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CME Objectives

After studying the Commentary and the ACADEMIC HIGHLIGHTS, you should be able to:

- Recognize factors that affect response to treatment of chronic depression.
- Formulate a treatment plan for the patient with depression and psychiatric comorbidity such as anxiety.

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This educational activity is eligible for AMA PRA Category 1 Credit through April 30, 2008. The latest review of this material was March 2006.

This pretest is designed to facilitate your study of the material.

1. **A large body of literature suggests that patients with chronic depression are usually treatment resistant.**
   a. True
   b. False

2. **What is the approximate lifetime prevalence of major depression in the United States?**
   a. 5%
   b. 17%
   c. 46%
   d. 89%

Pretest answers and Posttest on page 116.

See accompanying Perspectives From the Editor *on pp. 104–105.*

LEADING EXPERTS IN THE TREATMENT OF DEPRESSION EXPLORE CHRONIC DEPRESSION, ITS IMPACT, AND POSSIBLE TREATMENT STRATEGIES.

Chronic depression is difficult to manage and often represents a heavy burden to those with the disorder, their families, and even the health care system, since those with chronic depression often seek medical help for vague somatic complaints.

On September 26, 2005, Alan J. Gelenberg, M.D., Editor-in-Chief of *The Journal of Clinical Psychiatry* and an Executive Director of the CME Institute of Physicians Postgraduate Press, Inc., assembled a group of experts that included clinical psychiatrists and researchers who are specialists in the treatment of depression, especially chronic depression. Their discussion appears here.

This special Commentary is another in a series of independent projects undertaken by the CME Institute as a service to its members and the broader academic and clinical community. Visit www.psychiatrist.com/issues to listen to audio selections from this discussion.

Faculty affiliations and disclosures appear at the end of this Commentary.

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The State of Knowledge of Chronic Depression

Alan J. Gelenberg, M.D.; James H. Kocsis, M.D.; James P. McCullough, Jr., Ph.D.; Philip T. Ninan, M.D.; and Michael E. Thase, M.D.

The Definition of Chronic Depression

Dr. Gelenberg: Let's begin with a discussion of the definition of chronic depression. What is the clinical relevance of the subtypes of depression in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)?[1]

Dr. McCullough: My colleagues and I have reported on 1316 patients with chronic depression.[2,3] We found no differences when a wide variety of demographic, psychosocial, and health measures were compared. For the DSM-V, we have argued that the existing subtypes do not represent qualitatively distinct entities. We have recommended a 2-by-2 table to accommodate a 4-fold classification of the unipolar disorders: mild versus moderate-to-severe severity and acute versus chronic types of episodes (Table 1). We can greatly simplify the current subtypes of chronic depression by consolidating them into a single category termed *chronic depression*.

Dr. Gelenberg: Will you define chronic depression?

Dr. McCullough: Chronic depression lasts a minimum of 2 years without at least a 2-month hiatus or a full remission. We are not suggesting the elimination of the DSM-IV categories for depressive disorders, but are recommending the deletion of distinct chronic subtypes since these subtypes do not represent qualitatively different entities.

Dr. Ninan: Perhaps we should review the current diagnostic criteria for depressive disorders. The criteria for dysthymia require depressed mood for the majority of time and 2 additional symptoms that persist for 2 years, while the criteria for a major depressive episode stipulate 5 or more symptoms, including depressed mood or anhedonia, persisting for at least 2 weeks. Dysthymia followed by a major depressive episode is frequently labeled *double depression*. In the DSM-IV, *chronic depression* is defined as the persistence of the full criteria for a major depressive episode for at least 2 years. *Major depressive disorder with incomplete recovery* occurs when enough symptoms improve that the patient no longer meets the full criteria for major depressive disorder, but still has residual symptoms of depression (i.e., subsyndromal depression). If that patient later meets the full criteria for a major depressive episode without a period of remission in between, we consider it another episode of major depression (i.e., 2 episodes with incomplete recovery in between).

Dr. McCullough: On our 2-by-2 table, we recommend maintaining dysthymia on the chronic row and in the mild severity column. Most of the disorders that Dr. Ninan just delineated would be in the moderate-to-severe column. On the acute episode row, the mild disorder would be labeled minor depressive disorder and the moderate-to-severe episode would be termed episodic major depression. Dan N. Klein, Ph.D., has

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Table 1. Proposed Classification of Unipolar Disorders[a]

Course of Illness	Mild	Moderate-to-Severe
Acute	Minor depressive disorder	Episodic major depression
Chronic	Dysthymia	Chronic major depression Double depression Recurrent major depression without complete interepisode recovery

[a]Data from McCullough et al.[2]

conducted a 10-year naturalistic prospective study comparing dysthymia and double depression with episodic major depression that has also supported a unitary category for chronic depression.[4] He argues that dysthymia is a pernicious disorder that has a 60% probability of recurrence as major depression after it remits.

Dr. Kocsis: I have the impression that dysthymia tends to emerge earlier—in childhood or early adolescence—than chronic major depression, which tends to appear in the adult years. Do the data support my impression?

Dr. Thase: There is a late-onset variant of dysthymia, which appears to be distinct from early-onset mood disorder, that has been studied by Devanand and colleagues.[5] I think our discussion primarily concerns the early-onset variant of chronic mood disorder.

Dr. Gelenberg: Are the subtypes of chronic depression relevant to the clinician?

Dr. McCullough: Any practitioner who sees a depressed patient needs to ask 2 questions: (1) Is the disorder chronic or acute? and (2) Is dysthymia part of the course of illness? It is imperative to differentiate between an illness with a chronic course and one with an episodic course. If dysthymia is part of the course of illness, the disorder becomes very difficult to treat. The practitioner must make certain that the dysthymia is brought to remission. Dr. Thase's point about the existence of late-onset dysthymia is also crucial.

Dr. Kocsis: An early age at onset of chronic depression often leads to misdiagnosis as a personality disorder by clinicians—particularly nonmedical clinicians but also psychiatrists. The patients themselves often think that they have a personality disorder. Also, many patients have chronic somatic symptoms and present to primary care medical settings for treatment of insomnia or chronic pain. Once again, the depressive syndrome or the affective disorder diagnosis is missed.

Dr. Gelenberg: Which personality disorders or traits are clinicians and patients likely to consider in lieu of early-onset dysthymia?

Dr. Kocsis: Chronic depression can appear as personality traits of dependency or avoidance. These individuals often have deficits in social functioning that can be mistakenly identified as personality traits. I think cluster C personality disorder traits are the most common misdiagnosis.

Dr. Ninan: Children, in particular, often lack the cognitive capacity to make subtle distinctions between worry, which is the cognitive component of anxiety, and negative ruminations about the self, which is the cognitive component of depression. So practitioners may have difficulty distinguishing early-onset dysthymia and generalized anxiety disorder (GAD), which is also a chronic illness. Somatic symptoms are also common in GAD.

Children might also behaviorally act out their pathology or have problems in executive function. They might consequently be misdiagnosed with conduct disorder, attention-deficit/hyperactivity disorder, or a learning disability instead of chronic anxiety or depression.

Psychological Differences Between Chronic and Acute Recurrent Depression

Dr. Gelenberg: How do people with chronic depression differ psychologically from those with acute recurrent depression? Dr. McCullough, I know, has studied the influence of the type of depression on response to psychotherapy. Perhaps you could give us a succinct summary of what essentially has been a lifetime of work.

Dr. McCullough: At this point, I cannot make a distinction between these patients. I am seeing someone now who can recall 15 to 20 recurrent episodes of major depressive disorder. To me, she has chronic depression. Perhaps Dr. Thase or Dr. Kocsis can help fine-tune a distinction between a person who has many recurrent episodes and one who meets clear criteria for chronic depression.

Dr. Thase: I have noticed that people with chronic depression are disproportionately negative in the way they view themselves, their world, and their future. They are very pessimistic and unlikely to believe they have the capacity to take action to solve their problems. My colleagues and I have found that the Cognitive Behavioral Analysis System of Psychotherapy (CBASP),[6] developed by Dr. McCullough, helps patients with chronic depression make sense of their problems and learn new techniques for taking action to solve their problems.

Dr. Ninan: You raise an important point. Factors that have an impact on chronicity may differ from the factors that make one depressed. As an analogy, in panic disorder, extensive avoidance often leads to agoraphobia, which tends to persist even after the panic attacks are controlled or remitted. Similarly, there may be variables in depressed individuals that push them toward a chronic course of illness, even after the issues that led up to the acute episode have been settled. Therefore, while the same treatments may frequently be effective for both chronic and acute depression, some effective treatments for chronic depression may be different from those aimed at recurrent acute major depressive disorder.

Dr. Kocsis: Data suggest that individuals with chronic depression have more deficits in social function than those with recurrent forms of major depression.[7] I think these data make sense because chronic depression is associated with an early age at onset and a chronic course of illness. These individuals may fail to develop social learning and social skills because they lack sufficient intervals of wellness. As a result, they are left with more social deficits and disabilities than those with a more episodic course of illness.

Do you think chronic depression tends to respond less well to traditional cognitive-behavioral therapy (CBT) than to CBASP? If so, why?

Dr. Thase: When my colleagues and I studied CBT, we found that about 15% to 20% fewer patients with chronic depression remitted within a 12-week or 16-week interval than patients with acute illness.[8] I have always attributed this lack of response to the belief that patients with chronic depression are generally less responsive to treatment. However, that decrement was not apparent in the Keller et al. study[9] comparing CBASP and nefazodone, in which patients had about a 50% chance of responding to either monotherapy within 12 weeks.

Dr. McCullough: CBASP takes a broader approach than traditional cognitive therapy. CBASP includes skill training and looks at interpersonal issues that usually have a long, problematic history. The CBASP therapist recognizes that the origin of these interpersonal issues is usually found in the early stages of development and often involves some early trauma that stems from maltreatment by significant persons in the patient's life.

Dr. Gelenberg: One feature that distinguishes CBASP from traditional cognitive therapy is that CBASP places less emphasis on abstract cognitive concepts like catastrophic thinking and more emphasis on situational analyses, i.e., how the person began feeling passive and victimized and what practical steps the person can take to affect his or her environment.

Dr. McCullough: That is an excellent point. It is hard to feel helpless when you stare at the consequences of your behavior that you have choreographed. CBASP changes the cognitive focus to situational interpersonal consequences that are identified within a person-to-person encounter. We first teach patients the effects their behavior has on others and then show them that if they do not like the consequences, they have to change their behavior. The CBASP model has a situational orientation and includes a strong interpersonal component, which makes the approach a bit broader than traditional cognitive therapy.

Treatment of Chronic Depression

Dr. Gelenberg: Imagine a patient who has had ongoing depression for more than 2 years—one of the subtypes that Dr. Ninan described. This patient is sitting in your office. How should this patient be treated? Should the treatment differ from that given to someone who is experiencing a first or second discrete episode of recurrent major depressive disorder?

Dr. Kocsis: The 2 current options are antidepressant medications and psychotherapy. The literature supports the efficacy of various classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and some of the newer agents.[10]

One treatment trial showed lower response rates to antidepressant monotherapy for chronic depression than for various forms of acute recurrent major depression.[11] There is some evidence that switching nonresponders to a treatment from a different class of antidepressant may improve response, so 2 or 3 trials of antidepressant medications may be indicated.[12]

The only available research on psychotherapy as a treatment for chronic depression involves CBT, interpersonal therapy (IPT), and CBASP. Keller et al.[9] provided the best evidence for efficacy and high response rates for CBASP. One issue that remains unresolved which we need to consider is how to select the most effective specific first-line treatment for an individual patient. We have a menu of treatments that we know may work, but we know little about how to predict the best starting treatment for an individual patient.

Dr. Gelenberg: If I see a patient with a first or second episode of nonchronic, mild-to-moderate, uncomplicated major depressive disorder, I would reasonably begin by asking the patient if he or she preferred psychotherapy or medication. If that patient preferred medication, the newer antidepressants—most commonly an SSRI but possibly a serotonin-norepinephrine reuptake inhibitor—are accepted first-line treatments. If that patient chose psychotherapy, CBT and IPT are well-accepted treatments.

Following Dr. Kocsis' line of thought, if the patient had had depressive symptoms for 2 or more years and met the criteria for chronic depression, I would also start by asking for the patient's treatment preference. If the patient selected medication, I would prescribe one of the newer antidepressants. I assume that the dose would be similar to the starting dose for acute depression. If the patient preferred psychotherapy, I would start with CBASP because it has the best evidence for efficacy. What do you think?

Dr. McCullough: I would return to a point raised by Dr. Thase: age at onset. There seems to be increasing evidence in the journal literature that patients with late-onset chronic depression have a milder, healthier developmental history than patients with early onset. Patients with late-onset as opposed to early-onset chronic depression may have a better chance of remission.

Dr. Thase: Psychiatrists are partial to combining psychotherapy and pharmacotherapy, but there is no strong

evidence that combining treatments is more beneficial than monotherapy for patients with a first episode of mild depression. However, I think combining psychotherapy and pharmacotherapy is clearly the first-choice treatment for chronically depressed patients.

Dr. Gelenberg: So the combination of an antidepressant medication and the targeted CBASP form of psychotherapy would provide a chronically depressed patient with the most robust chance for recovery and remission. Of course, the patient's insurance coverage would also probably play a role in the choice of treatment.

Dr. Thase: In the Keller et al. study[9] in which we all participated, the average patient given the combination of an antidepressant and CBASP had a 20% greater likelihood of responding or remitting than the average patient given one or the other therapy alone. That effect is as large as the typical drug-placebo differences in clinical trials and provides evidence of an advantage for combined treatment in chronic depression.

Dr. Gelenberg: To summarize: (1) The combination of an antidepressant and CBASP psychotherapy has the best evidence for a high remission rate. (2) The antidepressants appear to have similar response and remission rates, but most clinicians choose newer antidepressants first for reasons of convenience and safety. (3) Among the various forms of psychotherapy, there seems to be preferential evidence in favor of CBASP.

Dr. Ninan: What were the comparative response and remission rates in the imipramine versus sertraline study?[12]

Dr. Gelenberg: There were no statistical differences in either the intent-to-treat or observed-cases analysis. The response rate was about 50%.

Dr. Ninan: Can we make a general statement that the response and remission rates with pharmacology are about 5% to 10% lower in chronic depression studies than in nonchronic depression studies?

Dr. Kocsis: They may be even lower.

Dr. Gelenberg: The rates for chronic depression may be affected by a lower floor of the placebo effect in most chronic depression studies. Dr. Thase, didn't you find similar response rates in a study of sertraline in dysthymic disorder?

Dr. Thase: Yes. The study[13] included a placebo arm, and the placebo response rate was only about 20%. I agree the rate of response to antidepressant monotherapy in chronic depression is around 45% to 50%.

Dr. Gelenberg: Would it be fair to say that the overall response rate is lower in chronic depression, but the treatment effect size may be comparable to that in studies of nonchronic depression by virtue of a lower placebo response rate in those studies that include placebo?

Dr. Kocsis: I think that is correct. A 1988 study[14] that my colleagues and I conducted supports your argument. The placebo response and remission rates were quite low, but the magnitude of difference between the active drug and the placebo was comparable to the effect in the Thase et al. study.[13]

Dr. Ninan: So we are suggesting that patients with chronic depression are not necessarily treatment resistant, because a substantial number of them respond and remit to treatment with the first antidepressant as well as to specific forms of psychotherapy, but the absolute number of responders is slightly fewer than with nonchronic depression treatments.

Dr. Gelenberg: Yes, with the corollary that failure on the first round of treatment still gives someone roughly a 50-50 chance of responding to the second round of treatment. A patient who does not respond to the first antidepressant has a reasonable chance of responding to a second antidepressant or psychotherapy.

Dr. Kocsis: We are all currently involved in a National Institute of Mental Health (NIMH) chronic depression study. One question we are asking is whether patients with chronic depression are inherently treatment resistant. About 700 patients are currently enrolled in this study. Approximately 75% have not failed previous antidepressant trials, so there is clearly a difference between having chronic depression and being treatment resistant. Many patients with chronic depression do not have a history of treatment resistance.

Dr. McCullough: In the NIMH study from the early 1980s,[15] almost one fourth of patients with acute episodic depression did not remit and went on to develop a chronic course. I wonder if part of the treatment resistance we see comes from patients like those.

Long-Term Course and Treatment Response in Chronic Depression

Dr. Gelenberg: Dr. Kocsis, will you discuss long-term course and treatment response in a chronically depressed population?

Dr. Kocsis: Data from the few existing studies of maintenance treatment of chronic depression including SSRIs, TCAs, and some of the newer agents suggest that patients who respond to treatment—whether it's with antidepressant medication or CBASP psychotherapy—tend to do well and remain well as long as they continue their treatment.[10] When treatment is discontinued, the recurrence rate is substantial (more than 50% over 1 to 2 years),[16] so long-term treatment is indicated for many patients with chronic depression.

There does appear to be a subpopulation of patients with chronic depression who will respond to a 6-month course of treatment and remain well when treatment is discontinued. I recommend that patients continue treatment for at least 6 to 12 months. Then, if they elect to discontinue treatment—either medication or psychotherapy—they should be followed closely. I recommend restarting treatment if symptoms recur.

Dr. McCullough: The Keller et al. study[9] included a cell with a substantial group of patients who received CBASP only. The survival rate (meaning lack of symptom recurrence or relapse) in that cell was 90%.

Dr. Ninan: Was the survival rate substantially different for patients who continued taking medication?

Dr. McCullough: The comparison is different because of the size of the cells. About 55% of the placebo-treated patients relapsed during the maintenance phase, and 75% of the medication-treated patients were maintained without recurrence or relapse.

One reason that patients may not maintain the benefits of psychotherapy after discontinuation is that they forget the skills they have learned. The danger is that patients will get out of practice and simply forget to do the work of psychotherapy. I do not know if there is a comparable issue with medication treatment.

Dr. Gelenberg: There appears to be benefit in chronic depression from ongoing CBASP sessions since, in the absence of booster sessions, patients often slip back into their old patterns of passivity and pessimistic thinking.

Dr. McCullough: From the beginning, I have tried to describe CBASP as an acquisition learning methodology.

Dr. Ninan: Perhaps we should clarify our terms. Once something has been learned—particularly at an emotional level—it can seldom be wiped out. The neurobiological literature uses the term *extinction*, where new learning counters the previous learning. However, such previous patterns may return in a new context or under stressful conditions. Therefore, the psychotherapist and the patient must craft a context that tilts toward what has been learned in therapy against the old depressive patterns.

One could argue that the situation analysis is what differentiates CBASP from traditional CBT. Situation analysis is true exposure, since the patient is encouraged to face the situations that contribute to the maintenance of depression. Then he or she learns new techniques for handling these situations; the new techniques counter the cognitive schemas and behaviors that might maintain the depression. In traditional CBT, learning is not necessarily translated into behaviors, so we could argue that the maintenance value of CBASP lies in the patient continuing to challenge problematic interpersonal situations. When he or she starts avoiding such situations, it is easy to slide back into a previous depressive pattern.

Dr. McCullough: Dr. Ninan's description is excellent. Patients with chronic depression are often under a lot of stress for a variety of reasons. There may be a parallel between extinction and stopping medication. Perhaps patients with chronic depression are not armed with adequate neurotransmitters for handling stress, which may explain why stopping medication can potentiate the recurrence or relapse rate.

Effect of Childhood Abuse on the Course of Depression

Dr. Gelenberg: There is a growing body of literature about the effect of early life stress on the course of depression. Dr. Ninan, what is the effect of childhood abuse on treatment response in chronic depression?

Dr. Ninan: Early adversity, including childhood abuse, can have an influence on the developing brain that might be qualitatively and quantitatively greater than adversity in adulthood when the brain is more completely developed. Nature wants to be able to sculpt the developing brain beyond the imprint provided by genes. This sculpting is based on early experiences since such environmental experiences are often predictive of later experiences. Early experiences calibrate brain responses to stress and thus strongly influence adult responses to stress. So, someone who is born into a stressful environment develops a strong stress response, whereas an infant who is born into a relatively low-stress environment does not need to calibrate a powerful response to stressors.

Toning the stress response to a high level might make the individual more vulnerable to the later development of depression. Research that has looked at adults with depression has shown a greater likelihood of a history of early abuse than the general population.[17] The pattern of depression in this population is associated with increased activation of the hypothalamic-pituitary-adrenal axis, which is the prototypical stress axis. This conclusion is supported in animal models of depression.

An important question is whether early adversity predicts the likelihood of benefit from medications compared with psychotherapy like CBASP. The one study[18] that examined this question found that a higher proportion of chronically depressed patients with a history of early life stress were more likely to achieve remission with CBASP compared with nefazodone, the antidepressant medication used.

Dr. Gelenberg: So a patient who has both chronic depression and a history of childhood abuse, neglect, or trauma may be differentially likely to respond to CBASP compared with medication.

Dr. Ninan: That is correct. The likelihood of achieving remission in 3 months is about 10% higher with CBASP than with nefazodone.

Conclusion

Dr. Gelenberg: As we conclude, do you have other comments?

Dr. Thase: When we began studying chronic depression more than 15 years ago, we were shocked to discover that the vast majority of patients with chronic depression had never received treatment, and treatment for most of the rest was inadequate, i.e., low doses of antidepressant medications, short duration of treatment, and exposure to counseling but not professional psychotherapy.

Even though we are saying the prognosis for chronic depression is poor, the fact remains that many patients with chronic depression are still not receiving proper treatment. With proper treatment, particularly a combination of psychotherapy and pharmacotherapy, patients have a strong chance of getting well relatively quickly.

Dr. Gelenberg: We can end with a message of optimism. We have at least one form of effective psychotherapy, and medication is often beneficial. If the first round of treatment is not effective, a second treatment trial may help. Many patients who have been told they have a personality disorder may, in fact, have chronic depression, which can be treated.

Dr. Ninan: Sometimes the initial choice of treatment may be based on factors other than efficacy, such as cost and availability of a professional psychotherapist with experience in CBASP. Pharmacology might be less costly than intensive CBASP in the short term, but the issue of cost must be factored into the longitudinal value of CBASP in terms of greater protection from recurrence.

Dr. Gelenberg: And we can take some encouragement from the fact that Dr. McCullough is in the process of training psychotherapists around the country in CBASP.

Dr. McCullough: If the appropriate diagnosis is made early (and I think Dr. Kocsis pointed out how important it is to make an accurate diagnosis), the prognosis is optimistic.

Dr. Gelenberg: It is nice to leave our discussion of a disorder characterized by pessimism with the feeling that we, as clinicians, have a growing sense of optimism that is informed by science, and our body of knowledge is growing every day.

Drug names: imipramine (Tofranil and others), sertraline (Zoloft).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

Affiliations: From the Department of Psychiatry, Arizona Health Sciences Center, Tucson, Ariz. (Dr. Gelenberg); the Department of Psychiatry, Cornell University Weill Medical College, New York, N.Y. (Dr. Kocsis); the Department of Psychology, Virginia Commonwealth University, Richmond, Va. (Dr. McCullough); the Anxiety Disorders Program, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Ga. (Dr. Ninan); and the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pa. (Dr. Thase).

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For the CME Posttest for this article, see pages 116–117.

Managing Depression in Primary Care: Achieving Remission

This ACADEMIC HIGHLIGHTS section of The Primary Care Companion to The Journal of Clinical Psychiatry *presents the highlights of the teleconferences "Review of the Pharmacologic Management of Depression," which were held in December 2005. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc. and was supported by an educational grant from GlaxoSmithKline.*

The teleconferences were chaired by ***Michael E. Thase****, M.D., Department of Psychiatry, University of Pittsburgh School of Medicine and Western Psychiatric Institute and Clinic, Pittsburgh, Pa. The faculty were* ***Maurizio Fava****, M.D., Depression Clinical and Research Program, Massachusetts General Hospital and the Department of Psychiatry, Harvard Medical School, Boston;* ***Mark Zimmerman****, M.D., Department of Psychiatry and Human Behavior, Brown University School of Medicine, Rhode Island Hospital, Providence; and* ***Larry Culpepper****, M.D., M.P.H., Department of Family Medicine, Boston University, Boston, Mass.*

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Managing Depression in Primary Care

Larry Culpepper, M.D., began his presentation by pointing out that in the United States, about 17% of the population develops major depression at some point during their lifetime[1]—20% to 25% of women and 7% to 12% of men.[2] In a typical episode of depression, individuals sink into depression symptomatology over a period of 4 to 6 weeks, experience those symptoms for anywhere from a few months to 2 years, and then gradually improve if left untreated. A major goal of treatment is to shorten the duration of these symptomatic episodes. With each additional episode of depression, the episodes tend to become more severe and longer in duration and have a shorter interepisode interval.[3]

Recognizing Depression in Primary Care

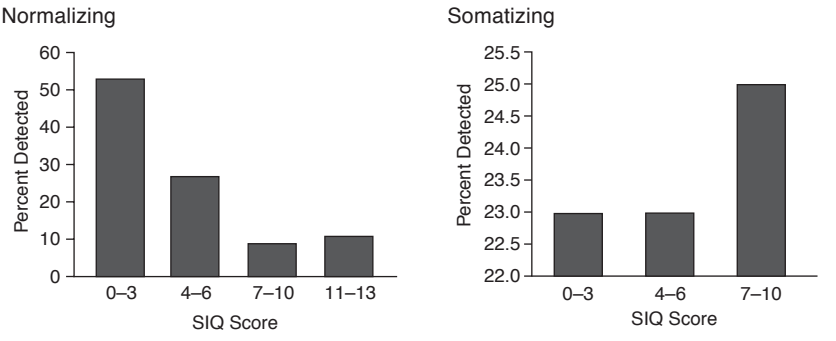
Dr. Culpepper reported that, given the diverse presentations of depression in primary care, screening tools are very useful. In 2002, the United States Preventive Services Task Force[4] reversed a long-standing recommendation that opposed screening for depression in primary care settings. Such screening has now been found to not only lead to improvement in the recognition of depression but also to a true improvement in patient well-being over time.[4]

The Preventive Services Task Force[4] further found that 2 questions are useful as initial screening tools for recognizing depression: "Over the past 2 weeks, have you felt down or hopeless?" and "Over the past 2 weeks, have you felt little interest in doing things?" If patients respond "yes" to either of these questions, it is appropriate to further investigate the possibility of major depression. The 9-item Patient Health Questionnaire (PHQ-9),[5] the Zung Depression Scale,[6] and the Beck Depression Inventory[7] are all helpful for the exploration of symptoms in patients suspected of having major depression.

A key issue in primary care is to avoid being misled by the patients' explanation of their symptoms. General practitioner researchers in United Kingdom[8] identified a pattern of physician agreement with patients that led to the lack of recognition of major depression. They found that if patients attributed their symptoms to a medical explanation, the physicians frequently agreed with that attribution and failed to uncover the underlying major depression or anxiety disorder that was truly the cause. General practitioners missed the underlying diagnosis of major depression or anxiety in nearly 80% of patients who somatized or normalized their symptoms (Figure 1). Recognizing symptom attribution by the patient is a helpful step in understanding the patient, making the correct diagnosis, and then working with him or her to gain acceptance of the diagnosis of depression.

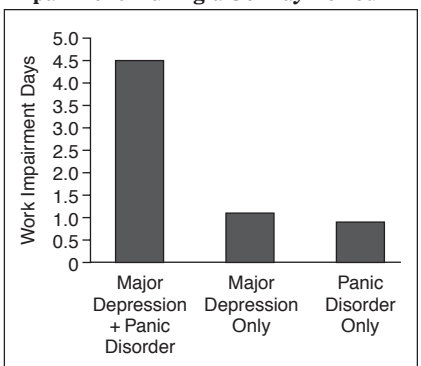
Depression can present in primary care in a variety of ways; understanding this fact can help the physician accurately diagnose patients. For example, somatic symptoms that are not otherwise explained by medical illness are frequent indicators that the patient may have underlying major depression. In addition, the majority of patients who are high utilizers of primary care have a lifetime history of either major depression or anxiety, and a

Figure 1. Detection of Anxiety or Depression by Primary Care Physicians in Patients Who Normalized or Somatized Their Symptoms[a]



[a]Data from Kessler et al.[8] Patients were considered to be either normalizers or somatizers if they scored ≥ 7.
Abbreviation: SIQ = Symptom Interpretation Questionnaire.

Figure 2. Impact of Comorbid Depression and Panic Disorder on Work Impairment During a 30-Day Period[a]



[a]Data from Roy-Byrne et al.[12]

large number have current major depression, so a pattern of high utilization also can be an indicator of underlying depression.[9]

Patients presenting with anxiety are often depressed as well. If the anxiety is more bothersome to them and to their families than depression, it also becomes more problematic for the physician, who then may not recognize the comorbid major depression that could be worsening the anxiety.

Comorbidity of Depression With Other Illnesses in Primary Care

According to Dr. Culpepper, comorbid anxiety tends to make major depression more severe, more prolonged, less likely to respond to treatment, and more functionally impairing in work activities, social accomplishments, and family roles. Ultimately, comorbid major depression and an anxiety disorder profoundly impair the individual's overall quality of life. More than 80% of depressed patients with comorbid anxiety will continue to be depressed at 1-year follow-up, compared with less than 60% if comorbid anxiety is not present with depression.[10] Treatment outcomes are also worse in patients with comorbid anxiety disorder given pharmacotherapy or psychotherapy.[11] For example, comorbid anxiety disorder has been shown to impair the ability to work (Figure 2).[12] Comorbid depression and anxiety is also an indication for an evaluation of suicidality. The patient who has anxiety and major depression is likely to have a past history of suicide attempts, and such a past history is one of the best predictors of future suicidal thoughts, ideations, and suicide attempts (L.C., data on file, Brown University, Providence, R.I.).

Dr. Culpepper emphasized that not only is major depression comorbid with psychiatric illness, it is also comorbid with many medical illnesses. Patients with medical illnesses develop depression at a much higher rate than the general population.[13] Unfortunately, major depression is less frequently recognized and appropriately diagnosed in the presence of physical symptoms than in patients who do not complain of physical symptoms.[14,15] Prevalence rates of major depression in patients with cardiovascular disease,[16] diabetes,[17] cancer,[18] or Parkinson's disease[19] are between 20% and 30%.

Not only do major depression and medical illnesses occur together frequently, they also tend to make patient outcomes worse. A bidirectional interaction exists between major depression and medical illness in which both the major depression and the medical illness fare more poorly when they are comorbid than when they are separate.[20] Depression and medical illnesses are associated with poorer prognoses, increased morbidity and mortality, and increased medical costs.

Dr. Culpepper noted that several specific conditions have a documented association with depression.[21] The relationship between cardiovascular illness and depression has been extensively investigated.[22,23] New cardiovascular disease occurs almost twice as frequently in patients with major depression compared with patients without major depression. Once patients have developed cardiovascular disease, the risk of subsequent cardiovascular morbidity and mortality is markedly elevated for at least 20 years following the patient's initial diagnosis with major depression.[23] It is the major depression itself that is associated with the increase in mortality. Lesperance and colleagues[24] identified that anxiety and hostility do not relate to poor prognosis in the way that major depression does; it is specifically depression that is associated with the poor prognosis.

Diabetes and cancer are similar to cardiovascular disease in their relationship with depression. Patients with diabetes have more than double the rate of depression than those without diabetes, even when controlling for all risk factors.[25] The outcomes for patients with diabetes are worse if they also experience depression. Cancer develops more frequently in patients with major depression, and the prognosis

for patients with cancer is worsened in the presence of major depression.[18]

Dr. Culpepper explained that one of the mechanisms through which depression has a negative impact on medical illnesses is its effect on compliance. Patients with depression have a 3-fold increase in the likelihood of being noncompliant with other medical treatment compared with patients without depression.[26] Compliance not only includes taking medications as directed, but also adherence to diet, exercise, self-monitoring such as diabetes glucose testing, special programs such as smoking cessation, and even return visits for medical care. The successful management of major depression is an important factor in how primary care physicians can affect the outcome of not only medical illness, but the quality of life for patients.

Treatment of Depression in Primary Care

Dr. Culpepper pointed out that there is room for improvement in the quality of care that primary care providers give to patients with major depression. Only a small minority of patients treated for major depression in the primary care setting receive treatment that meets quality standards for adequacy of amount of treatment and adequacy of duration of treatment; in fact, in one evaluation of quality care in the United States, only 20% of patients who were treated by primary care physicians alone (that is, did not see a mental health specialist) received adequate treatment.[27]

Many different treatment modalities are available to primary care physicians. Psychotherapies are available, including cognitive-behavioral therapy, interpersonal therapies, and psychodynamic therapies. Pharmacologic treatment is highly valuable, either as monotherapy or as an augmentation of psychotherapy. Other treatment options such as electroconvulsive therapy and phototherapy may be useful for patients with either treatment-resistant depression or depression related to seasonal affective disorder, respectively.

Because it has been shown that patients who have residual symptoms are at high risk for relapse,[28] a key in successful treatment of depression is treating patients with an intensity that achieves adequate and full control of symptomatology. In a study by Paykel et al.,[28] 76% of treated patients who had persistent symptoms relapsed, whereas only 25% of patients whose symptoms were fully controlled by treatment relapsed.

Continuation of functional impairment is also more likely in patients who do not achieve a full remission of symptoms.[29,30] The lack of functional improvement does not just involve difficulties related to depression but any comorbid medical illness, so attaining remission is critical not only in improving outcomes for depression, but in attaining an optimal outcome for comorbid conditions.[31]

One strategy to improve patient outcome is the adoption of screening instruments that provide valid measures of severity and symptomatology not only at the onset of depression, but in response to treatment. The PHQ-9 is such an instrument; it has been well-validated, not only for diagnostic purposes,[32] but also to measure treatment outcome.[33] A copy of the PHQ-9 can be found in the MacArthur Foundation Initiative on Depression and Primary Care's *Depression Management Tool Kit*, which has many helpful resources for primary care physicians (www.depression-primarycare.org/clinicians/toolkits). Dr. Culpepper reiterated that other rating scales such as the Zung Depression Scale and the Beck Depression Inventory can also be used to measure progress during treatment.

In order to achieve the highest improvement in outcome of depression, primary care physicians should actively manage their depressed patients and involve the whole practice in patient care.[4] Developing a practice approach that utilizes not only the physician but other resources in encouraging patient compliance can aid in improving outcomes. Having a nurse or a medical assistant in the practice call newly diagnosed patients within 1 or 2 days of their visit to assess whether they have had prescriptions filled, whether they have started the prescription, or, if psychotherapy is recommended, if they have followed through in initiating an appointment for such psychotherapy can be very helpful in improving the beginning of treatment and treatment adherence. The patient should be queried further at various points in time, particularly over the first couple of months, to ensure medication adherence and identify any new problems or adverse effects requiring tailoring of treatment.

Table 1. Patient Education Messages That Improve Early Adherence[a]

You should take your medicine every day
The medicine may take 2 to 4 weeks to show effect
Do not discontinue taking the medication without discussing it with the physician
Continue to take the medicine even when you feel better
This is what you should do if you have questions (followed by specific instructions)

[a]Data from Lin et al.[34]

An important part of the active management of patients is patient education. A study by Lin and coworkers[34] identified several specific patient educational messages that significantly improved adherence to treatment within the first month (Table 1). In addition to relaying these messages, physicians need to educate patients about the common misperception that depression is akin to an infectious disease in which an antibiotic is continued for as long as the infection is present but then stopped once the patient is better. Instead, patients should view their depression through a chronic disease model, similar to diabetes, in which the medication must be continued long-term. Also, the physician should tell the patient that mild side effects are common and that significant side effects should be reported

to the physician so that they can be actively managed. Finally, the physician should let the patient know that remission is the goal of treatment, and, most importantly, that it is achievable, even if it requires several modifications of the treatment regimen over time. When these messages are communicated to patients in primary care, there can be a marked improvement in outcome.

Dr. Culpepper stated that the critical components that contribute to improved outcomes include using an evidence-based approach to diagnose and monitor treatment response, enhancing patient education systems, using active case management to support the patient in adhering to treatment, and having the backup of a mental health specialist, when required, for the patient with multiple comorbidities or the patient who does not respond to treatment.

Coordinated care models, in which a team of clinicians works together to treat the patient in the most effective way possible, have been demonstrated to lead to marked improvement in long-term outcome of patients.[35] This improvement can be especially seen in the number of prescriptions filled, not only for the first or second time, but over the long-term, and in overall patient adherence.

Conclusion

Dr. Culpepper concluded his presentation by emphasizing that major depression is common in primary care settings and has a variety of presentations, including somatic presentations and high health care utilization. Major depression is highly comorbid both with anxiety disorders and medical conditions and greatly worsens patient outcomes in medical illnesses, both in the short-term and long-term. Primary care physicians have tools to increase not only the recognition, but also the effectiveness of long-term management of major depression. When these tools are used, the short-term and long-term outcome for patients can be substantially improved.

The Concept of Remission: Validity and Limitations

Remission, according to Michael E. Thase, M.D., can be defined as a level of depressive symptoms basically indistinguishable from that of someone who has never been depressed. Being in remission means that the depressed individual has been able to return to a normal level of social functioning. Remission is one of several outcomes for patients with depression (Figure 3).[3] Before a patient is considered to be in remission, the patient must respond to treatment. Typically, response is defined by a 50% change in symptom intensity. Functionally, the difference between response and remission is simply the level of improvement: a patient in remission has a greater level of improvement than one who is a responder. If a patient's remission is not sustained, then the patient experiences a relapse.

Remission leads to recovery. Generally, a patient needs to be in remission for at least 6 to 9 months before he or she is declared to be in recovery. In practical terms, however, it is difficult to distinguish between remission and recovery.

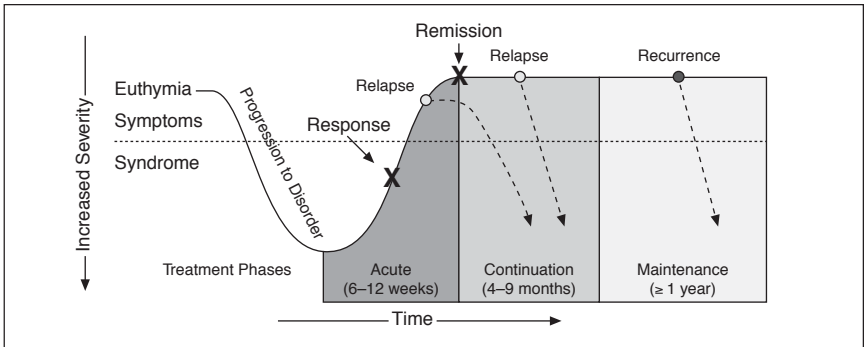
Validating the Concept of Remission

Dr. Thase next explained that the most desired outcome of the acute phase of treatment is remission, which ideally occurs within the first 6 to 12 weeks of therapy (see Figure 3). The primary goal of the second phase, the continuation phase, is to sustain remission and prevent relapse. The third phase, maintenance, targets patients who are at high risk for recurrent depressive episodes. The maintenance phase begins at the time that the physician considers the patient to be recovered but still at a risk for recurrence, and it may last many years, perhaps even indefinitely.

Dr. Thase then asked, how do we know when patients have reached a symptom level similar to that of people who have never been depressed? In one study,[36] outpatients who presented with a major depressive episode had a mean score of 20 on the Hamilton Rating Scale for Depression (HAM-D). Very few patients with depression had scores below 14, and none of the patients with major depressive disorder had scores below 10. Conversely, none of the healthy control participants had HAM-D scores above 6, indicating that for a patient with depression, a score on the HAM-D of 6, 7, or 8 is the best indicator that he or she has completely moved to a level of residual symptoms that is similar to that of a never-ill person.

According to Dr. Thase, the concept of remission in depression is validated by several characteristics of the

Figure 3. Distinguishing Response and Remission[a]



[a]Adapted with permission from Kupfer.[3]

Table 2. Risks of Incomplete Remission

Responders who do not remit or remit incompletely
Remain at greater risk for relapse than patients who achieve remission[28,37,38]
Are more likely to suffer longer chronic depressive episodes[37]
Are more likely to have less well time between episodes[37]
Are more likely to have impairment at home, in the workplace, and in personal relations[29]
May have a more difficult time managing common conditions such as diabetes and heart disease.[39–43]
Do not obtain a complete reduction in the risk of suicide[44]

condition (Table 2).[28,29,37–44] The substantial improvement in social functioning that accompanies remission is also an important validator for the concept of remission. Miller et al.[29] conducted a double-blind study of patients with chronic depression (N = 635) who were randomly assigned to treatment with imipramine or sertraline. Patients who responded but did not remit were more similar in social functioning to the nonresponders than they were to the healthy community sample. By endpoint, patients who achieved remission had a level of social functioning that was almost indistinguishable from that of the community sample used in the study.

Limitations of the Concept of Remission

In depression, remission is not a pathophysiologic description, unlike in physical disorders such as cancer, in which remission means a complete absence of illness activity. Because the pathophysiologic basis of depression is not fully understood, a low level of signs and symptoms has traditionally been used as a guide for measuring remission in major depressive disorder.

Dr. Thase noted that inadequate treatment dose, insufficient duration of treatment, or, in the case of psychotherapy, inadequate frequency of sessions all could contribute to a delay in or a lack of complete remission. Individuals who have comorbidities with other psychiatric disorders or medical illnesses or who have more chronic episodes of depression may also take longer to achieve remission than someone who is less severely ill. Dr. Thase emphasized that physicians should monitor patients' symptoms and functional status at each follow-up visit and encourage patients to track their persistent symptoms so that the physician can gauge what changes in treatment might be needed. On occasion, it may be necessary to increase a dose of antidepressant medication or to prolong the course of treatment, whether it is pharmacotherapy, psychotherapy, or the combination of the two. Also, antidepressant therapy may be augmented with an additional treatment. For example, lithium, thyroid hormone, buspirone, an atypical antipsychotic, modafinil, or another agent may be added to standard antidepressant pharmacotherapy to try to alleviate the patient's last remaining symptoms. For those patients with severe and complex conditions, psychotherapy in combination with pharmacotherapy may be the best approach.

Conclusion

Dr. Thase concluded by emphasizing that remission is the optimal outcome of treatment of the acute phase of major depressive disorder. People who obtain symptomatic remission within the first 6 or 8 weeks of the acute phase of therapy have lower relapse risks than those who respond without achieving remission. Patients who achieve remission are also more likely to have longer periods of recovery and to have near-normalization of social function. Although the concept of remission in depression has some limitations, remission as the goal for treatment gives physicians a standard by which to compare treatments, and in doing so, find the best possible treatment for their patients.

Efficacy and Tolerability of Antidepressants

Maurizio Fava, M.D., began his presentation by reporting that antidepressant medications have been successfully used in the treatment of depression over the past 5 decades. Their overall efficacy, however, is not as robust as initially thought. A 1996 meta-analysis[45] of the overall response rates to treatment with antidepressants showed response rates of between 50% and 70%. The rate of remission in patients given antidepressants, defined as the achievement of a state of very few or no symptoms or having a score on the 17-item HAM-D < 8, was between 30% and 40%. The rate of patients with no response to antidepressant treatment ranged between 19% and 34%, and the rate of partial responses was between 12% and 15%.

One reason for this lower-than-expected response rate may be that many patients drop out of antidepressant treatment prematurely, possibly because of the tolerability issues with antidepressants. With the newer antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs), the most common side effects that emerge during acute treatment are nausea, agitation, anxiety, insomnia, somnolence, headache, and fatigue. Other side effects that contribute to discontinuation of treatment may emerge in the long-term phase of treatment and include anxiety, sleep disturbances, fatigue, sexual dysfunction, weight gain, apathy, and cognitive dysfunction.

Antidepressants are perceived to be well-tolerated with minimal side effects, perhaps because most clinical studies use spontaneous patient reporting to assess side effects, which underestimates their prevalence. Much greater accuracy in assessing side effects is obtained by a systematic assessment of patients, including direct questioning through a self-rated form or a clinician-rated form. Dr. Fava then went on to review the most common

short-term and long-term side effects of antidepressants and common approaches to their management.

Common Side Effects of Antidepressant Treatment

Anxiety and nervousness. Dr. Fava stated that anxiety and nervousness are common side effects of antidepressant treatment. They tend to emerge early in treatment but can appear later. These side effects are especially important because they are risk factors for the emergence of suicidal ideation.

Fava and colleagues[46] looked at anxiety and nervousness during double-blind acute treatment with 3 different SSRIs—fluoxetine, sertraline, and paroxetine. In that study, a substantial proportion of patients developed anxiety and nervousness while being treated with SSRIs, but the differences in rates of anxiety and nervousness among the SSRIs studied were not statistically significant.

The most common approach to managing anxiety and nervousness is using adjunctive medications such as benzodiazepines.[47] Anticonvulsants have also been used to treat anxiety and nervousness, with some success, as have buspirone and atypical antipsychotics.

Insomnia and somnolence. According to Dr. Fava, insomnia and somnolence are also common side effects of antidepressant treatment. Data from the prescribing information of most antidepressants show that somnolence and sedation are reported at rates greater than placebo with almost all antidepressant treatments with the exception of bupropion (Table 3).[48–55] In the study by Fava and colleagues[46] on the use of SSRIs for depression, spontaneous reports by patients showed that somnolence was reported by more than 10% of patients and insomnia was reported by more than 15% of patients.

Several treatments have been shown to be effective in treating insomnia associated with antidepressant treatment. In particular, benzodiazepines,[56,57] nonbenzodiazepine hypnotics such as zolpidem[58] and eszopiclone,[59] melatonin,[60] and trazodone[61] have all been shown to be more effective than placebo in treating insomnia when coadministered with antidepressants. Other treatments for insomnia for which the efficacy is mostly anecdotal include mirtazapine, ramelteon, anticonvulsants, atypical antipsychotics, low-dose tricyclic antidepressants (TCAs), and antihistamines.

Table 3. Incidence of Somnolence/Sedation and Fatigue/Asthenia During Antidepressant Treatment, Active Drug Versus Placebo (%)

	Somnolence/Sedation		Fatigue/Asthenia	
Drug	Drug	Placebo	Drug	Placebo
Bupropion[48]	20	20	5	9
Citalopram[49]	18	10	5	3
Fluoxetine[50]	13	6	11	6
Mirtazapine[51]	54	18	8	5
Nefazodone[52]	25	14	11	5
Paroxetine[53]	23	9	15	6
Sertraline[54]	13	7	12	7
Venlafaxine[55]	23	9	12	6

Adjunctive medications are also available for the treatment of hypersomnia associated with antidepressant treatment. Somnolence can be either due to poor sleep quality at night or to a sedating effect of the antidepressant. If poor sleep quality is believed to be causing a patient's somnolence, the physician should consider adding a hypnotic such as trazodone, a benzodiazepine, or a nonbenzodiazepine.[62] If the somnolence is not due to poor sleep quality, adjunctive treatments such as psychostimulants, modafinil, bupropion, norepinephrine uptake inhibitors, and protriptyline may be helpful.

Fatigue and asthenia. Dr. Fava continued by adding fatigue and asthenia to the list of common side effects of antidepressant treatment. As with somnolence, a greater rate of fatigue and asthenia is seen in almost all antidepressants—except bupropion—compared with placebo (see Table 3).[48–55] Fatigue and asthenia associated with antidepressant treatment can be lessened with adjunctive medications such as psychostimulants, modafinil, bupropion, norepinephrine reuptake inhibitors such as reboxetine or atomoxetine, and protriptyline.[63]

Sexual dysfunction. Dr. Fava then advised that one of the most common side effects of antidepressant treatment is sexual dysfunction, including decreased desire (libido), arousal, orgasm, and satisfaction. In a study by Clayton et al.,[64] the prevalence of sexual dysfunction in patients given one of several different antidepressants in a subpopulation without probable causes of sexual dysfunction was fairly high. In this study, almost 1 of 4 patients reported sexual dysfunction when this symptom was systematically elicited with the Changes in Sexual Functioning Questionnaire.

Several approaches are effective in the management of sexual dysfunction associated with antidepressants. Physicians may wait for tolerance to occur, reduce the dose of the medication, or switch the patient to another antidepressant that is not as likely to produce sexual side effects, all of which may affect efficacy. Cognitive-behavioral approaches have also been used to treat sexual dysfunction, but so far, the most common approach has been that of using adjunctive pharmacologic options. Pharmacologic options for treating sexual dysfunction include yohimbine, bupropion, maca root, and phosphodiesterase type 5 (PD-5) inhibitors such as sildenafil and tadalafil.

Weight gain. Dr. Fava stated that antidepressant-induced weight gain is another frequent long-term side effect of antidepressant treatment. TCAs are known to cause weight gain, and although SSRIs are generally considered to be weight-neutral, there is some evidence that they may have more

of an effect on weight than is widely believed.[65–67]

Dr. Fava suggested that some antidepressants, such as bupropion[68] and duloxetine,[69] may be more weight-neutral than the SSRIs. Diet, including caloric restriction and carbohydrate restriction, and exercise are often effective options for the management of weight gain. Switching antidepressants can be helpful, but there is a risk that the patient may not respond to the new antidepressant. A number of add-on therapies are being used in clinical practice, including topiramate, bupropion, phentermine, and atomoxetine, although there is not yet any evidence for their efficacy from controlled studies.

Apathy and cognitive symptoms. Dr. Fava noted that apathy and cognitive symptoms are also side effects of long-term antidepressant treatment and can be associated with discontinuation. For example, a study by Bolling and Kohlenberg[70] showed that unwanted psychological side effects, including apathy and cognitive dysfunction, were experienced by about 75% of patients and were given as the primary reason for discontinuing an antidepressant as frequently as were physical symptoms. Adjunctive medications used to treat apathy and cognitive dysfunction include psychostimulants, modafinil, bupropion, norepinephrine reuptake inhibitors such as reboxetine and atomoxetine, and dopamine agonists such as pramipexole.

Conclusion

The overall efficacy of antidepressants for the treatment of depression may not be as substantial as originally thought, perhaps due to tolerability issues that can emerge during acute and long-term treatment. Several strategies have been proposed for the management of side effects of antidepressants, including adjunctive medications and medication switching. However, most of these strategies are based on anecdotal reports; only a few have been evaluated in placebo-controlled studies. There is a clear need for new studies assessing the efficacy of these strategies.

Anxiety Disorders in Depressed Outpatients: Prevalence, Detection, and Clinical Significance

Mark Zimmerman, M.D., began by explaining that recognition of comorbid conditions such as anxiety disorders in patients seeking treatment for depression is clinically important because the presence of these disorders might influence treatment selection or predict the chronicity of the depression. Anxiety disorders, as a group, are a frequent current comorbid disorder in depressed patients. To illustrate, Dr. Zimmerman reviewed 4 studies[71–74] of the comorbidity rates of all DSM-defined anxiety disorders in depressed psychiatric outpatients. Each study found that when diagnoses were based on semistructured diagnostic interviews, more than 40% of the patients had a current comorbid anxiety disorder (Table 4).

Are Anxiety Disorders Underrecognized in Depressed Patients?

According to Dr. Zimmerman, during the last few years, several reports have questioned the adequacy of the unstructured clinical diagnostic interview.[75] Zimmerman and Mattia[75] examined diagnostic frequencies in 2 separate samples of 500 patients drawn from the same outpatient practice. One group was diagnosed by raters administering the Structured Clinical Interview for DSM-IV (SCID sample), and the other was diagnosed by clinicians using an unstructured clinical evaluation (non-SCID sample). Panic disorder, social phobia, specific phobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) were all diagnosed significantly more frequently in the SCID sample compared with the non-SCID sample.

A subsequent report focused on the detection of anxiety disorders in depressed patients.[76] As an indicator of clinical importance, the investigators asked patients whether they were interested in having treatment directed toward the comorbid anxiety disorder. Dr. Zimmerman reported that depressed patients evaluated with the SCID most often wanted treatment of comorbid GAD, panic disorder, and PTSD. These results suggest that in psychiatric outpatients with a principal diagnosis of major depressive disorder, psychiatrists underrecognized anxiety disorder comorbidity, and when an anxiety disorder was present, patients usually wanted their treatment to address the comorbid anxiety disorder.

Improving the Recognition of Anxiety Disorders in Depressed Patients

Dr. Zimmerman emphasized that the purpose of screening is to improve diagnostic recognition. In examining the performance of screening scales, a distinction should be made between principal and additional diagnoses. In mental health settings, diagnostic recognition should be adequate for the principal disorders for which patients seek treatment (i.e., the chief complaint). In contrast, the recognition of comorbid disorders that are not the principal reason for seeking treatment may be problematic. Dr. Zimmerman suggested that when evaluating a screening scale's performance in psychiatric patients, the focus should be on its diagnostic properties for disorders that are not the principal reason for seeking treatment.

Zimmerman and Chelminski[77] examined the ability of the Psychiatric Diagnostic Screening Questionnaire (PDSQ) to screen for anxiety disorders in depressed patients. The PDSQ is a self-report questionnaire that consists

Table 4. Prevalence (%) of Current Anxiety Disorders in Psychiatric Outpatients With a Principal Diagnosis of Major Depressive Disorder

Anxiety Disorders	Fava et al[71] (N = 255)	Melartin et al[72] (N = 269)	Sanderson et al[73] (N = 197)	Zimmerman et al[74] (N = 373)
Panic disorder	8	17	10	17
Specific phobia	15	25	2	14
Social phobia	26	20	15	33
Obsessive-compulsive disorder	5	7	4	10
Posttraumatic stress disorder	Not assessed	1	0	13
Generalized anxiety disorder	10	14	20	15
Any anxiety disorder	45	57	42	57[a]

[a]The inclusion of partial remission and not-otherwise-specified diagnoses increased the frequency of any anxiety disorder from 57% to 67%.

Table 5. Comorbid Conditions Influencing Antidepressant Choice in 1137 Depressed Outpatients[a]

Comorbid Disorder	N	%
Generalized anxiety disorder	185	16.3
Panic disorder	140	12.3
Posttraumatic stress disorder	58	5.1
Obsessive-compulsive disorder (OCD)	48	4.2
Social phobia	41	3.6
Attention deficit disorder	32	2.8
Impulse control disorder	16	1.4
Bulimia	12	1.1
OCD spectrum disorder	4	0.4

[a]Reprinted from Zimmerman et al.,[83] with permission.

of 126 questions assessing the symptoms of 13 DSM-IV disorders in 5 areas: eating, mood, anxiety, substance use, and somatoform disorders.[78] The PDSQ assesses 6 specific DSM-IV anxiety disorders: panic disorder, agoraphobia, PTSD, OCD, GAD, and social phobia.

Dr. Zimmerman explained that the PDSQ was intended as a diagnostic aid to be used in clinical practice to facilitate the efficiency of conducting the initial diagnostic evaluation. From a clinical perspective, it is most important that the diagnostic aid have good sensitivity and corresponding high negative predictive value. With high negative predictive value, the clinician can be confident that when the test indicates that the disorder is not present, there is little need to inquire about that disorder's symptoms. Because the PDSQ's anxiety disorder subscales have been shown to have high sensitivity and negative predictive value,[77] they could function well as a screening instrument in depressed patients.

Clinical Significance of Anxiety Disorders in Depressed Patients

Dr. Zimmerman stressed that the underrecognition of comorbid anxiety disorders is not simply of academic interest—it has important potential clinical significance. Epidemiologic studies such as the National Comorbidity Study[79,80] have demonstrated that depressed individuals with a history of anxiety disorders are at increased risk for hospitalization, suicide attempt, and greater impairment from depression. The co-occurrence of anxiety disorders in depressed patients has been associated with a more chronic course of depression in psychiatric patients[81] and primary care patients as well.[82]

The clinical implications of underdiagnosing comorbid anxiety disorders in depressed patients, Dr. Zimmerman explained, depend on 2 factors: (1) whether or not anxiety disorders have an impact on the longitudinal course of depression, and (2) the availability of effective treatment that is specific for anxiety disorders. The literature[79–82] suggests that the presence of a comorbid anxiety disorder is associated with a poorer outcome. One might speculate that improved diagnostic practice, resulting in improved detection of anxiety disorders and treatment directed to the additional concerns related to anxiety disorders, will result in improved treatment outcome. However, it is also possible that the presence of a comorbid anxiety disorder will be associated with poorer outcome even when the diagnosis is known. In studies[81,82] finding that the presence of a comorbid anxiety disorder was associated with a greater likelihood of depression chronicity, it is not clear whether the health care providers were aware of the researchers' anxiety disorder diagnoses. It is, therefore, unknown if the greater chronicity of depression in patients with high levels of anxiety was due to the failure of appropriate treatment or the failure to provide appropriate treatment.

Influence of Comorbid Anxiety Disorders on Antidepressant Selection

No studies have examined the important question of whether the treatment of depressed patients with and without comorbid anxiety disorders should differ. Few scientific data demonstrate that treatment outcome can be enhanced or optimized by selecting an antidepressant based on a patient's clinical profile (with the exception of monoamine oxidase inhibitors for atypical symptoms). Zimmerman and colleagues[83] hypothesized that clinicians nonetheless base their selection of antidepressants on patients' clinical characteristics. The study found that the presence of comorbid anxiety disorders, particularly panic disorder and generalized anxiety disorder, most frequently influenced antidepressant selection (Table 5). Thus, although few empirical data are available to guide clinicians in selecting an antidepressant based on patients' clinical characteristics, these factors are often used as the basis for antidepressant choice.

Conclusion

Dr. Zimmerman reiterated that the literature is consistent concerning the prevalence and impact of anxiety disorder comorbidity in depressed patients. Substantial rates of comorbid disorders have been found in epidemio-

logic and clinical populations using structured research diagnostic interviews. However, much lower comorbidity rates have been found in clinical populations using unstructured clinical interviews. Given that the structured interview is considered the diagnostic gold standard, this finding suggests that comorbidity is underdiagnosed in routine clinical settings.

Structured interviews such as the SCID are too long and unwieldy for routine use. It is more likely that clinicians would use an inexpensive screening instrument that does not intrude on the clinician's usual practice but provides clinically relevant diagnostic information. A reliable and valid self-report screening questionnaire, such as the PDSQ, would potentially enhance, not obstruct, usual clinical practice.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), duloxetine (Cymbalta), eszopiclone (Lunesta), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), modafinil (Provigil), paroxetine (Paxil, Pexeva, and others), phentermine (Adipex-P and others), pramipexole (Mirapex), protriptyline (Vivactil), ramelteon (Rozerem), sertraline (Zoloft), sildenafil (Viagra), tadalafil (Cialis), topiramate (Topamax), trazodone (Desyrel and others), venlafaxine (Effexor), zolpidem (Ambien).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, atomoxetine, buspirone, lithium, and modafinil are not approved by the U.S. Food and Drug Administration for the augmentation of antidepressants; pramipexole is not approved for the treatment of depression; topiramate is not approved for use for weight loss; reboxetine is not approved in the United States as an antidepressant; and bupropion and yohimbine are not approved for the treatment of sexual dysfunction. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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Answers to Pretest: 1. b 2. b

Commentary pp. 60–65

1. Differences in the diagnostic criteria for dysthymia and major depressive episode include:
a. Number and description of required symptoms
b. Number and duration of required symptoms
c. Duration and description of required symptoms
d. Number, description, and duration of required symptoms

2. What diagnostic question should come to a clinician's mind when seeing a patient with symptoms of depression?
a. Does the patient have a personality disorder?
b. Does the patient abuse drugs?
c. Is the disorder chronic or acute?
d. Is the disorder mild or severe?

3. The Cognitive Behavioral Analysis System of Psychotherapy (CBASP) model has a situational orientation and includes a strong affective component, which makes the approach broader than standard cognitive-behavioral therapy (CBT).
a. True
b. False

4. You are seeing a patient who has had ongoing depression for more than 2 years. What treatment should you suggest?
a. A dual-action antidepressant
b. CBT
c. A monoamine oxidase inhibitor
d. CBASP, an antidepressant, or the combination

5. A patient who has had ongoing depression for more than 2 years does not remit after an adequate course of treatment. The evidence is strongest for which next step?
a. Adding an atypical antipsychotic
b. Switching from CBASP to CBT
c. Increasing the antidepressant dose
d. Switching to another antidepressant or to CBASP

Academic Highlights pp. 88–97

6. The lifetime prevalence of major depression in the United States is higher among women than among men.
a. True
b. False

7. Depression and medical illness are associated with all of the following *except*:
a. Poorer prognoses
b. Increased morbidity and mortality
c. Decreased medical costs
d. Increased medical costs

8. The most desired outcome of the acute phase of treatment of depression is:
a. Response
b. Remission
c. Recovery
d. Recurrence

9. An accurate method of assessing antidepressant side effects in patients includes:
a. Waiting for spontaneous self-report
b. The use of self-rated forms
c. The use of clinician-rated forms
d. The use of both self-rated and clinician-rated forms

10. Selecting an antidepressant based on whether a depressed patient has comorbid anxiety is a strategy well-supported by the medical literature.
a. True
b. False

REGISTRATION FORM

Circle the one correct answer for each question.

1.	a	b	c	d	**6.**	a	b		
2.	a	b	c	d	**7.**	a	b	c	d
3.	a	b			**8.**	a	b	c	d
4.	a	b	c	d	**9.**	a	b	c	d
5.	a	b	c	d	**10.**	a	b		

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