population, leading to subtherapeutic benefit (Dunbar-Jacob 1995) and costing more than $100 billion annually, because of increased medical and other costs (Grahl 1994).

Antidepressant medication is a critical component in the effective treatment of patients with depression. Clinical guidelines for the treatment of depression recommend the continuation of antidepressant medication for 4 to 9 months after the resolution of depressive symptoms (AHCPR 1993, Schulberg 1998). Nevertheless, premature discontinuation can reach as high as 44 percent as soon as 3 months after initiation of antidepressant treatment (Katon 1995). By contrast, the average nonadherence rate across conditions is nearly 25 percent (DiMatteo 2004).

Adherence interventions have occurred in a context of lacking clear specific guidelines that are generated by scientifically validated studies that are designed to show which approaches are most effective in ensuring adherence. A number of theoretical approaches to adherence are discussed in the literature, including the biomedical model, social learning theory, operant conditioning, rational belief approaches, and communication and self-regulation theory (Leventhal 1987). Although these models have utility for researchers, they often are difficult to convert into concrete, brief interventions that practitioners can use. This article reviews the adherence literature and looks at how it relates specifically to antidepressant medication, and suggests brief interventions that have empirical support and can be effective for increasing adherence with drug therapies for depression.

**ADHERENCE COUNSELING MODEL**

The adherence counseling model developed herein integrates counseling theory with specific interventions that have some research support for facilitating adherence. The adherence model does not address cost and access to medication, although these can be barriers to adherence. These policy issues need to be addressed on a health care system level. Individual practitioners at least should assess inability to pay for medications as a potential barrier, however, and should attempt to resolve these issues by referral to appropriate human service agencies.
The culture of health care delivery has evolved from an active-passive model to a shared decision-making style preferred by most patients and leading to patients’ satisfaction with their health care (Bertakis 1991). These philosophical shifts in health care delivery have been paralleled by activism among consumers. Many consumers feel empowered, owing to an explosion in the amount of health care information that has become available from varied sources. This change makes it all the more important for clinicians to hone their communication skills, especially if miscommunication fosters nonadherence.

The basics of good communication skills include involving the patient, addressing patient concerns, offering options and explanations, and periodically checking for understanding. Involvement of the patient should also include eliciting the patient’s perspective, which extends to determining how much the patient desires to participate in decision making; assessing the patient’s perception of the disease and its treatment; and encouraging the patient to express concerns about regimens. Treatment options should be discussed and information tailored to the concerns of the patient (Maguire 2002).

This assessment and information sharing occurs within the context of a professional relationship. The primacy of relationship has become less of a focus in the time-constrained “business” of medicine. Encouraging active engagement in the therapeutic process has been a hallmark of psychotherapeutic treatment but has been lost to an occasional overemphasis on technological advances in medicine. Too often, practitioners view medication from their perspective of specialized medical training and fail to understand the patient’s unique appropriation of subjective meaning to the medication-taking process (Conrad 1985). In its simplest form, adherence counseling involves understanding the patient’s unique and sometimes idiosyncratic perspective and then attempting to modify the perspective to align beliefs, feelings, and behaviors more favorably with effective medication-taking behavior. Problems related to effective communication of information to patients, patients’ understanding of information, and the lack of collaboration between practitioner and patient have been found to lead to poor adherence (DiMatteo 1994). Within this context, an essential first step in the adherence counseling process is the demonstration of active empathy, nonjudgmental acceptance, and genuine understanding of the illness from the patient’s perspective. Numerous studies concerning positive behavioral change in counseling have documented the critical importance of the presence of these practitioner qualities (Krupnick 1996).

Health beliefs
Nonadherence to drug regimens has been related to patients feeling stigmatized by their illness and experiencing threats to their self-reliance (Conrad 1985). The first step in adherence counseling is to explain the neurobiological basis of depression, so that the patient can perceive depression as a medical condition and not a function of weak character or a flawed personality. Medication-taking can then be reframed as an action by the patient that enables him or her to take control of the illness by compensating for the biochemical deficit in naturally occurring mood-altering substances. Then specific health beliefs can be addressed.

The health belief model has been demonstrated to be useful in facilitating medication adherence. The patient’s

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Adherence counseling model</th>
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<tbody>
<tr>
<td>1. Establish therapeutic alliance with patient.</td>
<td></td>
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<tr>
<td>2. Destigmatize the illness.</td>
<td></td>
</tr>
<tr>
<td>3. Encourage and explain positive health beliefs regarding depression.</td>
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<tr>
<td>4. Encourage and explain the positive perception of benefits outweighing barriers regarding medication taking.</td>
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<tr>
<td>5. Dispel and dispute irrational health beliefs regarding disease state and medication.</td>
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<tr>
<td>6. Use behavioral interventions to tailor the regimen or choice of medicine and dosage form to the lifestyle of the patient and reduce the impact of side effects.</td>
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<tr>
<td>7. Use collaborative agreements and relationships with pharmacists and psychotherapists to continually monitor and evaluate adherence.</td>
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</table>
cognitive representation of the illness may be at variance with the provider’s perspective and play a significant role in nonadherence (Scott 2002). The health belief model hypothesizes that the probability that a patient will adhere to a therapeutic regimen is a function of the perceived susceptibility to negative consequences of an illness, as well as being a function of the perceived value of adherence to a regimen versus barriers and costs (including side effects, inconvenience, and the stigma associated with an illness) (Becker 1975). The model argues that adherent patients will accept fully that they have the illness of depression, will understand the negative emotional and physical consequences, and will recognize the value of the benefits of antidepressant medications relative to any barriers. In practice, this means the patient must understand the illness and how the medication compensates for the illness, and the patient must make a rational calculus that the benefits of taking the medication outweigh any inconveniences or costs.

Once the stigma of the illness has been resolved and an understanding of the illness communicated, specific information regarding side effects and patient measures to control or ameliorate them should be the focus of counseling. Some physicians selectively provide patients with information about the side effects that might be encountered with a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI), believing that imparting the knowledge itself may engender reports of side effects, real or not, from patients. One study, however, showed that 55 percent of patients receiving an SSRI may experience at least one adverse side effect described as “a lot” or “extremely” bothersome (Bull 2002). In the interest of increasing the likelihood that patients will adhere to therapy, a complete discussion of a drug’s side-effect profile may be warranted when treatment options are presented. Such a discussion should encompass not only the potential side effects, but also strategies for managing them. In counseling patients about potential side effects of an antidepressant medication, the practitioner should also determine whether the patient already experiences these problems so they are not erroneously ascribed to the medication (Rollman 1997). Along with patients’ favorable attitudes toward antidepressant therapy, patients’ confidence in managing the side effects of drug therapy is a statistically significant predictor of adherence to long-term (up to 12 months) therapy (Lin 2003).

Both encouraging the patient’s belief in the value of the regimen and addressing the patient’s concerns about the therapy will enhance adherence (DiMatteo 1993). Finally, the choice of antidepressant should involve a side-effect profile that addresses the needs, desires, and lifestyle of the patient.

### TABLE 2 Patient beliefs that contribute to nonadherence

<table>
<thead>
<tr>
<th>Belief</th>
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<tbody>
<tr>
<td>Medication is addicting.</td>
</tr>
<tr>
<td>Medication is a crutch.</td>
</tr>
<tr>
<td>Medication is only needed occasionally when I am really depressed.</td>
</tr>
<tr>
<td>I will be unable to tolerate the side effects.</td>
</tr>
<tr>
<td>I will never be able to discontinue the medication.</td>
</tr>
<tr>
<td>If I don’t feel well immediately, the medication isn’t working.</td>
</tr>
<tr>
<td>The medicine cannot solve my problems.</td>
</tr>
<tr>
<td>Medication will make me tired all the time.</td>
</tr>
</tbody>
</table>

The second stage in addressing health beliefs is to assess and then educate patients regarding dysfunctional perceptions of medication. These underlying beliefs will vary for each patient. Many of these dysfunctional beliefs for antidepressant medication have been catalogued (Beck 1979). They are summarized in Table 2.

Many of these beliefs can be addressed after soliciting the patient’s feelings regarding the taking of medication. For example, the lag time between the initiation of an SSRI or SNRI and therapeutic effect should be addressed routinely, because patients expecting immediate symptomatic relief may conclude mistakenly that the medication is ineffective. Other patient beliefs should be addressed in a respectful but matter-of-fact discussion about the medication. For example, the belief that medication is a crutch can be reframed by explaining that concentration deficits and low energy are core symptoms of depression and can be helped by medication, thus freeing the patient to take the measures necessary to recover. Medication can be explained as offering enough “biological comfort and freedom from symptoms” to help the patient make changes that he or she feels are necessary. The existence of these negative beliefs and the specific refutation of these beliefs will vary with each patient.

### Cueing and monitoring

Once positive beliefs have been encouraged and negative beliefs are brought to light, the mechanics of adherence can be addressed. A simple explanation of the dosing regimen will not ensure adherence, because forgetfulness can be a contributory factor in nonadherence. For antidepressant medication, according to one study, 72 percent of physicians reported telling patients to take an SSRI for at least 6 months, while only 34 percent of the patients recalled receiving that information. The authors stated that patients’ forgetfulness could account for at least part of the communication gap, thus emphasizing the need for periodic reinforcement of instructions (Bull 2002). It is worthy of note, however, that
in relying on their own memories, physicians may also have overstated the rate at which they provided patients with information.

The most effective behavioral techniques to ensure adherence are cueing and monitoring. Attaining stimulus control through cueing can be accomplished by pairing a dosing regimen with naturally occurring rituals in the patient’s life. Establishing recurrent cues for medication taking in the patient’s environment has been found to be associated with increased adherence (Haynes 1976, Logan 1979). Associating medication taking with meals and other routine activities, as well as enlisting family members for periodic reminders or using medication organizers with slots for days and times, can be simple low-cost techniques to cue memory.

Monitoring and reinforcing medication adherence once medication is initiated can be especially effective. It has been shown that physician and pharmacist monitoring of patient response increased both patient satisfaction and adherence with antidepressant medication (Bull 2002, Bultman 2002). Physician follow-up of three or more visits increased adherence, and pharmacist problem-solving and support with medication problems after initiation of therapy were associated with better adherence for first-time users. Follow-up monitoring reminds the patient of the regimen’s importance, confirms the practitioner’s concern for the patient, and reinforces the importance of adherence in the patient’s mind through the practitioner’s investment of time and attention. Monitoring also can address the occurrence of side effects.

TEAM APPROACH

Treatment of depression is frequently delivered in primary care settings. The combination of medication and psychotherapy represents an effective approach to treating depression (Craighead 1998). Behavioral health is now more frequently integrated into health care, and a number of brief-oriented methods of psychotherapy have been found to be effective with depression (Wells 1990); more recently, Schulberg (2002) found that though psychotherapy is more costly than a primary care physician’s usual care, a depression-specific psychotherapy produces better clinical outcomes than a primary care physician’s usual care and outcomes similar to those produced by pharmacotherapy.

Prescribing physicians can utilize psychotherapists through behavioral health networks to monitor therapeutic response and discuss and reinforce adherence, paying particular attention to such psychological barriers as guilt and demoralization as part of the psychotherapeutic enterprise. Pharmacists can play an important role in identifying early stages of nonadherence and also are educated to provide pharmaceutical care by identifying and responding to drug-related problems (Bultman 2002). Within primary care practices, depression care managers have been found highly effective in supporting patient adherence to antidepressant medications and monitoring side effects (Unützer 2002, Bruce 2004).

These professionals can assist physicians in busy practices to support adherence. This is especially true because treatment for depression can be chronic, and information is better retained when spread out over multiple sessions rather than amassed in one session. Also, patients’ needs and conditions change over time, thus reinforcing the need for continued monitoring. Managed care organizations are well positioned to encourage collaboration and case management within their networks.

Within a managed care setting, the use of clinical pharmacy specialists to augment psychiatric services provided for patients with mild to moderate depression has resulted in a higher medication-possession ratio (0.81 vs. 0.66), higher switching rates (24 vs. 5 percent), and a reduction in subsequent office visits to primary care physicians (39 vs. 12 percent), compared with a control group during a 6-month follow-up period (Finley 2002).

On the other hand, there are limits to what MCOs can accomplish with labor-intensive interventions, given the competitive environment in which MCOs function. This makes it of paramount importance for MCOs to exploit any characteristics of antidepressant medications in and of themselves that might improve adherence.

From this perspective, a recent study of discontinuation rates for SSRIs merits examination, especially because it was based on real-world data from managed care environments. This retrospective analysis of a large managed care database (36 million lives covered by more than 60 MCOs) showed that, after 180 days, patients who received a controlled-release SSRI (paroxetine) were 28 percent less likely to discontinue treatment than patients receiving an immediate-release SSRI (Eaddy 2003).

The study examined medical and pharmacy claims for more than 82,000 patients who experienced new SSRI therapy from April 2002 through December 2002 for a depressive disorder or an anxiety disorder, or both. Patients lacking a diagnosis of depression or anxiety were classified as undiagnosed and were included in the study, but patients diagnosed with schizophrenia or a bipolar disorder were excluded, as were patients who were receiving antipsychotics.

In this population, sertraline was prescribed most frequently (28 percent), followed by citalopram (25 percent), immediate-release paroxetine (23 percent), fluoxe-
The incidence of anxiety-related diagnoses was higher among the patients receiving controlled-release paroxetine than among patients receiving an immediate-release SSRI (32.5 vs. 19.3 percent). After 30 days, about 75 percent of patients remained on their therapy, regardless of what it was; after 60 days, about 70 percent; and after 90 days, about 60 percent. At each of these time points, the percentages of patients remaining on controlled-release paroxetine and fluoxetine were virtually identical, with the rates for the other immediate-release SSRIs being slightly lower (and immediate-release paroxetine, lowest of all). From that point on, however, the curves gradually separated, and after 180 days, 55 percent of patients remained on controlled-release paroxetine versus 43 percent on the immediate-release SSRIs (Figure). Adjustments for demographic and clinical variables showed a 28 percent reduction in the risk of treatment discontinuation among patients receiving controlled-release paroxetine versus an immediate-release SSRI. The study was not designed to identify reasons for discontinuation.

These results gain added interest, however, when considered in the context of randomized controlled studies demonstrating that certain interventions that were seen to improve treatment adherence (and depressive symptoms) at 4 and 7 months (Katon 1995, Katon 1996) did not lead to better adherence or better outcomes than that achieved with routine care after 19 months (Lin 1999). The enhanced interventions, which involved education of patients and physicians, along with a reorganization of primary care services, were provided during the first 12 weeks of therapy, after which patients reverted to routine care. These studies were conducted prior to the availability of controlled-release paroxetine. Given the financial constraints that presumably would preclude extending enhanced interventions much beyond 12 weeks in many real-world settings, additional studies with extended-release paroxetine, delayed-release fluoxetine, and extended-release venlafaxine might be warranted in the interests of ascertaining whether these products can improve long-term outcomes.

**SUMMARY**

Methods of counseling for adherence lack a well-researched experimental basis for determining which approaches are the most effective. An extensive history of descriptive adherence research, however, can provide data for building a multifaceted model of adherence counseling. First, the health care provider must develop a caring and collaborative relationship with patients for any counseling to be effective. Second, positive beliefs and attitudes concerning the regimen must be encouraged, and irrational and negative beliefs and attitudes must be disputed. Third, patients must view the benefits of the regimen as outweighing any barriers. Fourth, the regimen must be tailored to the patient’s needs and the patient must be given cognitive-behavioral control over the regimen by anticipating, understanding, and managing side effects. Fifth, simplification of the dosing regimen should be considered through the possible use of controlled-release dosage forms.

Finally, periodic monitoring and reinforcement using pharmacists and psychotherapists in a collaborative and comprehensive model of physical and psychological care will offer the most effective approach to long-term treatment.

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A Review of HEDIS Measures and Performance for Mental Disorders

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SUMMARY
Performance on mental health HEDIS measures has been modest, with only minimal improvements in recent years. Performance on mental health measures has been consistently worse than that for other medical conditions. A critical step toward improving performance is to understand where care is provided and then to identify clinicians who are responsible for ensuring that care is delivered appropriately.

Approximately 35 million Americans experience a major depressive episode in their lives (Kessler 2003). Depression is both highly prevalent and extremely costly, placing a significant economic burden on our health care system. In 2000, depression incurred an estimated $83.1 billion in the United States in combined medical costs, lost productivity, and premature mortality (Greenberg 2003).

There is a wide range of effective treatments for depression, yet this disorder is underdiagnosed and undertreated. Only about half of individuals with depression are correctly diagnosed, and only about half of those begun on treatment receive guideline-concordant care (Hirschfeld 1997).

The majority are seen and treated in primary care settings (Regier 1993). The Agency for Health Care Policy and Research (AHCPR), now the Agency for Health Care Research and Quality (AHRQ), developed guidelines to provide recommendations for depression treatment in primary care settings (AHCPR 1993a, AHCPR 1993b).

The AHCPR guidelines serve as the basis for the depression measures used in the Health Plan Employer Data and Information Set, the nation's most widely used health care "report card." HEDIS rates health plans that cover 90 percent of Americans enrolled in HMOs and is the set of quality indicators used most by purchasers in selecting and rating plans. Performance on this report card can provide important insights into plan quality as it is currently measured and reported in the U.S. health care marketplace.

HEDIS measures: evaluating performance to improve outcomes
The National Committee for Quality Assurance (NCQA) is an independent not-for-profit organization dedicated to measuring and maintaining health care quality through regular evaluation and accreditation processes. HEDIS was developed in the early 1990s to provide insight into the success of managed health care plans in serving their constituents’ needs (NCQA 2000). HEDIS data reflect performance in areas of health care and service, including quality of care, access to care, and member satisfaction with the plan and physicians.

NCQA selects indicators for HEDIS evaluation based on their scientific soundness, relevance, feasibility, and standardization as measures of health care provider performance. Scientific soundness is ascertained based on the accumulated literature supporting the accuracy, reproducibility, and validity of the measure. The AHCPR...
guidelines on depression in primary care provide the primary scientific basis for the HEDIS depression measures. Relevance is determined by the measure’s potential clinical and economic significance. Feasibility is defined by the accessibility of the data and the nature of the costs for obtaining the data. Finally, standardization is the ability to create precise specifications for measurement across multiple institutions.

Five mental health care quality measures are used in the HEDIS report card (Table 1). Two measures assess follow-up after discharge for any mental disorder; three specifically assess depression medication management during the acute phase (first 3 months), continuation phase (first 6 months), and appropriate practitioner follow-up (at least three follow-up visits from a mental health care professional in the 3 months after a new depressive episode).

**HEDIS PERFORMANCE**

Mental health performance on HEDIS measures based on data collected from 1999 to 2002 has been consistently modest (Figure 1), with only minimal improvements during this period (NCQA 2003). In commercial health plans, an average of 50 percent of patients with mental illness received follow-up care 7 days after onset of a depressive episode. Follow-up rates were even lower among Medicaid and Medicare populations, who had a less-than-40 percent rate of follow-up within the week after discharge. As would be expected, follow-up rates at 30 days postdischarge were higher; nearly 75 percent of patients insured through a commercial health plan, and 60 percent insured through Medicaid and Medicare, had a follow-up visit during this period.

Table 2 shows antidepressant treatment trends from 1999 to 2002 (NCQA 2003). About 60 percent of patients received prescriptions during the acute phase of an episode; only about 40 percent were contacted by a mental health care professional and renewed a prescription during the continuation phase of therapy. Follow-up rates (based on the AHCPR recommended number of contacts with a mental health care professional) decreased from 21.4 percent in 1999 to 19.2 percent in 2002.

Mental health performance on HEDIS has consistently been worse than performance for other conditions. Compared with the HMOs’ rate on nine nonmental health care measures, mean rate of performance on mental health care measures was much lower (48.0 vs 69.2 percent) (Druss 2002). Rates of improvement on mental health performance have also been less robust than for improvement on general medical domains (NCQA 2003).

**TABLE 1** HEDIS: Five measures of mental health care quality

<table>
<thead>
<tr>
<th>Measure</th>
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<tbody>
<tr>
<td>1. Percentage of members hospitalized for a mental disorder who had an</td>
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<tr>
<td>ambulatory visit with a mental health care provider within 7 days of</td>
</tr>
<tr>
<td>discharge</td>
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<tr>
<td>2. Percentage of members hospitalized for a mental disorder who had an</td>
</tr>
<tr>
<td>ambulatory visit with a mental health care provider within 30 days of</td>
</tr>
<tr>
<td>discharge</td>
</tr>
<tr>
<td>3. Effective* treatment in the acute phase (ongoing in the 3-month period</td>
</tr>
<tr>
<td>after a new depressive episode)</td>
</tr>
<tr>
<td>4. Effective* continuation therapy (ongoing for 6 months after a new</td>
</tr>
<tr>
<td>depressive episode)</td>
</tr>
<tr>
<td>5. Optimal practitioner contacts (at least three follow-up visits from</td>
</tr>
<tr>
<td>a mental health care professional in the 3 months after a new depressive</td>
</tr>
<tr>
<td>episode)</td>
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</table>

* Effective: NCQA defines this as ongoing treatment. SOURCE: DRUSS 2000

**FIGURE 1** Increases in mental illness follow-up rates, 1999–2002

Percentage of patients in plan population, diagnosed with major depression, who received follow-up care. Figures correspond with measures 1 and 2 in Table 1.
Why do plans score lower on mental health?

A number of patient, provider, and system-level factors are likely to explain the continuing low scores on HEDIS performance measures. In a recent study of patient and provider factors, Bull and colleagues surveyed patients to understand the reasons for early discontinuation of SSRI medications. The study found miscommunication between physicians and patients regarding duration of therapy and side effects to be the most important cause of premature discontinuation (Bull 2002).

In a second study, Druss and colleagues examined plan-level predictors of poor HEDIS mental health performance. Poor scores on general medical indices, failure to report findings publicly, and low medical-loss ratio (proportion of revenues spent on clinical care) all predicted poor performance on the mental health measure (Table 3).

A major challenge to understanding and improving mental health performance among HMOs is the fact that many of these plans carve out their mental health care to behavioral health managed care organizations (Frank 2003). Depression care may be provided solely within the HMO, within a carve-out, or in a combination of the two. A first critical step in plans improving their mental health performance is to understand where care is provided, and then to identify the clinicians or clinics responsible for ensuring that it is delivered appropriately.

IMPROVING QUALITY OF DEPRESSION CARE

The health care system is primarily organized around providing acute, episodic care, and is often ill-suited for caring for persons with chronic conditions. The most widely tested approach to improving this care is the chronic care model, developed by Edward Wagner at Group Health Cooperative of Puget Sound (Wagner 1996). These interventions use multidisciplinary teams to follow patients with chronic diseases over time, actively engaging them in managing their illnesses and ensuring that they follow up with treatment regimens. This model has been shown to be effective in improving care for a range of chronic illnesses, and it also has the potential to reduce costs of care (Bodenheimer 2002a, Bodenheimer 2002b).

More than a dozen studies have shown that the chronic care approach can improve care for major depression in primary care settings. In a recent review of the literature, Gilbody (2002) found that whereas simple guidelines and educational programs generally were inadequate, complex programs that also included nurse case management and better integration between mental health and primary care led to substantial improvements in depression care. Badamgarav and colleagues conducted a meta-analysis of this literature (Figure 2) and found that such programs resulted in improved detection and treatment of depression (Badamgarav 2003).

SUMMARY AND CONCLUSIONS

While not perfect, HEDIS measures have placed quality squarely on the table along with cost for health care purchasers and consumers. Scores on the mental health measures continue to lag those on other general health indices, likely due to a complex combination of patient,
provider, and system-level factors. A first step in improving those scores is for plans to understand who is caring for patients with depression within their organizations, and to ensure that specific clinicians and clinics are held accountable for improving that care by following accepted guidelines for treatment. Organized approaches similar to those used for other chronic conditions are highly promising for improving the effectiveness and cost effectiveness of depression care in the United States.

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Social anxiety disorder (SAD) is the nation’s third most prevalent psychiatric disorder, exceeded only by substance abuse and major depressive disorder. Though not recognized as a disorder until 1994 when the American Psychiatric Association (APA) published the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), SAD’s precursors were well established in previous editions of DSM.

The U.S. lifetime prevalence of SAD among primary care patients is 13.3 percent — 11.1 among men and 15.5 percent among women, with the mean age at onset of SAD being 15.5 years (Magee 1996). With onset prior to age 10, the condition tends to be severe. SAD is a chronic condition with a mean duration of 19.4 years from the time of diagnosis. It is somewhat more common among women and — compared with unaffected persons, persons with specific phobias or agoraphobia — SAD sufferers are less likely to be married (Davidson 1993a).

**CLINICAL PRESENTATION**

Individuals with SAD have an excessive fear of being scrutinized and negatively evaluated in social and performance situations. They also recognize that their fears are excessive, interfering, and distressing. Those with SAD may experience significant anticipatory anxiety before entering the feared situation and suffer panic attacks when in the phobic situation. They may cope through avoidance.

SAD is classified as non-generalized (NGSAD) when fewer than three phobias are present; fear of public speaking is the most frequent non-generalized phobia. In two thirds of all SAD cases, the person has many of the following multiple avoidances: interacting with strangers or persons in authority; being assertive and refusing unreasonable requests; confronting the behaviors of others; dating; attending parties; using public restrooms; eating or working while being watched.

Persons with the generalized subtype of SAD (GSAD) tend to be more functionally disabled (Kessler 1998), experience onset at an earlier age, be less educated, and unemployed (Heimberg 1990b). Children who consistently respond to novel or unfamiliar situations with behavioral inhibition may be predisposed to developing SAD later in life (Kagan 1988). The prevalence of SAD in parents of children predisposed to developing the disorder is 18 percent; in contrast, only 3 percent of parents of noninhibited children are affected (Rosenbaum 1994).

**Differential diagnosis and diagnostic tools**

SAD differential diagnoses include the other anxiety disorders, particularly panic disorder. The diagnostician should also consider other conditions, such as avoidant personality disorder, shyness, or psychosis.

Two reliable, easy-to-administer tools are available to help to diagnose SAD:

- Module G of the Mini International Neuropsychiatric Interview (MINI) (Figure 1) uses five screen-
The LSAS is widely available online. A printable version is accessible at «http://www.psychmeds.com/liebowitz.html»; an interactive version is accessible at «http://healthnet.umassmed.edu/mhealth/LiebowitzSocialAnxietyScale.pdf».

Mood disorders and the LSAS

• The Liebowitz Social Anxiety Scale (LSAS)\(^2\) is a clinician-rated scale that covers 24 feared social and performance situations. Each phobic situation listed is rated for the intensity of fear it provokes and the frequency with which the individual avoids it. LSAS offers a convenient way to monitor patient progress during treatment (Liebowitz 1987, Heimberg 1999).

Consequences and comorbidity

Comorbidity with SAD is 69 percent (most commonly: specific phobia, 59 percent; agoraphobia, 45 percent) (Schneier 1992b). With comorbid psychiatric conditions, the prognosis for recovery decreases (Davidson 1993a). Comorbidity increases the likelihood of a suicide attempt 15-fold. Rates of alcohol abuse range from 15 to 27 percent (Schneier 1992b).

GSAD tends to be more disabling than NGSAD; two thirds of sufferers are single or divorced, half have completed high school; and 1 in 5 is on disability (Kessler 1998). These patients utilize more outpatient medical treatment than do controls. Compared with those with the pure disorder, those with comorbid psychiatric conditions are more likely to seek treatment (Schneier 1992b).

TREATMENT

Treatment options include pharmacotherapy and behavioral interventions. Selective serotonin reuptake inhibitors (SSRIs) and high-potency benzodiazepines are medications of choice. The first step toward developing an effective treatment plan is to make the diagnostic distinction between GSAD and NGSAD, as therapeutic options tend to differ. Given that SAD has an early age of onset, treatment should begin ideally during adolescence, as early intervention may halt progression and prevent such complications as depression, panic disorder, substance abuse, and suicide.

Pharmacologic options

Pharmacotherapy is an important first step in treating most GSAD patients. Evidence shows considerable efficacy for some SSRIs, reversible inhibitors of monoamine oxidase (RIMAs), monoamine oxidase (MAO) inhibitors, and some benzodiazepines (Table 1, page 54).

These classes of medication differ, and one way to compare their efficacy is to assess their weighted effect size (ES). This kind of analysis detects differences between the proportions of response to the drug versus placebo, adjusted for sample size. ES ratings for selected classes of SAD therapeutics, in descending order, are benzodiazepines, 1.00 (van Vliet 1994, Davidson 1993b); phenelzine, 0.98 (Hidalgo 2001); anticonvulsants, 0.46 (Davidson 2003); RIMAs, 0.41 (Davidson 2003); buspirone and beta blockers, 0.14 (Davidson 2003).

To date, paroxetine and sertraline are the only two medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of GSAD.

SSRI therapy

Paroxetine. In an 11-week, open-label study, 36 GSAD patients were treated with paroxetine and rated, at completion, using the Clinical Global Improvement (CGI) scale. Of 30 patients who completed the study, 23 were much improved or very much improved. The mean effective dosage of paroxetine was 47.9 mg/day (range: 20–50 mg). Sixteen subjects who continued to participate in a double-blind, relapse-prevention study were randomly assigned either to continue receiving paroxetine or to receive placebo for another 12 weeks. Of the eight patients in the placebo group, five relapsed; 1 of 8 in the paroxetine group relapsed (Stein 1996). Efficacy of paroxetine also was established in a 12-week, multicenter, double-blind, placebo-controlled trial in which 187 patients were randomly assigned to paroxetine or placebo. At the clinician’s discretion, the dosage was titrated by increasing it by 10 mg/week to a maximum of 50 mg/day. At a mean effective dosage of 36.6 mg/day, 55 percent of the paroxetine group and 24 percent of the placebo group were either much improved or very much improved on the CGI scale. The paroxetine group also showed significantly greater improvement on the LSAS (Figure 2) and on the social disability and work disability subscales of the Sheehan Disability Scale (Stein 1998). Further support for paroxetine in treating GSAD patients derives from a study in which subjects randomized to paroxetine had a 70 percent response rate compared with an 8 percent response rate with placebo (Allgulander 1999).

Sertraline. In a double-blind, placebo-controlled, crossover study of sertraline in GSAD, 12 patients received either sertraline or placebo for 10 weeks, no treatment for 2 weeks, and subsequently the other treatment for an additional 10 weeks. Starting at 50 mg/day, the dosage was increased by 50 mg every 2 weeks, at the clinician’s discretion. The researchers established the mean effective dosage of sertraline to be 133.5 mg/day. They found a statistically significant reduction in the mean LSAS score in 50 percent of patients receiving sertraline and only 9 percent receiving placebo (Katzelnick 1995). In a larger, more recent, double-blind, placebo-controlled study, investigators found a 53 percent response rate (71 of 135) for sertraline and a 29 percent response rate (20
of 69) for placebo; sertraline responders averaged an improvement of 17 points (reduction from baseline) on the Brief Social Phobia Scale, while placebo responders’ average improvement was 9 points (Van Ameringen 2001). An open-label study showed sertraline, at mean dosages of 123 mg per day, to be effective in children age 10 to 17 (Compton 2001). Several large international clinical trials of SAD therapy among children and adolescents are continuing. Until results are available, clinicians will need to extrapolate from studies in adult populations.

Other SSRIs. Even though fluvoxamine has not been approved by the FDA for the treatment of SAD, there is credible evidence for its efficacy. A randomized 12-week, double-blind, placebo-controlled study compared fluvoxamine 50–150 mg/day, with placebo in the treatment of GSAD. Of 30 patients in the study, 46 percent responded to fluvoxamine and 7 percent responded to placebo, with reduced LSAS scores. In the 12-week continuation phase, 14 of 16 fluvoxamine patients improved further (van Vliet 1994). Another double-blind, placebo-controlled multicenter study replicated findings on fluvoxamine’s efficacy and safety in the acute treatment of GSAD, with a final mean effective dosage of 202 mg/day (Stein 1999).

In dosages ranging 20–60 mg/day, fluoxetine has shown efficacy in four case series reports of 2 patients (Sternbach 1990), 12 patients (Schneier 1992a), 14 patients (Black 1992), and 16 patients (Van Ameringen 1993). An open trial of venlafaxine in 10 patients shows promising results (Emmanuel 1995).

Extended-release venlafaxine is under study, and citalopram has not yet been tested for relief of SAD. While no SSRI study has included either another SSRI or non-SSRI direct, active comparator, expert consensus favors SSRIs to alternatives, as they are safer than the MAO inhibitors and less likely to cause dependence than the benzodiazepines.

### Benzodiazepine therapy

To date, two double-blind, placebo-controlled studies and nine open-label studies of benzodiazepines indicate efficacy for this drug class. Open-label studies suggest that clonazepam (Ontiveros 1990), alprazolam (Reich 1988), and bromazepam (Versiani 1997) are effective in many cases. The double-blind studies suggest that clonazepam (Davidson 1993b) but not alprazolam (Gelertner 1991) is superior to placebo. In a 10-week study of 75 pa-
patients, 78 percent of the clonazepam group but only 20 percent of the placebo group responded to therapy. The mean dosage of clonazepam at endpoint was 2.4 mg/day (Davidson 1993b).

Other classes

Drugs from other classes, including MAO inhibitors, RIMAs, tricyclic antidepressants, and beta blockers have been studied in the treatment of SAD. Table 1 lists response rates from selected placebo-controlled studies.

Treatment response

Response is associated with duration of therapy, which has been minimally studied, resulting in a dearth of useful data. In one study, patients with SAD who responded to therapy continued to improve beyond the 8th week of active treatment (van Vliet 1994). Poor response is associated with symptom severity at baseline, family history of SAD, higher systolic blood pressure, abnormal heart rate, and alcohol consumption. Relapse is high following discontinuation of successful pharmacotherapy. Patients suffered a relapse rate of 20 percent when they switched from clonazepam to placebo (Gelertner 1991); 62 percent of those switching from paroxetine to placebo relapsed, compared with 12 percent of patients continuing paroxetine therapy (Stein 1996) or switching to sertraline (Van Ameringen 2001).

Nonpharmacologic options

Behavior therapy often helps patients overcome social anxiety. Exposure therapy has been shown to be effective (Fava 1989), and the treatment of choice for NGSAD is in vivo exposure behavior therapy. It eliminates excessive fear by placing the patient, repeatedly and for prolonged periods, in the specific situation that evokes the phobic response. Self-help groups — such as Toastmasters International, a global network of clubs that foster the development of public speaking in a practicum environment — are useful and recommended.

Adjunctively, in some cases, a beta blocker — for example, propranolol, 10 to 40 mg, taken 1 to 2 hours before a specific nongeneralized performance anxiety situation, may reduce tachycardia or hand tremor, though there have been no controlled trials to support it. Further, studies investigating beta blockers in GSAD have found that they are not superior to placebo (Liebowitz 1992). In a study by Turner (1994), flooding, a form of behavior therapy, was found to be more effective than atenolol (62 vs. 38 percent).

Other behavior-therapy studies have found exposure therapy to be superior to placebo (Turner 1994), waiting-list controls (Butler 1984, Newman 1994), and progressive relaxation therapy (Al-Kubaisy 1992, Alström 1984). Most evidence suggests that therapist-guided exposure is superior to exposure without guidance, in which case patients cope alone with their social anxiety (Mattick 1989). Phobic patients tend to be noncompliant with exposure instructions, and compliance with exposure instructions between sessions has been linked with better outcomes immediately following treatment (Leung 1996) and at 6-month follow-up (Edelman 1995).

Combination treatment — cognitive restructuring plus behavior therapy — was found to be superior in patients receiving both educational/supportive therapy (Heimberg 1990a) and in waiting-list control groups (DiGiuseppe 1990, Hope 1995). Yet the debate continues over whether cognitive techniques enhance efficacy compared with exposure alone. Some studies show equivalent results for cognitive restructuring plus exposure, and for exposure alone (Feske 1995, Gould 1997), while others find only cognitive restructuring combined with exposure to be significantly superior to placebo (Taylor 1996). In a recent meta-analysis, researchers compared five CBTs — exposure therapy, cognitive restructuring, exposure with cognitive restructuring, social skills training, and applied relaxation — and found all to be moderately effective for...
SAD, with no significant differences between them immediately following or at later follow-up (Federoff 2001).

Individual and treatment-group formats appear to be equally effective. The results of social-skills training to treat SAD are mixed (Falloon 1981, Lucock 1988). The only controlled study of social-skills training, applied over 15 weeks, found no significant difference between treated patients and a control group (Marzillier 1976). Progressive muscle-relaxation training has shown little efficacy in the treatment of SAD (Alström 1984), and there are no controlled studies of psychotherapy in SAD.

SUMMARY

In the past decade, we have learned that GSAD is much more common and disabling than previously realized. This chronic condition has significant comorbidity and increased risk for substance abuse/dependence and suicide. Current data indicate that several pharmacologic and behavioral treatment options are effective in easing symptoms, alleviating disabilities, and mitigating the complications from which these patients suffer.

REFERENCES


CONTINUING EDUCATION POST-TEST

P&T DIGEST Depression

On the combined answer sheet/evaluation form on page 60, please place an X through the box of the letter corresponding with the correct response for each question. There is only one correct answer to each question.

1. In the United States, the lifetime risk of major depression is:
   a. 1–3 percent.
   b. 10.3 percent.
   c. 15 percent.
   d. 17.3 percent.

2. Which is true of practice guidelines for depression in primary care?
   a. They are known to be widely used.
   b. Pharmacoeconomic studies show they improve outcomes.
   c. Use and careful interpretation of guidelines improves detection and reduces relapse and suicide risk.
   d. None are available.

3. For selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) to produce an antidepressant response:
   a. Increasing or reducing brain levels of serotonin only is probably sufficient.
   b. Increasing or reducing brain levels of serotonin only is probably insufficient.
   c. Increasing and reducing levels of serotonergic, noradrenergic, and other neurotransmitter activity may be needed.
   d. Answers a and c only.
   e. Answers b and c only.

4. Poor compliance with antidepressant therapy can result from:
   a. Miscommunication between practitioner and patient.
   b. Lack of collaboration between the practitioner and patient.
   c. Patient-perceived stigma of depression and antidepressants.
   d. All the above.

5. To evaluate follow-up care after a new depressive episode, the Health Plan Employer Data and Information Set (HEDIS) report card consists of several key measures, including:
   a. Effective therapy in initial 3-month period.
   b. Effective continuation therapy for 6 months.
   c. At least 3 follow-up visits from a mental health care professional in 3 months.
   d. Answers a and c only.
   e. Answers a through c.

6. Lifetime prevalence of social anxiety disorder (SAD) in the United States is:
   a. 7.3 percent.
   b. 11.1 percent.
   c. 13.3 percent.
   d. 15.5 percent.

7. The mechanism of action of SSRIs and SNRIs may be associated with alterations in gene expression that produce sustained changes in the function of selected brain cells.
   a. True.
   b. False.

8. During the past 2 decades, pharmacoeconomic literature regarding depression management has generally focused on all but which of the following questions:
   a. Are neurotransmitter receptor-specific antidepressants cost-effective alternatives to older agents?
   b. Are there differences in clinical and economic outcomes between the newer antidepressants?
   c. What are the direct and indirect costs of patients’ noncompliance with antidepressant therapy?
   d. Does compliance with clinical guidelines regarding the recommended length of antidepressant therapy translate into beneficial economic outcomes?

9. In primary care, which costs more?
   a. Diagnosis and treatment of depression.
   b. Subsequent laboratory costs searching for other diagnoses.

10. An AHRQ national initiative found that __ percent of patients with depression received appropriate care in primary care settings.
   a. 25.
   b. 30.
   c. 35.
   d. 40.

11. For dysthymia and acute major depression, the American College of Physicians–American Society of Internal Medicine recommends drug treatment at the same dose for at least:
   a. 4 weeks.
   b. 12 weeks.
   c. 4 months.
   d. 6 months.
12. Components of effective adherence counseling are:
   a. Empathy with patients’ wishes and individualism.
   b. Explaining how treatment benefits outweigh barriers.
   c. Addressing patients’ concerns about side effects.
   d. Explaining the neurobiologic basis of depression.
   e. All the above.

13. The following characteristics are typical of individuals with generalized SAD:
   a. Early-age onset.
   b. Less education.
   c. Unemployment.
   d. Answers a and b only.
   e. Answers a through c.

14. Using a human-capital approach, the annual cost of depression in the United States has been estimated at $____ billion.
   a. 29.7.
   b. 34.8.
   c. 43.7.
   d. 51.2.

15. Effective practice guidelines:
   a. Define the clinical setting for which the guidelines are appropriate.
   b. Consider all important treatment options and their consequences.
   c. Clearly recommend interventions.
   d. Devise a mechanism for dissemination, evaluation, and updates.
   e. All of the above.
   f. Answers b, c, and d only.

16. Which is an inherent limitation of randomized clinical trials with an economic component?
   a. Inability to control confounders.
   b. Inability to generalize to a broader population.
   c. Data are subject to publication and/or selection bias.
   d. Nonexperimental design and limited internal validity.

17. At 30 days after onset of a depressive episode, nearly 75 percent of patients insured through a commercial health plan receive follow-up care, compared to approximately 60 percent through Medicaid and Medicare.
   a. True.
   b. False.

18. Even with antidepressant treatment, relapse of major depression occurs in ____ percent of patients:
   a. 15 percent.
   b. 10–30 percent.
   c. 20–40 percent.
   d. 50 percent.

19. Total health care costs for patients older than 65 with significant symptoms of depression are approximately ____ percent more than for non-depressed elderly patients.
   a. 30.
   b. 40.
   c. 50.
   d. 60.

20. All are true of professional society guidelines except:
   a. There is a 3–5 year gap between updates.
   b. Preparation involves many steps and checks.
   c. They must be peer reviewed.
   d. They are mandates that practitioners must follow in order to be reimbursed.

21. Increasing length of antidepressant therapy to a duration consistent with national clinical guidelines translates into a reduction in total health care expenditures.
   a. True.
   b. False.

22. After 6 months, what effect did controlled-release formulations of SSRIs have on compliance with antidepressant therapy?
   a. Significantly increased compliance.
   b. Decreased compliance.

23. Regarding health care performance as measured by HEDIS, which of the following statements is false?
   a. HMO performance is substantially lower on mental health care measures versus nonmental health care measures.
   b. High medical-loss ratio also is associated with poor performance.
   c. HMOs that do not report their quality of care data are more likely to perform poorly on the HEDIS mental health care assessment.
   d. Expenditures of HMOs are directly related to the quality of care they provide.

24. Pharmacologic options that show considerable efficacy for SAD or generalized SAD include the following classes of drugs with the exception of:
   a. SSRIs.
   b. Reversible and irreversible MAO inhibitors.
   c. Tricyclic antidepressants.
   d. Benzodiazepines.

25. Paroxetine is indicated for a wide range of anxiety and mood disorders, with the exception(s) of:
   a. Obsessive-compulsive disorder.
   b. Premenstrual dysphoric disorder.
   c. Social anxiety disorder.
   d. Bulimia nervosa.
   e. Answers a and d.
   f. Answers b and d.
CONTINUING EDUCATION ANSWER SHEET/CERTIFICATE REQUEST
P&T DIGEST Depression

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EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on pages 58 and 59. There is only ONE answer per question. Place all answers on this form:

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PROGRAM EVALUATION
So that we may assess the value of this self-study program, please fill out this evaluation form.

Have the activity's objectives been met?
1. Illustrate the prevalence of depression, as well as the clinical and economic implications thereof. □ Yes □ No
2. Describe major published treatment guidelines for depression, as well as their shortcomings as advanced therapies have reached the market. □ Yes □ No
3. Identify various SSRI treatments for depression and explain their mechanisms of action. □ Yes □ No
4. Understand the dynamics of pharmacoeconomic evaluation of SSRI therapy. □ Yes □ No
5. Elucidate strategies for therapeutic compliance and the consequences of noncompliance. □ Yes □ No
6. Discuss NCQA guidelines for depression—medication management and follow-up after hospitalization for depression. □ Yes □ No

Was this publication fair, balanced, and free of commercial bias? □ Yes □ No

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