Supplements to the *Journal of Managed Care Pharmacy* are intended to support medical education and research in areas of clinical practice, health care quality improvement, or efficient administration and delivery of health benefits. The following standards are applied to all supplements to assure quality and assist readers in evaluating potential bias and determining alternate explanations for findings and results.

1. Disclose the principal sources of funding in a manner that permits easy recognition by the reader.

2. Disclose the existence of all potential conflicts of interest among supplement contributors, including financial or personal bias.

3. Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.

4. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.

5. Seek and publish content that does not duplicate content in the *Journal of Managed Care Pharmacy*.

6. Subject all supplements to expert peer review.

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### Target Audience:
Managed care pharmacists and other health care practitioners

### Learning Objectives
After completing this continuing education module, the pharmacist will be able to
1. describe the incidence and onset of major depressive disorder;
2. list the numerous ways in which MDD presents in general and, specifically, in people who belong to minority groups;
3. describe barriers to care and adherence experienced by people from minority populations;
4. understand the currently available antidepressants and their differences; and
5. appreciate and discuss the importance of adequate and sustained treatment and careful planning if switching becomes necessary.

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The Impact of Age, Gender, Race, and Ethnicity on the Diagnosis and Treatment of Depression

PATRICE A. HARRIS, MD

ABSTRACT

OBJECTIVE: To review issues related to culture and ethnicity that influence diagnosis, treatment, and response for patients who have major depressive disorder (MDD).

SUMMARY: People from different ethnic and cultural groups may present with MDD differently. Communication, clarity, and collaboration are key to successful patient-provider relationships. Often, patients’ presentation involves somatic complaints, or symptoms that have not traditionally been associated with a diagnosis of depression. People from minority groups may be less trusting, less adherent, and more skeptical than others. Further, chronic medical illnesses may result in MDD, and patients from ethnic minorities often respond to medications differently from whites. Each patient’s culture and ethnicity must be addressed when they present. Clinicians should always ask, “Are there any cultural issues at work here?”

CONCLUSION: Cultural competence is a journey, not a destination, and every provider must learn to question carefully, appreciate culture’s role, and help patients work with them to achieve a better mental and physical health status.

KEYWORDS: Culture, Ethnicity, Cultural competence, Major depressive disorder, Metabolizers

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Caring for patients in mental health settings means fully engaging them using the 3 “C’s”: communication, clarity, and collaboration. Ample opportunity also exists for clear communication and collaboration among different health care providers. Two important documents are essential reading for clinicians who practice in mental health:

1. the Institute of Medicine’s (IOM’s) 2002 report, “Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care,”

2. the Surgeon General’s supplement to his 1999 report on mental health in the United States, “Mental Health: Culture, Race and Ethnicity.”

The Institute of Medicine report starts with this quote from Goethe: “Knowing is not enough; we must apply. Willing is not enough; we must do.” For all health care providers, the impetus now is to know our individual patients’ wants, needs, and differences and to do what is necessary to help them become well.

The World Health Organization (WHO) has estimated that as many as 340 million people worldwide will experience a major depressive episode. In the United States, about 18 million people have experienced a major depressive episode.

Depression causes significant morbidity, affecting people’s ability to work, function in relationships, and engage in social activities. Additionally, people with depression are at increased risk for mortality; up to 15% of those with severe major depressive disorders (MDDs) die by suicide, with the elderly disproportionately at risk. The elderly have the highest rate of suicide in this country. Death rates increase 4-fold (not just from suicide) in people older than 55 years with MDD. During the reproductive years in men, the point prevalence for suicide is 2% to 3%, and, in women, the point prevalence is 5% to 9%; thus, women are affected about twice as often as men. In the elderly, the risk of suicide is greater in men.

MDD may begin at any age. Most commonly, it starts in the mid-20s, but exceptions occur; its age of onset occurs in a broad range. Early adolescents and older people diagnosed with MDD present somewhat differently from other adults.

The onset of depression at any age may follow a severe psychosocial stressor, after which almost anyone may feel sad, distressed, or anxious. Should these feelings continue for 2 weeks or more after the event passes, many people will seek treatment. Often, they make an appointment with a primary care provider or some other helping professional.

The Influence of Setting

In general medical settings, those with MDD usually exhibit increased pain and physical illness, although they may also report decreased social, physical, and role functioning. The typical patient will present with somatic complaints and impaired func-
tioning at work or in relationships. Often, they do not think they are experiencing a major depressive episode. Research in nursing homes has found that residents with untreated MDD are at increased risk of death in the first year. Thus, significant morbidity and mortality are possible.6

WHO, World Bank, and Harvard University conducted a study, in which they used disability-adjusted life-years (DALYs), measuring unhealthy years of life. In 1990, they ranked lower-respiratory infections as the primary cause of disability worldwide; unipolar major depression ranked fourth. In 1990, the annual cost of depression was conservatively estimated at $44 billion. These experts predict that unipolar major depression will be a significant cause of DALYs in 2020, probably moving into second place behind ischemic heart disease. Since many people who have MDD remain untreated, the cost in real dollars and in years of life lost is considerable and difficult to estimate accurately.7

**Accurate Diagnosis**

Once patients seek or are referred for treatment, accurate diagnosis is very important. In addition to accurately diagnosing MDD, clinicians must gauge its severity and measure dangerousness, especially to self (suicidality). Chronicity is also an issue. Depression is a chronic medical illness like diabetes or hypertension. Communicating that most mental disorders are chronic is crucial.

Myths about depression abound. People who embrace these myths view depression as a serious spiritual weakness or character flaw, which it is not. They perceive moodiness or depression in adolescents and elders as normal. Teasing out normal (periodic sad moods) from abnormal can be difficult, but true clinical depression is never normal.

Psychiatry’s cornerstone is the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*), researched and published by the American Psychiatric Association (APA). A diagnosis of major depression requires the presence of 5 or more specific symptoms in the same 2-week period (Table 1). Should the symptoms occur with decreased ability to function, the criteria for an MDD are met.

**Societal Stigma**

Psychiatric illness is still plagued by stigma. According to Lawrence Martin, director of the Mood Disorders Clinic at St. Joseph’s Hospital in Ontario, “[Depression] is a very lethal illness. It’s very painful. People who have been depressed and had cancer . . . have said they would rather have cancer again than depression. With cancer they knew what was happening. There was pain, but it was just pain. With depression it was pain, self doubt, feelings of guilt about their lives, emptiness, and hopelessness.”8

In addition, clinicians must probe further with patients who offer vague complaints. We must broaden how we think about the illness so we don’t miss people with atypical presentation (data confirm physicians miss this diagnosis often).9 Vague aches and pains are symptoms of depression; the APA recently decided to add these symptoms to the *DSM-IV-TR* criteria, and this change deserves additional attention.

**TABLE 1 DSM-IV-TR Criteria for Major Depressive Episode**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep</strong></td>
<td>insomnia or hypersomnia</td>
</tr>
<tr>
<td><strong>Interest</strong></td>
<td>depressed mood,* loss of interest or pleasure*</td>
</tr>
<tr>
<td><strong>Guilt</strong></td>
<td>feelings of worthlessness</td>
</tr>
<tr>
<td><strong>Energy</strong></td>
<td>fatigue</td>
</tr>
<tr>
<td><strong>Concentration</strong></td>
<td>diminished ability to think or make decisions</td>
</tr>
<tr>
<td><strong>Appetite</strong></td>
<td>weight change</td>
</tr>
<tr>
<td><strong>Psychomotor</strong></td>
<td>psychomotor retardation or agitation</td>
</tr>
<tr>
<td><strong>Suicidality</strong></td>
<td>preoccupation with death, hopelessness</td>
</tr>
</tbody>
</table>

*Must include 1 of these.

**Shifting Focus**

Our focus must shift, especially with racial and ethnic minorities. African Americans, for example, often come to our clinical attention complaining more about general and migrating aches and pains. They may initially complain of a headache, then a stomachache, a knee-ache, back pain, and then GI disturbances, including constipation, diarrhea, some vomiting, joint pain, or fatigue. A significant appetite change may follow.

Concerned that a substantial proportion of physical complaints and minor illnesses remain poorly understood, researchers interviewed 13,538 individuals in the Epidemiologic Catchment Area Program. Focusing on 26 common symptoms, they found that 24 had been problems for more than 10% of participants at some point. Most often, subjects reported joint pains (36.7%), back pain (31.5%), headaches (24.9%), chest pain (24.6%), arm or leg pain (24.3%), abdominal pain (23.6%), fatigue (23.6%), and dizziness (23.2%). Subjects considered these severe 84% of the time and said that they interfered with activity, required medications, or prompted a visit to a physician. The researchers associated most symptoms with at least a 2-fold increased lifetime risk for a psychiatric disorder.10

**Influences Affecting Major Depressive Disorder**

In the past, clinicians had a tendency to partition medical and psychiatric illness, considering them separate and distinct. Yet, significant data exist indicating that 20% to 25% of individuals with serious or chronic medical conditions will develop MDD.11 Additionally, studies confirm that people who have myocardial infarctions have less-favorable prognoses if they have untreated MDD.12

Although researchers acknowledge a relationship between hormones and mood symptoms, the connection has not been elucidated. Depressive disorders occur twice as frequently in women in their reproductive years as in men. Sometimes, symptoms worsen in women with MDD several days prior to menses. And, work with perimenopausal women proves that hormones can affect mood, memory, and thinking.13

**Culture’s Role**

Culture can influence diagnosis, experience, and communication of symptoms. Some patients may have difficulty saying “I am...”
sad” or “I am depressed” but can more easily say “I have bad nerves” or report vague somatic complaints.14

The direct language from the DSM-IV-TR says it best: Underdiagnosis or misdiagnosis can be reduced by being alert to ethnic and cultural specificity in the presenting complaints of a Major Depressive Episode. For example, in some cultures, depression may be experienced largely in somatic terms, rather than with sadness or guilt. Complaints of “nerves” and headaches (in Latino and Mediterranean cultures), or weakness, tiredness, or “imbalance” (in Chinese and Asian cultures), of problems of the “heart” (in Middle Eastern cultures), or of being “heartbroken” (among the Hopi) may express the depressive experience. Such presentations combine features of the Depressive, Anxiety, and Somatoform Disorders. Cultures also may differ in judgments about the seriousness of experiencing or expressing dysphoria (e.g., irritability may provoke greater concern than sadness or withdrawal). It is also imperative that the clinician not routinely dismiss a symptom merely because it is viewed as the “norm” for a culture.

Applying likelihoods indiscriminately is stereotyping. Within a culture, other factors affect members’ perception, communication, and presentation. For example, first-generation immigrants will differ from subsequent generations. Additionally, no cultural competence workshop can make an individual culturally competent. Cultural competence is a journey, not a destination. Clinicians must anticipate variations and differences.15,16

In a study conducted in 1991-1992 and published in the New England Journal of Medicine in 1999, Simon and colleagues examined the relationship between somatic symptoms and depression from the WHO’s study of psychological problems in general health care. After screening 25,916 patients in 14 countries, they found that 69% of patients with depression reported only somatic symptoms. Hispanics, African Americans, and Asians were more likely to have physical complaints in depression than whites.17

### Treatment Versus Cure

Depression is treatable, but it is not curable. Fewer than half of those diagnosed with MDD seek treatment. This is particularly distressing because available treatments can prevent the significant morbidity and mortality associated with MDD. Why do so few people seek help? Stigma remains a significant barrier.

Funding discrimination also affects treatment. Copayments for physician visits can be discriminatory, especially if the patient is a Medicare beneficiary. Medicare requires a copayment of 20% for most physicians, but it increases to 50% for a psychiatrist’s outpatient visits. Patients are often unaware of this difference and may be unable to continue treatment because of the financial burden of the copay. Many insurance companies also discriminate when it comes to mental health coverage of benefits. Stakeholders are working on federal legislation to establish parity. In the public sector, adequate funding for the mental health system is often a lower priority.

Population trends, our increasing knowledge about culture’s impact, and the propensity for studies to underenroll or even exclude minorities indicate why improving cultural competence is essential. Table 2 shows how the U.S. population is distributed among different ethnic groups.

### What Is Culture?

Defining terms like culture, ethnicity, race, and cultural competency is difficult because of a variation in meanings. A working definition of ethnicity might be “a collectivity of people within a larger society defined on the basis of both common origins, shared symbols, and standards for behavior.”18 Race refers to broad divisions of the human species, based on a common geographic origin and certain shared characteristics and being distinguished from other such groups by a characteristic gene frequency distribution. Cultural competency—a state of having a demonstrated ability to incorporate cultural concepts and data into care—is an ever-evolving process. On every multidisciplinary treatment team, someone should ask the question, “Are there any cultural issues here?”

The IOM report and the Surgeon General’s report reiterate the need for each health system and clinician to have a process or system to examine cultural issues. Disparate access to care for racial and ethnic minorities is often based on socioeconomic status.12

### Racial Variation: An Overview

Universal access to health care is a primary challenge for health care administrators. When researchers examined cardiovascular health and corrected for socioeconomic status, care was still disparate, proving not everything can be blamed on socioeconomic status.19

Increasing evidence also points to racial variation in the way patients present with symptoms, are diagnosed and treated, and respond to treatment. For example, African American psychiatric patients are disproportionately diagnosed with schizophrenia compared with white patients, but the reason is unknown. Researchers looked at 195 African American and white patients with at least 1 psychotic symptom (delusions, hallucinations, or prominent thought disorder) at admission during a 6-month period. Each patient was diagnosed clinically, by structured-interview, and by an expert-consensus team. African American men diagnosed by expert consensus with an affective disorder were significantly more likely than others to be diagnosed with schizophrenia, clinically or by structured interview. First-rank symptoms were more common in African American men, but this failed to explain the diagnosis bias. The difference may be due to clinician perception that psychotic symptoms are more chronic or persistent than affec-

### TABLE 2  U.S. Population by Race and Hispanic Origin: 2025 Projection

<table>
<thead>
<tr>
<th>Population</th>
<th>Percentage</th>
<th>2000</th>
<th>2025</th>
<th>Projected Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>337.8 m</td>
<td>209.3</td>
<td>2025</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>209.3 m</td>
<td>152.6</td>
<td>152.6</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>43.5 m</td>
<td>36.8</td>
<td>36.8</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>61.4 m</td>
<td>55.6</td>
<td>55.6</td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaskan native</td>
<td>2.7 m</td>
<td>1.9</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>20.9 m</td>
<td>18.0</td>
<td>18.0</td>
<td></td>
</tr>
</tbody>
</table>

tive symptoms in African American males. Fortunately, this bias seems to be changing.

Despite available treatments, few people with depression, across races and ethnicities, receive appropriate care. Minorities have poorer health status and more chronic conditions than whites, with Hispanic and Mexican Americans most disabled; the differences are more striking when taking into account that the minority population is, on average, younger than the white population. In terms of communication, Hispanic Americans have a greater problem understanding and communicating, with 43% reporting at least 1 problem communicating with their physician. Obviously, when patients seek health care treatment where their primary language is not spoken, equal access to treatment is impossible. Communication problems cause very poor outcomes with prescription writing and medication.

Optimal health care is best delivered when the primary care provider knows the patient's history and sees the patient regularly. Minority adults are less likely to have a usual source of care for many reasons: funding, perception of cost, and lack of trust. For all minorities, the likelihood of not having a regular doctor exceeds 20%; for Asian Americans, it exceeds 30% and for Hispanic Americans, it exceeds 40%. The Tuskegee Study, in which 399 African American males were not treated for syphilis so researchers could see its natural progression, has led to lingering suspicion of “experimentation.” The belief by minorities that such research conduct still exists has had a significant impact on clinical trials even though certain human rights protections are now in place. Society must reconcile minority people's perception of clinical trials with today's realities.

Minority adults also trust physicians less than do their white counterparts. A study that examined how closely patients followed doctors' orders found that whites followed orders 91% of the time, but minority adults did so only 84% of the time, a small but significant difference. The study found that only about half of patients, regardless of race, trust physicians.

Minority patients are also less likely to be treated by doctors of their own race and ethnicity. Thus, having a culturally competent clinician is imperative. Because of the shortage of minority clinicians, a perfect race-ethnicity-gender match is unlikely, even though some people would prefer that. This is an important issue to discuss even if it represents an impossibility. Figure 1 describes the specific reasons why doctors' advice is not followed, broken down by race and ethnicity. Clinicians who are not culturally competent will miss subtleties such as advice that violates the patient's personal beliefs.

### Racial Variation and Ethnic Disparities

Disparities exist in the access and quality of mental health services and pharmacologic treatments that might be beneficial to patients of different ethnic backgrounds. Studies, including the IOM report, confirm disparities. In a national survey, a larger percentage of minority patients reported not receiving needed medical care than white patients. Minority adults report many barriers to receiving appropriate health care, including paying for care, waiting times, and receiving specialty and preventive care. Minorities also report having fewer location choices for health care delivery. A larger percentage of minority patients (29% of African Americans, 37% of Hispanics) lack insurance coverage than white patients (12%). A study of 15,578 people nationwide who sought care in emergency departments found that blacks were 1.5 times more likely than whites to be denied authorization by their managed care plans. Access to antidepressant treatment has been especially difficult in certain vulnerable populations. Specifically, in one study, Medicaid and African American patients were less likely to receive selective serotonin reuptake inhibitors (SSRIs) than tricyclic antidepressants (TCAs) than privately insured patients.

After controlling for potential confounding factors, researchers following patients after mental health hospitalization learned that clinical quality performance ratings were much lower for African Americans than whites. A smaller proportion of minority patients report being satisfied with their care than white patients (46% versus 60%, respectively). African Americans were significantly less likely to receive an antidepressant at the time of their initial depression diagnosis than whites (28% versus 44%, respectively).

### Response Variation

Response to psychopharmacologic agents varies by ethnicity. Therefore, access to a wide range of agents is necessary for the successful treatment of all patients. Both the patient profile and the drug profile are important considerations.

In terms of the patient, several factors are important: age, gender (sexual functioning, teratogenic risk, breastfeeding), ethnicity, cultural influences, behavior (adherence issues), and occupation (e.g., the need to remain alert). Consider a woman of child-bearing age; she may promise to avoid pregnancy but may discontinue...
Factors determining racial variations in response to medications are complex and interdependent:

- Biological (greater polymorphism in drug metabolism enzymes).
- Cultural or psychosocial may affect efficacy and adherence.
- Environmental (climate, smoking, alcohol) may affect metabolism and disposition.

birth control. Or consider occupation: a forklift driver or a pilot cannot take something very sedating because their occupations require them to be alert. Although all medications tend to cause some sedation initially, continuing sedation is an intrusive problem.

The patient’s health status is also a concern. Liver and kidney function will affect drug metabolism and excretion. Heart functioning, especially a tendency toward orthostatic hypotension, can be a concern. A history of allergic and idiosyncratic reactions will certainly sway any decisions. A history of vulnerability to neurotoxicity, especially in drug-addicted patients, is a concern. It is wise to ask patients if they abuse or have abused drugs, have had a brain injury, or have experienced any other illness that is directly neurotoxic.

Although these drugs target the brain, they affect the rest of the body, too. Medical history that considers comorbid diseases and the presence of any other risk factors (i.e., altered electrolytes) is important. Past treatment efficacy offers an excellent clue to what will work. When patients are adamant that a certain medication will not work, clinicians must listen and ask direct questions.

Identifying factors that determine racial variation in drug response is a burgeoning science. Figure 2 demonstrates our understanding of how biological factors, genetics, age, gender, disease, etc., interplay with cultural factors, attitudes, and beliefs.

Compliance, or the more patient-friendly term adherence, also varies with culture. Minorities may be less likely to be compliant. Cultural views about medication (i.e., the doctor gave you medication because you are “crazy”) or lack of information about pharmacotherapy can be barriers to compliance. Media and community suspiciousness (i.e., “they are doping up kids on attention-deficit/hyperactivity disorder medication”) and reports of side effects, even if they are just rumors, contribute to nonadherence.

Considerable cultural, genetic, and psychosocial interindividual and interethnic differences exist, which influence the effectiveness of pharmacotherapy. Cultural factors include diet and food preference, use of herbal products, physicians’ bias when diagnosing, patients’ beliefs and expectations, and placebo effect.

Genetic variations in drug metabolism may influence the effectiveness of pharmacotherapies in mental health. Certain people are slow metabolizers; others are fast metabolizers. Rates of metabolism vary individually, and they vary within groups. Up to 90% of psychotherapeutic drugs are metabolized by the cytochrome P450 system. Polymorphism of CYP2D6 (which is responsible for metabolism of the TCAs, the SSRIs, many of the conventional neuroleptics, and risperidone and clozapine) is influenced by gender, race, and age. Unfortunately, technology that would tell us in advance which patients have a variation is nonexistent. Clinicians must monitor patients’ responses, knowing that up to 10% of whites and up to 19% of African Americans are poor metabolizers.

Similarly, many of the TCAs and SSRIs are metabolized by CYP 2C19, which also occurs in various forms. These enzymes usually process more than 1 type of pharmacotherapy. Clinicians should be aware that up to 33% of African Americans, 37% of Asians, and 39% of Panamanians are slow metabolizers of antipsychotic drugs and antidepressants.

African Americans are more susceptible to the central nervous system side effects of TCAs, which achieve higher concentrations in the bloodstream. For benzodiazepines, usually diazepam or alprazolam, studies consistently find slower metabolism and more negative impact on psychomotor performance in African Americans. Populations with higher incidences of impaired enzymes have been associated with increased blood levels of these drugs, diminished pharmacological effect, and more frequent side effects. If the parent drug is a pro-drug, the patient may be insensitive to any effect at all.

Studies have shown that African Americans tend to respond more quickly to antipsychotic medication and TCAs than white patients, probably due to differences in drug metabolism in the cytochrome P450 microsomal enzyme system. Between 47% and 70% of African Americans and Asian Americans may be slow metabolizers, which could account for higher drug concentrations and incidences of side effects. Newer agents with less effect on the hepatic P450 (like SSRIs and serotonin-norepinephrine reuptake inhibitors) may reduce the likelihood of toxicity and overdose for ethnic minorities.

**Conclusion**

Every sector of our health care system has a role in improving care and creating a safety net for people with MDD. Cost-management strategies to restrict access to pharmaceuticals, such as formularies, step-care protocols, and tiered copayments, should be broad and flexible enough to enable rational choices of drugs and dosages for all patients regardless of race or ethnic origin. Physicians should give individualized treatment to each patient and resist the temptation to apply cookbook drug therapy that does not consider race and ethnicity. Pharmaceutical companies should promote inclusion of significant numbers of patients representing varied racial and ethnic groups in clinical trials.
DISCLOSURES
Patrice Harris received an honorarium from Eli Lilly and Company for participation in the symposium upon which this article is based. She discloses no bias or conflict of interest.

REFERENCES
Pharmacologic Considerations in Treating Depression: A Patient-Centered Approach

CHRISTOPHER B. TICKNOR, MD

ABSTRACT

OBJECTIVE: To review the tricyclic antidepressants, selective serotonin reuptake inhibitors, and dually acting antidepressants and their economic and treatment implications.

SUMMARY: Major depressive disorder’s cost to the U.S. economy is staggering, but the selection of drugs available to treat it has expanded to include drugs that have better side-effect profiles. Regardless, remission rates are high, and, often, patients are not treated aggressively enough. Somatic presentations are more common than previously thought, and pain, in particular, may be associated with depression. Pain and depression are both regulated by serotonin and norepinephrine, and several studies suggest that using dual-action antidepressants may be helpful in patients who have an element of pain to their disorder. Titration to an adequate dose of any antidepressant is important, as is sustaining treatment for months to years, depending on the patient’s history.

CONCLUSION: Increasingly, the mental health community is realizing that the goal of treatment for patients with major depressive disorder must be sustained remission.

KEYWORDS: Serotonin reuptake inhibitors, Suicide, Major depressive episode, Somatic symptoms, Dually acting antidepressants

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In the early 1980s, the U.S. Department of Defense (DoD) established the Tri-Service PharmacoEconomic Council at Fort Sam Houston, Texas, comparing the use of tricyclic antidepressants (TCAs) with the new generation of selective serotonin reuptake inhibitors (SSRIs) as one of the first efforts at establishing cost-effective treatment options for major depressive disorder (MDD) for the DoD. These 2 categories were specifically selected to study (among others) because of the dramatic differences in pharmacy costs between TCAs and SSRIs. The study’s mission was to determine if one class should be considered first-line treatment. The PharmacoEconomic Council determined that using TCAs cost about twice as much overall as SSRIs, although the pharmacy costs were certainly much higher for SSRIs.

These particular studies did not consider lost productivity or absenteeism. Instead, they looked at actual raw costs: the cost of intensive care unit stays after accidental or deliberate overdoses and emergency department visits for side effects and complaints like constipation, urinary retention, fainting spells, etc. The eventual summary DoD guidelines designated SSRIs as first-line treatment. This article endeavors to take the reader through a patient-centered-care approach for understanding how psychiatrists select antidepressants. It will cover the importance of identifying depression’s somatic symptoms and pursuing remission. It is no longer acceptable for patients to get better; they must get completely well.

Epidemiology of Depression

One of every 6 people (17%) in the United States will suffer from an MDD episode during their lives.1 Patients who required hospitalization for MDD have up to a 35% lifetime risk for suicide.2 Depression’s total annual cost to society is approximately $44 billion in direct costs, with an additional $55 billion in lost productivity.3

People who experience depression are much more likely to develop other serious medical problems. In patients with serious medical problems who consequently develop depression, the problems of stress, morbidity, and mortality increase significantly.

The Journal of the American Medical Association published a landmark article elucidating morbidity and mortality issues in 1993. The researchers evaluated 222 patients who had first-occurrence myocardial infarctions (MI) using the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for major depressive episode. After interviewing patients 5 to 15 days after an MI, researchers followed the patients for 6 months. They then divided those patients with depression into 2 groups—those who were treated with antidepressants for their symptoms and those who were not. Age varied, and the sample was 78% male. At 6-month follow-up assessment, 12 patients had died, all from cardiac causes. Depression significantly predicted mortality after control for various confounding factors. Patients who became
depressed following an MI but were untreated had a 5-fold increase in mortality compared with people who were treated for their depression. The researchers concluded that “major depression in patients hospitalized following an MI is an independent risk factor for mortality at 6 months. Its impact is at least equivalent to that of left-ventricular dysfunction and history of previous MI. Additional study is needed to determine whether treatment of depression can influence post-MI survival and to assess possible underlying mechanisms.”

The results of the study were quite controversial. Why? The study’s small sample size, limited university setting, and short duration raised questions. The findings implied that some morbidity and mortality in post-MI patients had little to do with medical interventions. Essentially, the study identified health decline as depression’s sequel in post-MI patients.

A follow-up study, commissioned by the National Institutes of Health and the American Heart Association, was published in the journal Circulation in 1995. This longer study expanded the parameters involved to multiple centers across the country and significantly more patients. After 18 months, the study was halted because at 6 months, 12 months, and 18 months, the study investigators affirmed the previous study’s findings. Patients experiencing depression following an MI who were untreated had a significantly greater increase in mortality.

### Treating Depression

Depression is a very treatable mental illness. However, with the advent of fluoxetine, sertraline, paroxetine, venlafaxine, bupropion, mirtazapine, citalopram, and all the other antidepressants introduced in the last 15 years, and with the logarithmic increase in the number of prescriptions written for patients with depression, the incidence of suicide in the United States is still higher than is acceptable. Historically, we believed that compliance problems with monoamine oxidase inhibitors (MAOIs) and TCAs led to substantial numbers of treatment failures; enhancing compliance might impact the suicide rate. Clinicians applauded the arrival of the new generation of antidepressants. Because their side-effect profiles were superior, a dramatic decline in the incidence of suicide in the United States was anticipated over the next 5 to 10 years. A significant decline did occur, but not to the extent clinicians had hoped.

This is a multifactorial problem, and solutions must also be multifactorial. Barriers and stigma dissuade people from taking antidepressants even if they seek treatment. And, even with better-tolerated agents, the average length of time that patients remain on a prescribed SSRI is in the range of 6 to 8 weeks. At least 20%—and perhaps higher percentages—of patients never even have their prescription filled. Yet, patients with first episode MDD should stay on medication for a minimum of 6 to 9 months, with the average being 9 to 12 months.

It appears that patients visit primary care physicians more readily than they visit psychiatrists, and primary care physicians seem to be more accessible to diagnose depression and prescribe antidepressant medication. But, because patients either fail to visit the pharmacy or eventually discontinue their medications prematurely, our impact on the suicide rate is unacceptable.

Many patients remain undiagnosed, but even if they are diagnosed, some may be inadequately treated. Only a third of patients achieve real remission. Busy clinicians, overwhelmed by the volume of patients they must see, may not be able to follow up to ensure patients are achieving a therapeutic response.

Psychiatrists generally move patients into the therapeutic range quickly, but many primary care physicians don’t have the time or may not have the knowledge to know that higher doses of particular medications have a greater chance of treatment success. Overall, 30% to 45% of treated depressed patients will show partial response or no response at all. Remission failure is associated with increased relapse risk. One current drawback: available antidepressants take 2 to 4 weeks for significant symptom relief.

It would be ideal if the next generation of antidepressants could help patients by the end of the first week. By definition, remission rarely occurs at the end of the first 2 to 4 weeks; it probably takes longer than that. By the same token, one reason people commit suicide is because they actually seek care and get help. When diagnosed, they may be started on the right antidepressant medication for them; however, in the next 2 weeks, they are actually at the greatest risk for suicide.

Why is this? Once patients are on antidepressants, their energy level increases, followed somewhat later by a heightened sense of hope. Initially, patients may feel overwhelmed by the things that have happened as a consequence of depression. So for patients who are hopeless, tearful, have not slept well for weeks or months,
and feel desperate and who are then given an antidepressant, it is not the 2 weeks before initiation of treatment that represent the greatest chance of that person harming themselves. It is actually the next 2 weeks, when the patient is energized that the person already necessarily the highest medical services users. Patients who are not ready—or able—to acknowledge they have an emotional condition, but suffer from the physical symptoms of depression, will return repeatedly to their primary care physicians and utilize medical resources heavily. Patients with chief complaints of pain are high medical resource utilizers.

NIMH studies have shown that patients with moderate to severe depression are more likely to have poor outcomes without medication than the patient receiving psychotherapy alone. So what is psychotherapy counseling's role in mental health? It is probably most applicable to people who have mild to moderate or nonsevere, nonacute depression; this form of depression is more prevalent. But for the patient with the less common moderate to severe depression, combining counseling with psycho-pharmacologic management consistently provides the best outcome.

The Diagnostic and Statistical Manual of Mental Disorders classification for depression focuses primarily on emotional symptoms, with less emphasis on physical symptoms. Figure 2 depicts the central nervous system (CNS). In patients who have painful physical symptoms of depression, ascending and descending pain pathways are critical for pain perception. CNS imbalances of serotonin (5-HT) and norepinephrine (NE) may cause concurrent 5-HT and NE imbalances in the spinal cord. Serotonin and NE are key modulatory nerve transmitters in the descending inhibitory pathway and may actually reduce patients' sensation of pain.

Organized medicine has focused on depression's emotional symptoms. An old joke goes something like this: Psychiatrists only worry about problems from the neck up. But, secondary physical complaints that probably accompany depression in many populations may be more important than sadness, hopelessness, worthlessness, or guilt. Consider, for instance, that about 16% of antidepressants are prescribed by nonpsychiatrist medical specialists (i.e., primary care physicians, nurse practitioners, etc.). Our colleagues who are not psychiatrists must acknowledge and address these secondary physical symptoms, as must psychiatric specialists.

One study reviewed 1,000 adult clinic patients, selected both randomly and by convenience and screened for the presence or absence of 15 common physical symptoms and whether symptoms were somatoform (i.e., lacked an adequate physical explanation). Each of the 15 common symptoms was frequently somatoform. Patients with any physical symptom were more than 2 to 3 times more likely to have a diagnosis of a mood or anxiety disorder. As the number of physical symptoms increased, so did the likelihood of a psychiatric disorder. The prevalence of a mood disorder in patients with 0 to 1, 2 to 3, 4 to 5, 6 to 8, and 9 or more symptoms was 2%, 12%, 23%, 34%, and 60%, respectively, and the prevalence of an anxiety disorder was 1%, 7%, 13%, 30%, and 48%, respectively. Notable functional impairment also increased significantly with physical symptoms of depression. Thus, multiple or unexplained symptoms may signify a potentially treatable mood or anxiety disorder.

A second study, conducted 6 years later, confirmed these findings. Based on findings that suggested that depressed patients in non-Western countries are more likely to report somatic symptoms than are patients in Western countries, these researchers used data from the World Health Organization's study of psychological problems in general health care to examine the relation between somatic symptoms and depression. Conducted in 1991 and 1992, the study examined 25,916 patients in 14 countries. Of these patients, 5,447 agreed to a structured assessment of depressive and somatoform disorders. Approximately 10% (N = 1,146) of patients met the criteria for major depression (Figure 1). A full half of depressed patients reported multiple unexplained somatic symptoms; 11% denied depressive symptoms when questioned. Their proportions were consistent among the 15 centers. Thus, somatic symptoms associated with depression are common in many countries. The frequency of somatic presentation varies greatly and may reflect clinician or system characteristics or cultural differences among patients.

Interestingly enough, patients who seek psychiatric care are not necessarily the highest medical services users. Patients who are not ready—or able—to acknowledge they have an emotional condition, but suffer from the physical symptoms of depression, will return repeatedly to their primary care physicians and utilize medical resources heavily. Patients with chief complaints of pain are high medical resource utilizers.

Specialists.11

Somatic Presentation

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Antidepressants and Pain Treatment

These neurotransmitters are also critical in the ascending pathway in terms of how the pain message from upper or lower extremities, (i.e., low back pain, pelvic pain) is actually transmitted to the CNS. Serotonin and NE imbalances may enhance pain perception.13,14

Silverstein, using data from the Epidemiologic Catchment Area (ECA) study, divided patients into the following groups: (1) those who met criteria for major depression and had appetite and sleep disturbances and fatigue (somatic depression) and (2) those who met depression criteria but were somatic symptom-free (pure emotional depression). He found that the prevalence of somatic depression was much higher among women and that somatic depression was more likely to be associated with higher rates of pain. In women, significantly higher rates of anxiety disorders and chronic dysphoria were also seen.15,16

Patients, when asked why they were referred to a psychiatrist, often answer “Because I am nervous.” Nervousness is not a diagnosis; it is a symptom. Ethnicity and culture will affect the meaning of “nervousness.” Nervousness may be anxiety, tremulousness, insomnia, weakness, or fatigue.

Antidepressants and Pain Treatment

Researchers identified the TCAs as preferred treatment for patients with chronic pain syndromes almost 30 years ago because TCAs potentiate both 5-HT and NE in the CNS. Today, physicians in all specialties use them for medical conditions such as migraine headaches, low back pain, fibromyalgia, and peripheral neuropathy. Often, physicians employ a cocktail of different medications for patients with severe unrelenting pain, few of whom respond to monotherapy.17 SSRIs, however, are not usually effective for patients with pain, unless they are combined with other agents.18,19 Polypharmacy can be costly. Agents with dual 5-HT and NE activity, like the TCAs, appear to benefit pain patients more consistently than single-action antidepressants. Therefore, pain-free patients may be good candidates for an appropriate first-line choice of a generic SSRI. Using a patient-centered approach, patients who report an element of physical or painful symptoms, or perhaps poor, may be good candidates for an appropriate first-line choice of a generic SSRI. Using a patient-centered approach, patients who report an element of physical or painful symptoms, or perhaps perceiving pain, unless they are combined with other agents.18,19 Polypharmacy can be costly. Agents with dual 5-HT and NE activity, like the TCAs, appear to benefit pain patients more consistently than single-action antidepressants. Therefore, pain-free patients may be good candidates for an appropriate first-line choice of a generic SSRI. Using a patient-centered approach, patients who report an element of physical or painful symptoms, or perhaps patients with comorbid medical conditions that contribute to their perception of pain, would be poor candidates for an SSRI.

When patients have depression with concurrent painful physical symptoms, achieving remission is critical.20 The degree of physical symptom improvement correlates with the ability to achieve remission. This select group of patients will need to be treated with an agent that affects both 5-HT and NE (e.g., not an SSRI) in order to help them manage their physical symptoms or the achievement of remission will be unlikely.

Paykel and colleagues found that more than 90% of patients with residual symptoms of depression who responded to antidepressant therapy (but did not achieve remission) had mild to moderate general somatic symptoms.6 Somatic symptoms include fatigue, gastrointestinal complaints, pain, and other physical manifestations of the depression. These findings, confirmed in a second study, found that depressed patients were most likely to report or have “musculoskeletal diseases.” With remission, which has become the goal of treatment for patients with MDD, if patients did not become completely better, the majority suffered from ongoing painful, physical symptoms.

What links dual-acting antidepressants and pain? Again, antidepressants that increase both 5-HT and NE also impact both depression and some pain syndromes—with or without depression. It is useful to note that many of the indications for which we use antidepressants are not U.S. Food and Drug Administration-approved, including conditions such as fibromyalgia, for which there are no FDA-approved treatments or evidence of efficacy.

The ultimate goal in treating depression is to achieve complete symptom remission.22 Settling for a partial response can have disturbing consequences: increased likelihood of relapse and increased risk of treatment resistance.23 In summary, many depressed patients are likely to present with both emotional and associated physical symptoms. In the treatment of depression, unmet needs include addressing not only emotional symptoms but also treating the physical symptoms. The goals of successful treatment include achieving remission and symptom relief as rapidly as possible.

Neurotransmitters: Current Scientific Thinking

In the CNS, the Raphe nuclei in the lower part of the brain are the densest concentration of 5-HT-producing neurons within the upper CNS. People who have inadequately functioning Raphe nuclei are 5-HT-deficient. The locus coeruleus is the primary source of NE-producing neurons in the CNS. The CNS has both 5-HT and NE projections ascending into the prefrontal cortex and the cerebral hemispheres of the brain. The very prominent downward projections of these nuclei into the spinal cord, however, have been neglected. Recall the spinal cords ascending and descending pathways (Figure 2). These downward projections must have adequate systems of 5-HT and NE, particularly for depressed individuals suffering from painful physical symptoms.24

Serotonin’s and NE have definite functional domains. Insufficient NE leads to disorders of vigilance and motivation—patients who may be amotivational, lack energy, communicate poorly, and so forth and, therefore, might be good candidates for a medication like bupropion, which has strong dopamine and NE-promoting properties. Serotonin deficits tend to cause problems with impulse control, aggression, appetite, and sexual functioning. So, patients who are impulsive, aggressive, and lack sexual energy or interest may respond to a 5-HT-enhancing medication.25-28

Serotonin’s and NE’s domains also overlap, and symptoms of anxiety, irritability, pain, cognitive function, mood, and emotion result in this area of overlap. Unfortunately, it is impossible to determine, based on clinical interview alone, if patients are suffering from a 5-HT, NE, or dopamine deficiency.

Two Danish University Antidepressant Group studies compared the TCA clomipramine with citalopram and then paroxetine. In both studies, clomipramine was found more efficacious than the SSRI. It is possible that antidepressants that incorporate
more importantly, a return to normal psychosocial goal (and the primary care physician 100% remission. For patients who comply with treatment, our considering more ambitious goals such as this. in oncology, the treatment goal is total eradication of tumor cells for 5 years before establishing successful remission. Other medical specialties might also consider more ambitious goals such as this.

Realistically, all patients with major depression will not achieve 100% remission. For patients who comply with treatment, our goal (and the primary care physician’s goal) should be to choose an antidepressant medication that has the potential to achieve the therapeutic dose during the first days of treatment. Additionally, it should be tolerable so that patients stay on the medicine long enough to achieve remission.

Research criteria still define antidepressant response as a 50% reduction in symptoms from the baseline HAM-D score. One observed outcome of the Paykel study in 1995 was the following: Depressed patients with residual symptoms who were treated for depression and did not achieve complete symptom resolution had a greater risk of relapse. In fact, 76% relapsed. Paykel determined that more than 90% of study participants had mild to moderate somatic symptoms. Patients treated to the point of remission, however, only relapsed at a rate of 25%. The long-term outcome of achieving remission was much more favorable.*

Paykel defined remission as minimal or no symptoms of depression and, more importantly, a return to normal psychosocial functioning. In general, depressed patients are not concerned with research definitions; they want to know if and when they will be better. They define “better” as feeling better, sleeping well, eating normally, improved concentration, and functioning well at work and home. They want effectiveness in the real world, not clinical research trial efficacy.

Many scales are often used (including the BECK, IAS, and Madras), but the HAM-D17 may be appropriate for both research and office use. Figure 3 depicts the HAM-D17, with a score of 7 or less defined as virtually complete symptom resolution. Scores of 15 or greater constitute ongoing symptoms of depression. So, if a patient enrolled in a clinical trial had scored 30 and treatment reduces the HAM-D17 total score to 15, it is likely that the patient will be pleased with the improvement. The patient will probably no longer be suicidal or tearful and may, in fact, be hopeful. Perhaps in an effort to please the physician, he or she will report feeling better. In response, the physician will reduce the current dose of medication even though the patient has not achieved remission and, therefore, it is not therapeutically appropriate to persist at this dose of the medicine. Using a depression measurement instrument, however, helps physicians assess actual improvement in functioning and directs dose modifications toward the achievement of remission. Those who disagree would indicate that the HAM-D17 fails to quantify reverse neurovegetative symptoms and is biased to sedating antidepressants.

This is an essential message to impart to primary care physicians. Although many are comfortable with quantifiable medical measurements like cholesterol levels, they seem to shun the psychiatric research diagnostic instruments. Ancillary personnel can, however, be trained to administer these instruments. Short of using an instrument, there is virtually no way to measure complete symptom remission.

A depressed patient’s clinical progression after diagnosis and treatment can be described using the 5 Rs: response, remission, relapse, recovery, and recurrence. Once diagnosed and treated, it is hoped that patients begin to respond. They may steadily improve to remission or recovery, or, at any time, they may relapse. Depression is not an illness that affects most people only once and never recurs. Depression is often a chronic, unrelenting medical illness that takes lives. The chance of recurrence following a first episode of depression is about 50%. After 2 episodes of depression, the chance of future episodes increases to about 70%. And after 3 distinct episodes of depression, the chance of recurrence exceeds 90%. Many practicing psychiatrists have indicated that length of treatment should follow the following paradigm: Treat a first episode depression for about 9 months. (Many psychiatrists never stop an antidepressant in the winter months, as the risk of relapse for patients prone to developing seasonal affective disorder is too great.) For a second episode of depression, treatment for 2 to

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*The HAM-D17 was selected as a measure because it is a widely used instrument in research and practice. It assesses depression symptoms using a 17-item scale, with scores ranging from 0 to 54, with higher scores indicating more severe depression. A score of 15 or greater is considered indicative of depression, while a score of 7 or less indicates remission. The figure illustrates the distinction between response (a 50% reduction in symptoms) and remission (a score of 7 or less).
3 years is prudent. A third (or more) episode(s) of depression reasonably invites treatment for 5 years to life. Only complete remission appears to reduce the incidence of suicide.

The idea of remission in depression is exactly like the concept of remission in any other medical illness. In 1998, Miller and colleagues examined this issue of the significant impairment many chronically depressed patients experience. The researchers compared sertraline and imipramine after patients with chronic depression were treated for 12 weeks. They examined the subjects’ psychosocial functioning data before and after treatment with normative data available from community samples. They found that treatment with sertraline or imipramine improved psychosocial functioning significantly, and these improvements were noted fairly early—at week 4. But despite early improvements in functioning, participants did not reach levels of psychosocial functioning similar to the nondepressed community sample unless they achieved full symptomatic response (remission) during acute treatment. These finding underscore the importance of achieving remission.

Treatment-resistant depression may account for up to 30% of patients diagnosed with depression. These patients may take 1 antidepressant for 3 or 4 months, then another for 3 or 4 months, until they have tried multiple antidepressants with limited benefit. Monitoring reports may indicate that this patient is a very high utilizer of medical resources. Often, polypharmacy is necessary with a dual-action antidepressant (perhaps extended-release venlafaxine) and/or an augmenting agent like bupropion, and/or a mood stabilizer like lamotrigine. The potential consequences of failing to achieve remission are summarized in Table 1.

### Limitations of Current Dual-Acting Antidepressants

Currently, only the TCAs and venlafaxine possess the dual action needed for optimal remission. Nevertheless, they have multiple limitations. The TCAs are associated with cardiotoxicity, orthostasis, anticholinergic effects, weight gain, and sedation. Accidental dose changes (i.e., forgetting and taking medication twice) can lead to prolonged QT interval on electrocardiogram or sudden death in patients with arrhythmia. Orthostasis (impaired ability to adjust to positional changes) is a serious concern, particularly in the elderly. It can lead to falls and fractures, complicating care. Anticholinergic side effects can cause noncompliance, as does weight gain and profound sedation, which is why dosing at bedtime is preferred.

Venlafaxine requires high doses to balance available 5-HT and NE reuptake inhibition. At 75 mg a day, venlafaxine XR is just an expensive SSRI; most patients will require at least 150 mg a day (and often more) in order to benefit from both 5-HT and NE enhancement with venlafaxine. Venlafaxine XR also has a worrisome cardiovascular profile, which includes hypertension at higher doses. In a venlafaxine study submitted to the FDA to establish efficacy and safety, 2% of patients on placebo developed clinical hypertension. The incidence was 3% with venlafaxine XR at 75 mg daily. At 150 mg of venlafaxine daily, however, the incidence of clinical hypertension increased to about 5%, and at more than 225 mg daily, it reached 8% to 13%. All venlafaxine XR patients must have their blood pressure monitored because, depending on the dose, as many as 1 in 8 may develop clinical hypertension.

A group at the University of Pittsburgh published data comparing remission rates using SSRIs and venlafaxine. Using data from 8 comparable randomized, double-blind studies of MDD, they examined response rates in 851 venlafaxine patients and 748 fluoxetine, paroxetine, or fluvoxamine patients, and compared the response rates with 446 placebo-treated patients. Of note, all studies were funded by the same pharmaceutical company, not all had been published, and the bias in patient selection was toward patients who had previously failed SSRIs. Forty-five percent of venlafaxine-treated patients reached remission, defined as <7 on the HAM-D17. For SSRIs, 35% of patients achieved remission, and for placebo patients, 25% reached remission. This study identified a relative benefit ratio of 40% for SSRIs compared with 80% for venlafaxine.

Duloxetine is an experimental dual-action antidepressant for treatment of depression, with FDA approval expected in 2004. Duloxetine also has limitations. The incidence of nausea approaches 20% during the first week of therapy. Discontinuation syndrome has been reported with duloxetine, as it also has with venlafaxine.

### Strategies to Achieve Remission

To ensure remission, several steps are necessary. First, clinicians must diagnose all symptoms appropriately. Then, choosing a treatment that can provide remission—that is, an antidepressant that works on multiple transmitters should be strongly considered—and employing it at adequate doses is the next step. Clinicians need to work with patients to help them adhere to treatment and educate them about the critical goal: remission. Finally, combination and augmentation strategies may be needed for treatment refractory of depressed patients after monotherapy fails.

Studies examining combination strategies have reported mixed results overall. This may be due to the treatment refractory nature of some of these patients. Use of a single-acting agent (e.g., SSRI) may be less likely to lead to remission than combining it with an agent that acts on a different neurotransmitter system.

### TABLE 1 Potential Consequences of Failing to Achieve Remission

- Three-time greater risk of relapse
- Continued psychosocial limitations
- Continued impairment at work
- Worsened prognosis of Axis III (other medical) disorders
- Increased utilization of medical services
- Sustained elevation of suicide and substance abuse risks

Source: references 22 and 38.
Pharmacologic Considerations in Treating Depression: A Patient-Centered Approach

(e.g., desipramine). Additionally, several studies confirm that combined treatment (combining medication with psychotherapy) produces better response in moderate to severe depression than either therapy alone. 30-42

Conclusion

As we look for new and better antidepressants, optimizing efficacy, improving safety, and increasing tolerability in both the acute and long-term will be essential goals. For now, the focus on enhancing treatment success is crucial. Nearly half of all patients discontinue their antidepressant medication within the first or second month of therapy, often due to poor tolerability. 43 Thus, choosing an antidepressant with the greatest likelihood of remission is important, as is achieving remission in a more rapid time frame. Selecting medications based on their side-effect profile may enhance adherence, although there is limited clinical trial data to support this hypothesis.

In mental health, clinicians are moving toward treatment algorithms as we accrue evidence about what works best. These algorithms address many possible clinical problems and include medication, therapy, and even electroconvulsive therapy for a very small percentage of the depressed population. As antidepressants have evolved, we have learned that multiple mechanisms may be the key to symptom remission. We know that improved outcomes occur because a better selection of antidepressants is available, evidence suggests appropriate dosing, and the importance of thorough and frequent monitoring is better appreciated.

DISCLOSURES

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Depression is an illness—a physical illness—that must be treated in very much the same way we would treat diabetes or hypertension. The outcomes of its treatment are identical to those sought with other illnesses:

- clinical response,
- improvements in quality of life and individual functioning,
- improved productivity and performance at work,
- decreased utilization of clinical and other resources, and
- decreased direct medical costs, indirect costs having to do with productivity, and some other costs, too.

Figure 1 shows how all of these factors interrelate. Scientists, as they design new drugs, are most interested in safety and efficacy, which ultimately contribute to tolerability and effectiveness. Clinicians select treatments by looking at tolerability and effectiveness. Drugs that cause adverse events increase service utilization and cost more. So, tolerability and safety are driving factors in the United States and Canada.

Effectiveness, or how the drug performs in real-world settings, has more to do with social functioning. Do people have an improved quality of life, feeling better about themselves? Can the differences be observed and measured? Can individuals “make it” on their own? Can they live in less-restrictive environments (i.e., the community instead of the hospital) or receive treatment in clinics or group settings? Are they able to return to work? Or, in more-severe cases, can a family member caring for them return to work? Can they function more effectively at work and be as productive as they were before becoming ill?

### Measuring Outcomes

Various methods of measuring effectiveness exist. Health economics is the study of the consequences (outcomes) and costs (inputs) of health care products or services. Pharmacoeconomics augments the study of consequences (outcomes) and costs associated with health care products and services to look specifically at:

- Efficacy
- Effectiveness
- Tolerability
- Safety
- Quality of Life
- Employment
- Social Functioning
- Resource Utilization
- Medical Costs

![Figure 1](image-url)
pharmaceutical products and services. We use a variety of instruments to assess patient improvement. But do these measures really make sense to us today as drugs have evolved? Many of the early antidepressants, for example, were highly sedating, and sedation and low energy and lethargy are symptoms associated with depression. Early rating scales for drugs that cause sedation as an adverse event may no longer make sense with newer antidepressants like selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) that cause very little sedation. A number of organizations and individuals are working to create better rating scales; however, until that time, regulatory bodies and investigators must depend on the present (gold standard) tools like the Hamilton Depression Rating Scale (HAM-D17) which may not be adequate for demonstrating new treatments with improved tolerability and safety.

Pharmacists are familiar with direct and indirect costs. In the mental health field, “other” costs include some things unique to altered thought processes, like family burden and involvement with the justice system. Various stakeholders (patients, providers, payers, and society) will have a different perspective on health care because they are affected by different drivers. Treatment measurements will be affected by who is measuring and the intent of the study. From the patient’s perspective, for example, a copayment or a fee when they have their prescriptions filled is a driver, and they may perceive the copayment as the actual cost of the drug. Patients may complain that a new drug costs triple what their previous drug cost because their copayment changed; in reality, it may be because the new drug costs the same or more but falls into a higher copayment rung. It’s important that pharmacists promote clinical decisions that encourage adherence; sometimes, this means making physicians aware of patients’ cost concerns.

## Economic Measurement Models

Managed care uses various types of economic evaluation models. These include cost-minimization analyses; cost-effectiveness analyses (CEA); cost-benefit analyses; and cost-utility analyses (see Sidebar). Among these, CEA deserves special attention, as the term is commonly misused in medicine. Sometimes, it is used as an excuse to use—or not use—drugs. It can be difficult to understand what researchers mean when they use CEA in their results because their study may lack effectiveness measures. What are they really trying to elucidate?

What is the most appropriate study design for a given set of health data or research questions? The answer often depends on the perspective. CEA focuses on actual cost of therapy and health benefits. The therapy’s effects are the outcome measures. When pharmacists see cost-effectiveness referred to in studies, they should determine if the cost-effectiveness measure(s) used in the analysis makes sense. Researchers sometimes make conclusions based on what they believe data means. Table 1 lists key questions requiring answers when evaluating health outcomes research.

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<th>Evaluating Health Outcomes Research</th>
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<td><strong>Cost-Minimization Analysis</strong></td>
<td>The most basic of pharmacoeconomic study designs, it compares the cost of 2 or more alternatives while assuming identical outcomes of each.</td>
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<td><strong>Cost-Benefit Analysis</strong></td>
<td>Differs from CMA in that the outcomes of alternatives are not considered equal. The outcomes are assigned a monetary unit, and a cost-benefit ratio is calculated to determine the greatest benefit relative to cost.</td>
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<td><strong>Cost-Effectiveness Analysis</strong></td>
<td>Measures outcomes of analysis assigning a natural or physical unit like years of life saved or complications avoided. It should only be used when comparing alternatives with similar outcomes.</td>
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<tr>
<td><strong>Cost-Utility Analysis</strong></td>
<td>Differs from CEA in that it incorporates patient preferences and measure quality-adjusted life-years, since patients do not value each year of life gained from an intervention equally.</td>
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**Source:** reference 1.

### SIDEBAR Pharmacoeconomic Definitions

- **Cost-Minimization Analysis:** The cost-minimization analysis makes sense. Researchers sometimes make conclusions based on what they believe data means. Table 1 lists key questions requiring answers when evaluating health outcomes research.

**What is the most appropriate study design for a given set of health data or research questions?** The answer often depends on the perspective. CEA focuses on actual cost of therapy and health benefits. The therapy’s effects are the outcome measures. When pharmacists see cost-effectiveness referred to in studies, they should determine if the cost-effectiveness measure(s) used in the analysis makes sense. Researchers sometimes make conclusions based on what they believe data means. Table 1 lists key questions requiring answers when evaluating health outcomes research.

**What is not cost-effectiveness?** Cost-effectiveness is not shifting the cost to another source. If medical costs are decreased when a drug is used but overall costs remain the same, that is not cost-effectiveness. Pressure to reduce costs in the pharmacy is great, and often it is exerted with the suggestion to use less-expensive drugs. For patients with major depressive disorder or schizophrenia, empirically switching from a medication that has been effective to another less-expensive option is hazardous and, in fact, represents an unacceptable practice. Once the difficult task of finding an effective drug is accomplished, and the patient is discharged from the hospital, switching can disturb a delicate balance and result in rehospitalization. The cost of the drug should never be the sole deciding factor.

CEA must address all costs, as well as the risks and benefits, of treatment choices under consideration. Typically, models examine combination or comparative drug therapies. Is it beneficial to actually demonstrate that patients continue to thrive with less-expensive therapies? A failed switch from one drug to another is very costly and can consume all of the dollars saved from hundreds of patients in whom the less-costly drug worked.

### Measurement Meets Perspective

Several key questions must be answered when decisions about health care are made. What perspective is being used? Every stakeholder’s perspective or potential perception must be considered. Are the costs relevant? What outcomes are important to the patient, to the health system, or to society? And, where is the burden of proof? If the parties responsible for proving or disproving a hypotheses have an interest in one outcome or another, the validity of the results may be weakened. Health care outcomes research
must focus on outcomes beyond the usual measures of clinical response and tolerability. It must assess the economic implications of clinical choices and decisions, and care must be exercised to ensure that these sciences are not misused in health care.

**Economic Burden of Depression: 1990 and 2000**

A comparison of the change in economic burden of depression in the last decade of the century starts with a study by Greenberg et al. using a human capital approach. They developed prevalence-based estimates of 3 major cost-of-illness categories: direct medical costs, psychiatric costs, and pharmacologic care costs; depression-related mortality costs (e.g., suicide); and workplace morbidity costs. In terms of workplace costs, they included reduced productivity while people with depression were at work during illness episodes (called presenteeism) and absenteeism. The annual costs of depression in the United States were estimated at approximately $43.7 billion, with 28% attributed to direct costs, 17% to mortality costs, and 55% to morbidity costs. In terms of workplace costs, they included reduced productivity while people with depression were at work during illness episodes (called presenteeism) and absenteeism. The annual costs of depression in the United States were estimated at approximately $43.7 billion, with 28% attributed to direct costs, 17% to mortality costs, and 55% to morbidity costs. The researchers acknowledged that many important cost categories had not been estimated, and the actual burden of depression was probably greater than implied.

This study estimated direct pharmaceutical costs at about 3% of total cost. Although few SSRIs were available, clinicians considered the tricyclic antidepressants (TCA) nortriptyline as having a favorable side-effect profile. It was one of the most expensive antidepressants; contrary to popular belief, even 10 years ago, drugs were costly. Another similar study, the National Comorbidity Survey (NCS), estimated a slightly higher depression-related cost: $53 billion,

\[ \text{FIGURE 2 Economic Burden of Depression: 1990 Versus 2000} \]

The direct costs did rise from 1990 to 2000. The 1990 NCS estimate of $53 billion corrected to 2000 dollars would be about $76 billion. So, the economic burden of depression in 2000 (NCS-R) is around $83 billion dollars, which is not terribly different from the burden in 1990. Morbidity in both years was reported at 62% of total costs, and direct costs increased, probably in part due to drug costs. The mortality rate, however, was halved. Simultaneously, the U.S. economy improved and antidepressant use expanded, 2 events that may have contributed to a decreased rate of suicide. These findings are exceptional if one considers that treatment rates tripled between 1987 and 1997; thus, treatment rates in 2000 were substantially higher.

Although direct payment costs did actually increase 31% from the year 1990 to 2000, the number of inpatient days decreased substantially, in part due to managed care influences and possibly improved tolerability and medication adherence. Clinicians were more able to treat patients with outpatient visits and, consequently, outpatient visits doubled. The number of people treated for depression who remained stable increased significantly.

**Economics of Care: Patients With Depression**

It is terribly important for all health care providers to recognize the facts about depression relapse: after 1 episode of depression, the likelihood of relapse is 50%; after 2, it increases to more than 70%, after 3, it exceeds 90%. Treatment refractory patients cost substantially more money to care for, and it is more difficult to identify effective treatments. Early treatment, therefore, has great value. The mainstream treatment for depression is medication, and the SSRIs are the drugs of choice. Each of the SSRIs is structurally quite different even though they occupy the same class based on inhibition of serotonin reuptake. The difference translates into response—some people will respond and others will not—and concern about switching. The same will probably be proven true.
of the SNRIs.

Finance can be a tremendous driver when pharmacists consider what drugs to carry and what not to carry, although its importance varies with different environments. In many environments, average wholesale price (AWP) is a preferred decision-making tool. Its application is increasing in its diversity. AWP is based on 120% to 125% of actual catalog price. It is not uncommon in today's market for managed care to reimburse pharmacies at 13% to 17% below AWP and for Medicaid to only pay 95% of in-office injectable costs. Hospitals do not use AWP using group purchasing organization contracts instead, and Medicaid reimburses at catalogue price but receives a rebate from industry. Medicare does not yet pay for prescriptions. The bottom line: Nobody pays AWP, but it is still the standard for pricing evaluation and comparisons. A better, more-relevant pricing index is needed.

Drug costs have many influences. The manufacturer's actual price increases about 3% to 5% annually, consistent with inflationary increases. Litigation costs have clearly driven up pharmaceutical prices, especially in the United States, where no damage caps currently exist. Research and development expenses of around $850 million per medication, including the average of 12 years it takes from inception to U.S. Food and Drug Administration approval and product failures due to unacceptable safety or efficacy, are factored into an approved product cost. Of every 5,000 compounds that are actually screened by companies, only 1 becomes commercially available and is approved by the FDA. Manufacturers must regain their investment during the few patent years left (often as little as 2 to 3 years) once the drug is FDA-approved.

Operating costs and regulatory adherence contribute to total costs, as do sales and marketing. Prescriber sampling and indigent-care programs also contribute to product cost. Financial support for medical education, middleman expenses (pharmacy benefit managers, group purchasing organizations, state and federal government), and shareholder expectations are additional issues. All these expenses ultimately influence the cost of marketed drugs.

In 1990, prescription drug spending increased almost 19% over the previous year. Of that increase, approximately 11% was associated with increased drug utilization, perhaps further demonstrating that more people are being treated. Newly approved and marketed medications accounted for only about 4%, as did inflation. A large proportion of the increase was attributed to utilization.6

Access Limits

Limiting access to drugs used in mental health, or switching solely for cost advantages, is a serious mistake.

As long ago as 1994, Soumerai et al. demonstrated the risks inherent in prescription drug limitations. They examined the effects of New Hampshire's 3-prescription-per-month payment cap that applied to psychotropic drugs and acute mental health care outpatients with schizophrenia in 1982 and 1983. They reviewed Medicaid claims data over a 42-month period and clinic-
A Managed Care Perspective of Individualized Care

continue to comply so they will ultimately benefit from the drug. Often after a week or two, clinicians increase the antidepressant dose because patients seem not to be responding or patients want “fast results.” The danger in rapid upward titration is that it may be premature. Patients may receive more medication than they need and may experience some adverse events or even toxic consequences, depending on the medication. Balancing the side-effect and cost profiles regardless of dose is an art.

It is essential for clinicians to compare side-effect burdens and to understand the overall burden. For example, with the older antipsychotics, the primary concern was extrapyramidal side effects (EPS). They occurred frequently and contributed to nonadherence. Clinicians and patients have to balance EPS with sedation, sexual dysfunction, and weight gain. And with the older antipsychotic drugs, for example, the primary concern was EPS, which occurred frequently and contributed to nonadherence. Clinicians tried to balance EPS with sedation, sexual dysfunction, and weight gain.

The new generation of antipsychotic drugs—the atypical antipsychotics—have a far lower EPS liability compared with other adverse events. So, clinicians and patients no longer express concern about EPS. With this positive change, the new focus is appearance, improving sexual activity, and engaging in social interactions.

Switching or Not?

Clearly, a patient’s tolerance for or response to a particular medication may prompt clinicians to consider switching medications. Certain actions are warranted before switching is started.

First, adherence with the current regimen must be elucidated. Clinicians should understand why patients have been nonadherent. Next, the adequacy of the current regimen should be examined. Doses that are too low should be increased, and other causes of failure to respond contemplated. If patients report complete adherence but they are not responding, clinicians should be wary. Many patients are less than truthful about adherence, and stockpile prescriptions.

Next, the clinician should determine the feasibility of a cross-taper plan. Does the patient have the ability or are there support people in the residence that can help the patient as one medication’s dose decreases and the other’s rises?

Additionally, prescribers must evaluate the potential for drug-drug interactions. Some of the drugs we use to treat depression have serious potential interactions.

If it appears that switching is both necessary and feasible, clinicians need to work closely with patients to develop a strategy to minimize medication errors. Once-daily dosing is the simplest of strategies and best for adherence, but it is not always possible. Other strategies include associating doses with routine daily events (e.g., with meals 3 times a day), labeling doses clearly and specifically, or distributing medication cards that reinforce the new schedule.

One step that clinicians often overlook is ensuring that the patient has adequate antidepressant coverage (doses sufficient to treat the patient) at all times during a cross-taper. Inadequate coverage may lead to break-through symptoms and may cause the plan to fail or result in misadventures for patients. As the cross-taper proceeds, it is important to reach an adequate therapeutic dose. Often, this means increasing contact with the patient to make periodic assessments.

Each trial with a new medication should be of adequate duration, and continuity of the treatment plan is essential. This is especially important as patients move from one level of care to another. The taper plan must be communicated to the new (or receiving) treatment team when patients are transferred or discharged, creating an opportunity for pharmacist involvement. The clinicians’ focus should be to make a reasonable attempt to finish the cross-taper; often, the clinician stops the cross-taper because the patient appears to be doing better on 2 drugs (i.e., the old medication lingers on the drug regimen because clinicians are concerned that 1 medication will not be as effective as 2, resulting in unnecessary polypharmacy.

Finally, members of the multidisciplinary team should decide in advance how to determine if the new agent can be used alone or if it is necessary to continue the old agent. Otherwise, the old medication may never be discontinued, and the new medication may not be increased to its effective dose, resulting in increased cost and suboptimal response and creating a potential opportunity for nonadherence. Early side effects due to combination therapy may discourage patients, prompting them to consider discontinuing the trial. The patient-provider team has to work through that period. All involved must remember that using subtherapeutic doses of multiple drugs is not helpful.

In special cases, it is appropriate to combine antidepressants although our goal should always be monotherapy unless a combination can be justified. These decisions should be made on a case-by-case basis and may require specialist care (e.g., a psychiatrist).

Cultural Concerns

Expectations about and the definition of “acceptable outcome” varies from culture to culture. In any illness, and in psychiatry in particular, placebo responses are important. Placebo responses only occur if patients have expectations and an outcome occurs. The opposite—a “nocebo” effect—occurs if no expectation exists and, indeed, nothing happens. Placebos are not nontreatment. Although their ingredient is inactive, if patients believe that they are receiving powerful medicine and we encourage them to continue to participate in a study because they are receiving powerful medicine, some will respond.

The International Council on Harmonization has moved to develop a standardized set of information for drugs to be presented to regulatory bodies. Pharmacokinetic and pharmacodynamic differences may complicate this project. For example, it is not possible to bring a drug to market in Japan unless it is studied, at least in part, in patients who are Japanese. Genetic differences may result in significant metabolic differences and clinical response.
And, further, ethnic groups are mixing all over the world, making it more difficult to describe populations based on ethnicity.9

■ Conclusion

So, what is depression? It depends on where and whom you ask, and also how you ask the question. It could refer to depressed mood, and in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revised (DSM-IV-TR, American Psychiatric Association), it may refer to Major Depressive Episode, Major Depressive Disorder, Dysthymic Disorder, Depression Secondary to a Medical Condition (e.g., following a stroke or myocardial infarction). Consider this finding from a large clinical trial conducted at 260 sites in 30 countries in 6 languages. The same questionnaire was used to collect data in all the countries. Patients were asked to describe their mood in the 2 weeks since their last visit and to write their impression in a box on a sheet of paper, about one third of a page. Typically, Germans provided very curt, short answers and gave very little information. In contrast, people in Italy and France filled the block with tiny writing and then continued on the back of the page, using flowery detail describing changes as frequently as hourly. Culture and genetic differences matter. A patient’s care should be individualized, with consideration given to the individuals (and family members’) past response to medication and their culture and expectations.

DISCLOSURES

Lawrence J. Cohen received an honorarium from Eli Lilly and Company for participation in the symposium upon which this article is based. He discloses no bias or conflict of interest.

REFERENCES

Continuing Education
Depression: New Perspectives, Understandings, and Treatments

Date: __________________________

In order to receive CE credit for this program, you must complete this form and the Program Evaluation form in addition to completing the posttest with a score of at least 70% (forms may be photocopied). Please mail all materials to the Academy of Managed Care Pharmacy, 100 N. Pitt Street, Suite 400, Alexandria, VA 22314. To receive credit, these forms must reach the Academy of Managed Care Pharmacy by March 1, 2007. CE certificates will be mailed to your address (below) as soon as possible after receipt of the Record of Completion and Program Evaluation forms and the posttest is graded and successful completion is determined.

This continuing education program is made available through an educational grant from Eli Lilly and Company.

All information will be kept confidential; it is used only for the processing and mailing of your CE statement. You must complete and sign this form in order to receive CE credit for completing this program.

❑ I verify that I have completed the program and posttest for “Depression: New Perspectives, Understandings, and Treatments.”

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Continuing Education
Depression: New Perspectives, Understandings, and Treatments

Please indicate the correct answers on the Record of Completion.

1. The number of people in the United States who will suffer a major depressive episode during their lifetime is
   a. 1 in 10.
   b. 1 in 15.
   c. 1 in 6.
   d. 1 in 4.

2. Patients who became depressed following a myocardial infarction but were untreated had which increase in mortality?
   a. 2-fold
   b. 5-fold
   c. 12-fold
   d. none

3. Which of the following statements about major depressive disorder patients is true?
   a. They visit primary care physicians less frequently.
   b. They visit primary care physicians about the same as psychiatrists.
   c. They visit psychiatrists 50% more frequently than primary care physicians.
   d. They visit primary care physicians more readily than they visit psychiatrists.

4. Overall, what percentage of treated depressed patients will show partial response or no response at all to medication?
   a. 30% to 45%
   b. 25% to 30%
   c. 45% to 60%
   d. 40% to 50%

5. Patients who seek psychiatric care are
   a. not necessarily the highest utilizers of medical services.
   b. very high utilizers of medical services.
   c. very low utilizers of medical services.
   d. no more or less likely to utilize medical services than any other group.

6. Patients who have depression with concurrent painful physical symptoms might respond better to which medication(s) in order to best manage their physical symptoms?
   a. Agents that affect 5-HT
   b. Agents that affect NE
   c. both a and b
   d. none of the above

7. The ultimate goal in treating depression is to
   a. achieve remission in 70% of cases treated.
   b. achieve complete symptom remission.
   c. achieve medication compliance with 80% of patients treated.
   d. none of the above

8. Scientists, as they design new drugs, are most interested in
   a. tolerability and safety.
   b. tolerability and effectiveness.
   c. safety and effectiveness.
   d. safety and efficacy.

9. Health economics is the study of
   a. pharmaceutical products and services.
   b. cost-effectiveness analyses and cost-benefit analyses.
   c. cost-utility analyses.
   d. consequences and/or costs of health care products and services.

10. The Centers for Disease Control estimate that approximately what percent of suicides are attributable to depression?
    a. 60%
    b. 45%
    c. 50%
    d. 40%

11. After 1 episode of depression, the likelihood of relapse is
    a. 65%.
    b. 40%.
    c. 50%.
    d. none of these

12. After 3 episodes of depression, the likelihood of relapse exceeds
    a. 90%.
    b. 75%.
    c. 65%.
    d. 50%.

13. The mainstay of treatment for depression is
    a. individual psychotherapy and medication.
    b. medication.
    c. individual psychotherapy.
    d. medication and group psychotherapy.
Please indicate the correct answers on the Record of Completion.

14. The drugs of choice for treatment of depression with medication are
   a. atypical antipsychotics.
   b. traditional antipsychotics.
   c. SSRIs.
   d. none of the above

15. Caring for patients in mental health settings means engaging them using the 3 “C’s,” which are defined as
   a. communication, clarity, and compassion.
   b. communication, clarity, and collaboration.
   c. compassion, clarity, and collaboration.
   d. clarity, collaboration, and communication.

16. Although major depressive disorder can begin at any time, it most commonly starts in
   a. the early 30s.
   b. the late teens.
   c. the mid-20s.
   d. puberty.

17. Suicides rates are highest in which of the following groups?
   a. Elderly women
   b. Women in their reproductive years and elderly men
   c. Girls aged 10 to 14 years
   d. It hasn’t been measured.

18. Depression is treatable with
   a. medication and therapy and is highly curable.
   b. medication and therapy but is not curable.
   c. medication and therapy, but a cure rate has not been established.
   d. medication and therapy, with a cure rate in the 50% to 60% range.

19. For patients with major depressive disorder, our goal should be to choose an antidepressant medication that has the potential to achieve therapeutic dose
   a. during the first 6 weeks of treatment.
   b. during the first 6 months of treatment.
   c. during the first few days of treatment.
   d. during the first few hours of treatment.

20. Which of the following is/are outcomes of treatment sought for patients with depression:
   a. Clinical response
   b. Improvements in quality of life
   c. Decreased utilization of clinical and other resources
   d. all of the above
Depression: New Perspectives, Understandings, and Treatments

Participant's name: ___________________________________________ Date: ___________________

Your assistance in the evaluation process is greatly appreciated. Please return this form with the posttest answers.

Using the scale above for questions 1-5, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program.

Objectives:
1. describe the incidence and onset of major depressive disorder;  
   1 = Not at all  
   2 = Not very well  
   3 = Somewhat well  
   4 = Well  
   5 = Very well

2. list the numerous ways in which MDD presents in general and, specifically, in people who belong to minority groups;  
   1 = Not at all  
   2 = Not very well  
   3 = Somewhat well  
   4 = Well  
   5 = Very well

3. describe barriers to care and adherence experienced by people from minority populations;  
   1 = Not at all  
   2 = Not very well  
   3 = Somewhat well  
   4 = Well  
   5 = Very well

4. understand the currently available antidepressants and their differences; and  
   1 = Not at all  
   2 = Not very well  
   3 = Somewhat well  
   4 = Well  
   5 = Very well

5. appreciate and discuss the importance of adequate and sustained treatment and careful planning if switching becomes necessary. 
   1 = Not at all  
   2 = Not very well  
   3 = Somewhat well  
   4 = Well  
   5 = Very well

Using the scale above for questions 6 and 7, please indicate the number that best expresses your opinion.

6. What is your overall rating of this program? ____

7. How would you rate the pertinence of this program material to your practice? ____

8. To what degree was there promotional bias (check one):
   a. Not at all ____
   b. Somewhat ____
   c. A great deal ____

9. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)
   1  2  3  4  5
   No change Significant change

10. Please indicate the length of time it took to complete this program: (circle selection)
    Hours:   1    2    3
    Minutes: 0   15   30   45

11. Please rate the difficulty factor for completing this CE program: (circle selection)  
    Easy  Moderate  Difficult

12. Please rate your willingness to recommend this program to colleagues: (circle selection) 
    Very willing  Willing  Not willing

13. Please indicate which venue you prefer for obtaining continuing education: (circle selection) 
    Written monograph  Slides  Videos  Internet-based

Live sessions Other: ____________________________