Review of the Pharmacologic Management of Depression

This ACADEMIC HIGHLIGHTS section of 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.*

Faculty disclosure: In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME article were asked to complete a statement regarding all relevant financial relationships between themselves or their spouse/partner and any commercial interest (i.e., a proprietary entity producing health care goods or services) occurring within the 12 months prior to joining this activity. The CME Institute has resolved any conflicts of interest that were identified. The disclosures are as follows: ***Dr. Thase*** *is a consultant for AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Novartis, Organon, Pfizer, and Wyeth and is a member of the speakers/advisory boards for AstraZeneca, Eli Lilly, GlaxoSmithKline, Organon, and Wyeth.* ***Dr. Fava*** *has received research support from Abbott, Lichtwer Pharma GmbH, and Lorex; has received honoraria from EPIX, Bayer AG, Compellis, Janssen, Knoll, Lundbeck, Dov, Biovail, BrainCells, Inc., Cypress, Fabre-Kramer, Inc., Grunenthal GmBH, MedAvante, Inc., Sepracor, and Somerset; has received both research support and honoraria from Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Johnson & Johnson, Novartis, Organon, Pfizer, Pharmavite, Roche, Sanofi-Synthelabo, Solvay, and Wyeth; and his spouse/partner has received research support from Parke-Davis and Pfizer Inc.* ***Dr. Zimmerman*** *has received grant/research support from UCB Pharma and is a member of the speakers/advisory boards for Bristol-Myers Squibb, Forest, GlaxoSmithKline, Pfizer, Sepracor, and Takeda.* ***Dr. Culpepper*** *is consultant for and is on the advisory boards of Eli Lilly, Forest, Pfizer, and Wyeth.*

The opinions expressed herein are those of the faculty and do not necessarily reflect the views of the CME provider and publisher or the commercial supporter.

The Concept of Remission: Validity and Limitations

Michael E. Thase, M.D., began his presentation by stating that *remission* can be defined as a virtually complete relief of symptoms; that is, a level of symptoms basically indistinguishable from that of someone who has never been depressed. In depression, remission is usually understood to mean the optimal level of improvement for the acute phase treatment of an episode of major depressive disorder. Being in remission means that the individual has been able to return to a normal level of social functioning. 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 to measuring remission in major depressive disorder.

Remission is one of several outcomes for patients with depression (Figure 1).[1] 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.

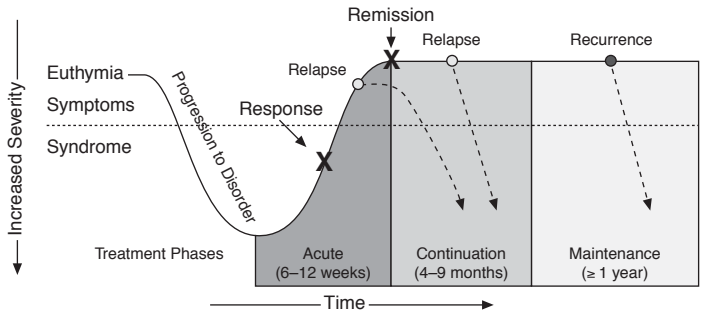
Remission leads to recovery. Generally, a patient needs to be in remission for at least 6 to 9 months before he or she is declared to be in recovery. In practical terms, however, it is difficult to distinguish between remission and recovery.

Validating the Concept of Remission

Dr. Thase next explained that there are phases of treatments that are tailored to match the goals of response and remission and prevent the negative outcomes of relapse and recurrence. Specifically, the goal of the acute phase of treatment is remission, which ideally occurs within the first 6 to 12 weeks of therapy. The second phase of treatment, the continuation phase, immediately follows the acute phase of treatment and typically lasts for 4 to 9 months. The primary goal of the continuation phase is to sustain remission and prevent relapse. The third phase, a maintenance phase, is for 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. The maintenance phase may last many years, perhaps even indefinitely.

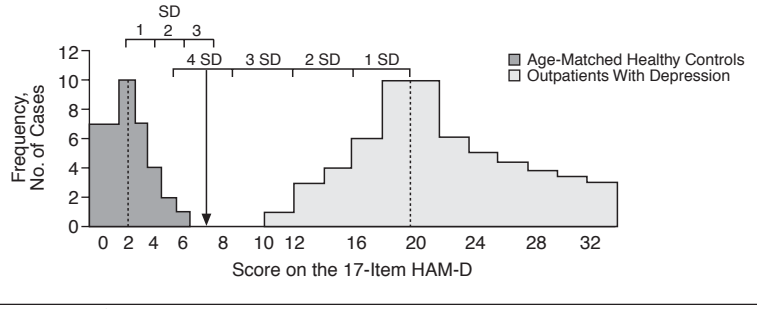
How do we know when patients have reached a symptom level below that of people with depression? In research studies at the University of Pittsburgh,[2] outpatients who presented with a major depressive episode had a mean score of 20 on the Hamilton Rating Scale for Depression (HAM-D) (Figure 2). Very few patients with depression had scores below 14, and none of the patients with major depressive disorder had scores below 10. It appears that individuals with a score below 10 on the HAM-D are clearly outside of the range of scores of depressed patients. However, none of the healthy control participants had HAM-D scores above 6, indicating that an improved patient with a score of 7, 8, or 9 still had symptoms that are distinguishable from those of a person who has never

Figure 1. Distinguishing Response and Remission[a]



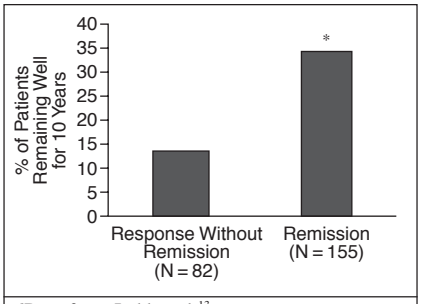
[a]Adapted with permission from Kupfer.[1]

Figure 2. Distribution of Scores on the 17-Item HAM-D in Patients With Depression and Healthy Controls[a]



[a]Data from Thase.[2]
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Figure 3. Comparison of Relapse in Patients Treated for Depression Who Either Had Residual Symptoms or Were in Full Remission[a]



[a]Data from Judd et al.[13]
*p < .001.

been depressed. 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, remission has been widely accepted as the goal for the acute phase treatment of depression. The concept of remission in depression is validated by several characteristics of the condition. Responders who do not remit or remit incompletely remain at greater risk for relapse than patients who achieve remission[3–5]; are more likely to suffer longer chronic depressive episodes[3]; are more likely to have less well time between episodes[3]; are more likely to have impairment at home, in the workplace, and in personal relations[6]; and may have a more difficult time managing common conditions such as diabetes and heart disease.[7–11] Residual depressive symptoms are also associated with a continued increase in the risk of suicide, so patients who do not remit do not obtain a complete reduction in the risk of suicide.[12]

The relationship between persistent residual symptoms and risk for relapse has been established in psychiatric settings,[4,13] primary care settings,[14] and studies of depression-focused psychotherapy.[5] In a 10-year follow-up of the National Institute of Mental Health Collaborative Depression Study,[13] patients who began the follow-up study with residual symptoms of depression had an 85% chance of suffering a relapse or recurrence during the 10-year follow-up period, whereas those who entered the follow-up study in full remission had a 35% risk of relapse (Figure 3). Treating patients to remission lowers the risk that they will relapse and improves the long-term course of illness.

The substantial improvement in social functioning that accompanies remission is also an important validator for the concept of remission. Miller et al.[6] conducted a double-blind study of patients with chronic depression (N = 635) who were randomly assigned to treatment with imipramine or sertraline. Within 12 weeks of beginning treatment, patients who achieved remission had a level of social functioning that was almost indistinguishable from normative data from a community sample. In contrast, patients who responded but did not remit were significantly worse in their social functioning than the community sample ($p \leq .05$). In fact, the patients who responded but did not remit were more similar in social functioning to the patients who did not respond to study treatment than they were to the population norms.

Limitations of the Concept of Remission

Dr. Thase noted that there are many reasons why a patient might not achieve remission. 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.

The more severe or complicated the illness, the longer the time to a state of remission.[15] Patients who are mildly ill may be able to achieve remission with supportive care or monitoring alone, so

the likelihood of remission is partly an inherent quality of the severity and complexity of the depressive disorder. Conversely, patients with more severe and complicated disorders are more likely to require vigorous treatment in order to achieve remission.

Dr. Thase emphasized that helping patients keep track of their symptom intensity and questioning them about their level of functioning is necessary to avoid confusing an incomplete response with an incomplete remission. Physicians should monitor a patient's 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 remaining symptoms. For those patients with severe and complex conditions, psychotherapy in combination with pharmacotherapy may be the best approach.

Although remission is a construct, it is not a physiologic fact for depressed patients. Research in depression has not yet reached the level at which illness activity can be assayed directly. The only way a physician can determine a patient's illness severity is to monitor symptoms, but a definition of remission that is based solely on symptoms ignores the fact that some patients can have substantial symptomatic relief but still have severe functional limitations. In clinical practice, physicians should look at symptom scales as well as simple measures of the quality of patients' lives—their ability to work, their relationships with others, and other measures of everyday functioning—as ways of gauging if patients have truly achieved remission. Also, some residual symptoms, such as insomnia and anxiety, may be more important than others in predicting relapse.

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[16] of the overall response rates to treatment with antidepressants showed response rates 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%.

The introduction of a number of new classes of antidepressant, including the popular selective serotonin reuptake inhibitors (SSRIs), has not substantially changed the fact that remission is achieved by fewer than half of all patients treated with antidepressants. One reason may be that many patients drop out of antidepressant treatment prematurely, possibly because of the tolerability issues with antidepressants. With the newer antidepressants, 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.

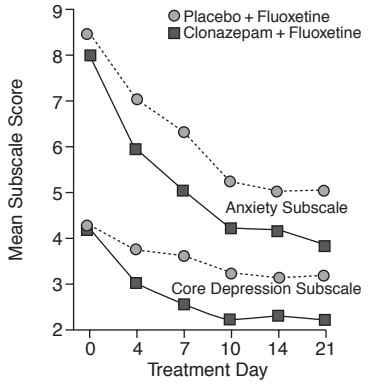
Antidepressants are perceived to be well-tolerated with minimal side effects, perhaps because most clinical studies use spontaneous patient reporting to assess side effects, which underestimates their prevalence. Much greater accuracy in assessing side effects is obtained by a systematic assessment of patients, including direct questioning through a self-rated form or a clinician-rated form. Although in some cases distinguishing side effects from residual symptoms of depression may be a challenge, a good knowledge of the baseline level of the patient's symptoms prior to treatment can help physicians discern the difference. 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.

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.

Dr. Fava and colleagues[17] looked at anxiety and nervousness during double-blind acute treatment with 3 SSRIs—fluoxetine, sertraline, and paroxetine. In that study, a substantial

Figure 4. Mean HAM-D Anxiety Subscale Scores of Patients Taking Fluoxetine Plus Placebo or Fluoxetine Plus Clonazepam[a]



[a]Reprinted with permission from Londborg et al.[18]
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Table 1. Incidence of Somnolence/Sedation and Fatigue/Asthenia During Antidepressant Treatment, Active Drug Versus Placebo (%)

	Somnolence/Sedation		Fatigue/Asthenia	
Drug	Drug	Placebo	Drug	Placebo
Bupropion[a]	20	20	5	9
Citalopram[b]	18	10	5	3
Fluoxetine[c]	13	6	11	6
Mirtazapine[d]	54	18	8	5
Nefazodone[e]	25	14	11	5
Paroxetine[f]	23	9	15	6
Sertraline[g]	13	7	12	7
Venlafaxine[h]	23	9	12	6

[a]Data from Physicians' Desk Reference.[19]
[b]Data from Forest Laboratories, Inc.[20]
[c]Data from Eli Lilly and Company.[21]
[d]Data from Physicians' Desk Reference.[22]
[e]Data from Physicians' Desk Reference.[23]
[f]Data from GlaxoSmithKline.[24]
[g]Data from Pfizer, Inc.[25]
[h]Data from Wyeth Pharmaceuticals, Inc.[26]

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 was not statistically significant.

The most common approach to management of anxiety and nervousness is using adjunctive medications such as benzodiazepines. Anticonvulsants have also been used to treat anxiety and nervousness, with some success, as have buspirone and atypical antipsychotics. The usefulness of benzodiazepines as an augmentation of antidepressants is supported by a study by Londborg and colleagues.[18] In this study, a greater reduction in symptoms on the anxiety subscale of the HAM-D was reported when clonazepam was added to fluoxetine compared with fluoxetine plus placebo (Figure 4).

Insomnia and Somnolence

According to Dr. Fava, insomnia and somnolence are also common side effects of antidepressant treatment. Sleep disturbances—both insomnia and hypersomnia—may emerge at the beginning of treatment or at any time during antidepressant treatment. Data from prescribing information show that somnolence and sedation are reported at rates greater than placebo with almost all antidepressant treatments with the exception of bupropion (Table 1).[19–26] In the study by Dr. Fava and colleagues[17] on the use of fluoxetine, sertraline, and paroxetine 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 for insomnia associated with antidepressant therapy. In particular, benzodiazepines,[27,28] nonbenzodiazepine hypnotics such as zolpidem[29] and eszopiclone,[30] melatonin,[31] and trazodone[32] 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, and low-dose tricyclic antidepressants (TCAs) and antihistamines.

Treating insomnia may improve symptoms of depression as well. A recent study by Dr. Fava and colleagues[33] demonstrated that the treatment of depression with an SSRI plus eszopiclone was associated with a significantly greater improvement in depressive symptoms than an SSRI plus placebo. Response and remission rates were also significantly ($p \leq .03$) higher at endpoint among those patients who had the combination treatment.

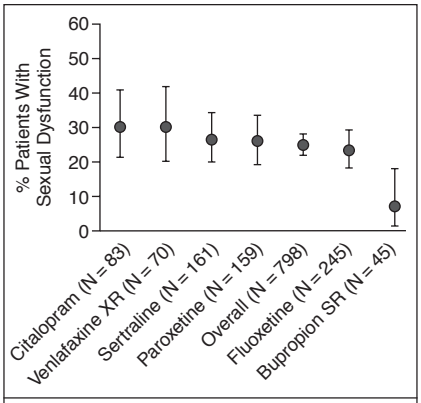
Adjunctive medications are also available for the treatment of hypersomnia associated with antidepressant treatment. Somnolence can be due to either poor sleep quality at night or a sedating effect of the antidepressant. If poor sleep quality is believed to be causing a patient's somnolence, the physician should consider adding a hypnotic such as trazodone, a benzodiazepine, or a nonbenzodiazepine.[34] 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 other than bupropion compared with placebo (see Table 1).[19–26]

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.[35] In a study by Dr. Fava and colleagues,[36] the level of fatigue in patients given modafinil or placebo in addition to antidepressant was examined. The patients given modafinil showed significant ($p < .05$) improvement in the worst level of fatigue they had experienced in the past 24 hours as measured by the Brief Fatigue Inventory when compared with patients given placebo.

Figure 5. Prevalence of Sexual Dysfunction in Patients Without Other Probable Causes of Sexual Dysfunction[a]



[a]Reprinted with permission from Clayton et al.[37]
Abbreviations: SR = sustained release, XR = extended release.

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.,[37] 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 (Figure 5). In this study, almost 1 in 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, 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 management options for the treatment of sexual dysfunction include yohimbine, 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. In fact, SSRIs have been found to increase weight in several studies.[38–40]

Dr. Fava suggested that some newer antidepressants may be more weight-neutral than the SSRIs. A 1-year, double-blind study by Weihs et al.[41] found that the amount of weight gained by patients taking bupropion was not greater than that of patients taking placebo; on the contrary, the patients taking bupropion lost weight. In a pooled analysis by Mallinckrodt et al.[42] of 7 double-blind trials, patients taking duloxetine lost a mean of 0.5 kg, while patients taking placebo gained a mean of 0.2 kg.

Currently no pharmacologic approaches to the treatment of weight gain associated with antidepressants are available. 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 from controlled studies for their efficacy.

Apathy and Cognitive Symptoms

Dr. Fava noted that apathy and cognitive symptoms are also side effects of long-term treatment with antidepressants that are often associated with discontinuation.[17] A study by Bolling and Kohlenberg[43] 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. However, rates of comorbidity vary among studies because they are influenced by several methodological factors, such as the number of disorders assessed, method of assessment (semistructured interview vs. clinical evaluation), time period covered (current vs. lifetime), handling of partial remission, and inclusion of not otherwise specified categories. Even when

Table 2. Prevalence of Current Anxiety Disorders in Psychiatric Outpatients With a Principal Diagnosis of Major Depressive Disorder

Anxiety Disorder, %	Fava et al[44] (N = 255)	Melartin et al[45] (N = 269)	Sanderson et al[46] (N = 197)	Zimmerman et al[47] (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 NOS diagnoses increased the frequency of any anxiety disorder from 57% to 67%.

Table 3. Desire for Treatment of Current DSM-IV Comorbid Anxiety Disorders in SCID-Assessed Patients With a Principal Diagnosis of Major Depressive Disorder[a]

	Frequency of the Disorder	Desire for Treatment	
Anxiety Disorder	N	N	%
Panic disorder	47	46	97.9
Specific phobia	37	21	56.8
Social phobia	98	72	73.5
Obsessive-compulsive disorder	26	21	80.8
Posttraumatic stress disorder	34	30	88.2
Generalized anxiety disorder	60	55	91.7
Any anxiety disorder	172	149	86.6

[a]Reprinted with permission from Zimmerman and Chelminski.[49]

standardized assessments are used, rates will vary between studies because of differences in the breadth of the evaluation.

Anxiety disorders, as a group, are a frequent current comorbid disorder in depressed patients. To illustrate, Dr. Zimmerman reviewed 4 studies[44–47] 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 2).

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.[48] In the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, Zimmerman and Mattia[48] examined diagnostic frequencies in 2 separate samples of 500 patients drawn from the same outpatient practice. The first group was diagnosed by clinicians using an unstructured clinical evaluation (non-SCID sample), and the second was diagnosed by raters administering the Structured Clinical Interview for DSM-IV (SCID sample). Panic disorder, social phobia, specific phobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) were all significantly less frequently diagnosed in the non-SCID sample.

A subsequent report from the MIDAS project focused on the detection of anxiety disorders in depressed patients.[49] As an indicator of clinical importance, the investigators asked patients whether they were interested in having treatment directed toward the comorbid anxiety disorder. More current anxiety disorders were diagnosed in the SCID sample than the non-SCID sample. Each anxiety disorder except PTSD was significantly more frequently diagnosed in the patients interviewed with the SCID. Dr. Zimmerman reported that depressed patients evaluated with the SCID most often wanted treatment of comorbid GAD, panic disorder, and PTSD (Table 3). 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 stated that he and a colleague found evidence of this in their study of clinicians' recognition of PTSD.[48] When PTSD was the principal diagnosis, then the frequency of PTSD diagnoses was similar according to unstructured clinical interviews and semistructured research evaluations. In contrast, when PTSD was an additional comorbid condition, clinicians were significantly less likely to detect its presence compared with the research evaluations. 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.

As a follow-up to that work, Zimmerman and Chelminski examined the ability of the Psychiatric Diagnostic Screening Questionnaire (PDSQ) to screen for anxiety disorders in depressed patients.[50] The PDSQ is a self-report questionnaire

that consists of 126 questions assessing the symptoms of 13 DSM-IV disorders in 5 areas: eating, mood, anxiety, substance use, and somatoform disorders.[51] Regarding anxiety disorders, the PDSQ assesses 6 specific DSM-IV anxiety disorders: panic disorder, agoraphobia, PTSD, OCD, GAD, and social phobia.

Eight hundred patients presenting for treatment at an outpatient practice first completed the PDSQ and were then evaluated by a trained diagnostic interviewer who administered the SCID.[50] The diagnostic interviewers did not review patients' responses on the PDSQ. Of these 800 patients, 295 had a principal diagnosis of MDD. Dr. Zimmerman reported that in these depressed patients, the PDSQ subscales maintained excellent sensitivity and had high negative predictive value. These results suggest that the anxiety disorder subscales of the PDSQ do a good job of identifying anxiety disorders in depressed psychiatric outpatients (i.e., they have high sensitivity) and an excellent job identifying individuals who are unlikely to have an anxiety disorder (i.e., they have very high negative predictive value). The specificity of the PDSQ subscales, however, decreased very slightly when the analysis was limited to anxiety disorders as comorbid conditions in depressed patients.

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 high sensitivity and negative predictive value, 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. As he already noted, most patients indicated that they wanted their treatment to address the comorbid anxiety disorder. Thus, from a consumer-oriented perspective, recognition and treatment of comorbidity might have an impact on patient satisfaction with care and treatment compliance.

Epidemiologic studies such as the National Comorbidity Study[52,53] have demonstrated that depressed individuals with a history of anxiety disorders are at increased risk for hospitalization, suicide attempt, and greater impairment from the depression. The cooccurrence of anxiety disorders in depressed patients has been associated with a more chronic course of depression in psychiatric patients[54] and primary care patients as well.[55]

According to Dr. Zimmerman, at least 3 controlled studies of the prognostic significance of anxiety disorders in depressed patients have been conducted. Fava and colleagues[56] treated nearly 300 depressed outpatients with fluoxetine and found that patients with a comorbid anxiety disorder were less likely to respond than depressed patients without a comorbid anxiety disorder. In Brown and colleagues'[57] primary care study of nortriptyline and interpersonal therapy, the presence of a comorbid anxiety disorder was associated with a nonsignificantly higher rate of premature discontinuation from treatment, and patients with a lifetime history of panic disorder had a lower recovery rate than patients without panic. Levitt and coworkers[58] treated 31 depressed outpatients who had seasonal affective disorder using light therapy and treated 25 depressed patients without seasonal affective disorder with desipramine or imipramine. The presence of a comorbid anxiety disorder did not predict response to light therapy in the patients with seasonal affective disorder, but in the patients without seasonal affective disorder who were treated with an antidepressant, the presence of a comorbid anxiety disorder was associated with a significantly lower response rate. None of these studies included a placebo group.

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[52–58] suggests that the presence of a comorbid anxiety disorder is associated with a poorer outcome. The second question is whether or not appropriate intervention for anxiety will improve outcome. It is logical to 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 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. Reviews of the treatment literature, including the American Psy-

chiatric Association's *Practice Guidelines for the Treatment of Depression*,[59] conclude that antidepressants are equally effective. Moreover, 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). Despite the lack of empirical evidence, Dr. Zimmerman and colleagues[60] hypothesized that clinicians nonetheless base their selection of antidepressants on patients' clinical characteristics. The results of the Rhode Island Factors Associated with Antidepressant Choice Survey (FAACS) study supported this hypothesis.

The FAACS study[60] is the only prospective study of the factors used by psychiatrists to select antidepressant medication. Immediately after an antidepressant was prescribed to treat a depressive disorder, the treating psychiatrist completed a 43-item questionnaire listing factors that might have influenced the choice of antidepressant medication. Data were collected for 1137 depressed patients. The presence of comorbid diagnoses and specific symptoms were 2 of 3 reasons that were each endorsed in approximately half of the prescriptions; desire to avoid a specific side effect was the third. Regarding specific disorders, the presence of comorbid anxiety disorders, particularly panic disorder and GAD, most frequently influenced antidepressant selection. 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.

Conclusions

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 epidemiologic 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 suggests that comorbidity is underdiagnosed in routine clinical settings.

Structured interviews such as the SCID are too long and unwieldy for use in routine outpatient mental health settings. A less time-consuming semistructured interview such as the Mini International Neuropsychiatric Interview[61] may be brief enough to be incorporated into clinical practice; however, this would require a significant change in how clinicians conduct their diagnostic evaluations. It is more likely that clinicians would use an inexpensive screening instrument that does not intrude on their usual practice but provides clinically relevant diagnostic information. Potentially, a reliable and valid self-report screening questionnaire, such as the PDSQ, would enhance and not interfere with usual clinical practice.

Finally, Dr. Zimmerman's review of the treatment literature indicates that few placebo-controlled studies have examined the effectiveness of treatments for patients with comorbid depression and anxiety disorders. Because of the high frequency of this comorbidity, this area of treatment research warrants further study. Also sparse are studies examining differences between active treatment and placebo in patients with and without an anxiety disorder. Dr. Zimmerman concluded that future treatment studies should examine whether the presence or absence of a comorbid anxiety disorder in depressed patients warrants different treatment approaches.

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[62]—20% to 25% of women and 7% to 12% of men.[63] In a typical episode of depression, individuals sink into depression symptomatology over a period of 4 to 6 weeks, then stay at full symptomatology 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.

Individuals with depression and comorbid anxiety disorders will typically have at least one anxiety disorder during their teenage years or younger and then, during their early 20s, experience their first episode of major depression.[63] In the 5 years following that first episode of major depression, half will have additional episodes. With each additional episode of depression, the episodes tend to become more severe and longer in duration and have a shorter interepisode interval.[1]

Recognizing Depression in Primary Care

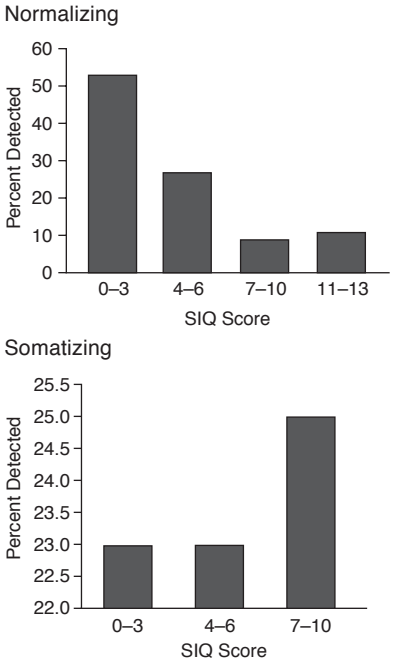
Dr. Culpepper reported that in primary care settings, major depression presents with a myriad of different symptoms and utilization patterns. Given these diverse presentations, screening tools for major depression are very useful in primary care. In 2002, the United States Preventive Services Task Force[64] reversed a longstanding recommendation not to screen for depression in primary care settings because screening had been found to not only lead to improvement in the recognition of depression, but lead to a true improvement in patient well-being over time.

The Preventive Services Task Force[64] further found that 2 questions are almost as useful as longer screening tools for the recognition of major depression. These 2 questions are "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 Patient Health Questionnaire (PHQ-9),[65] the Zung Depression Scale,[66] and the Beck Depression Inventory[67] are all helpful for the exploration of symptomatology 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 the United Kingdom[68] identified a pattern of physician agreement with patients that lead 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 6).

Figure 6. Detection of Anxiety or Depression by Primary Care Physicians in Patients Who Normalized or Somatized Their Symptoms[a]



[a]Data from Kessler et al.[68] Patients were considered to be either normalizers or somatizers if they scored ≥ 7.
Abbreviation: SIQ = Symptom Interpretation Questionnaire.

Awareness of the ways that depression can present in primary care can help the physician accurately diagnose patients. Somatic symptoms that are not otherwise explainable by medical illness are frequently indicators that the patient has underlying major depression. Of the small group of patients that are high utilizers in primary care settings, the majority have a lifetime history of either major depression or anxiety, and a large number have current major depression, so a pattern of high utilization also can be an indicator of underlying depression.[69]

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 bothersome to 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 impairs the individual's overall quality of life. For example, comorbid anxiety disorder impairs the ability to work. In a study by Roy-Byrne et al.,[70] the presence of both major depression and an anxiety disorder increased the number of days absent from work in the past 30 days from approximately 1 day in people with major depression alone to over 4 days in people with a comorbid anxiety disorder. Comorbid anxiety disorders also lead to a marked increase in suicidality. The patient who has anxiety and major depression is likely to have a past history of suicide attempts. Such a past history is one of the best predictors of future suicidal thoughts, ideations and suicide attempts, so comorbid depression and anxiety is an indication for an evaluation of suicidality (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. In specific illness groups within primary care, the prevalence of depression is 2 to 3 times higher than in patients without these comorbidities.[71] Prevalence rates of major depression are between 20% and 30% for patients with diabetes, cardiac disease, cancer, or Parkinson's disease.[72–74] Patients with medical illnesses develop depression at a much higher rate than the general population.[75]

Not only do major depression and medical illnesses occur together frequently, they also tend to make patient outcomes worse. There is a bidirectional interaction 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.[76] Depression and medical illnesses are associated with poorer prognoses, increased morbidity and mortality, and increased medical costs.

There are a number of mechanisms involved in the worsening of the course of illness in a patient with major depression and a medical illness. The symptom burden of the depression tends to be heightened, functional impairment of the medical illness is compounded by the depression, and the patient's health behaviors are less adaptive—there is less self-care, less adherence to medications, and higher utilization of medical resources.

The primary care physician is often faced with real dilemmas in interpreting symptomatology. For example, the primary care physician has to determine if, in a cardiac patient, fatigue is due to potential depression or to the cardiac condition. Unfortunately, major depression is less frequently recognized and appropriately diagnosed in the presence of physical symptomatology than in patients who do not complain of physical symptoms.[77,78] A key recommendation

is that a patient with a medical illness and symptoms that might be attributed to major depression should have those symptoms counted toward the DSM-IV criteria for major depression. A dual attribution will greatly improve the accuracy of recognition and diagnosis of major depression.

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. Primary care physicians provide most of the care for patients with major depression in the United States. Unfortunately, only a small minority of patients treated for major depression in primary care practices 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 of 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.[79]

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.

Because many studies have shown that patients who have residual symptoms are at high risk for relapse, a key in successful therapy for depression is treating patients with an intensity that achieves adequate and full control of symptomatology. In a study by Paykel et al.,[4] 76% of treated patients who had persistent symptoms relapsed, whereas 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.[6,80] The lack of functional improvement does not just involve difficulties related to depression but involves 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.[81]

A number of strategies are available to primary care physicians to improve outcome in depressed patients. One of these is adopting 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, but to measure treatment change. 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[66] and the Beck Depression Inventory[67] can also be used to measure progress during treatment.

In order to achieve the highest improvement in outcome of depression, primary care practices should actively manage their depressed patients.[64] 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 diagnosis 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 assure medication adherence and to identify any new problems or adverse effects requiring tailoring of treatment.

Table 4. 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]Based on Lin et al.[82]

An important part of active management of patients is education. A study by Lin et al.[82] identified several specific patient educational messages that significantly improved adherence to treatment within the first month (Table 4). 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 ear infection or the pneumonia is present but is 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 if the patient experiences significant side effects, he or she should report them 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.

Practices that actively manage patients often use a coordinated care approach. In coordinated care, a team of clinicians works together to treat the

patient in the most effective way possible. This team approach involves a psychiatrist who sees the patient, a care manager who is usually either a practice nurse or a mental health professional, members of the practice who use a record flow sheet to keep the patient engaged in care, and the patient, who may attend self-help support groups as recommended by the other members of the care team.

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 have been demonstrated to lead to marked improvement in long-term outcome of depressed patients.[83] This improvement can be 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. Care process improvements lead to an increase in both response and remission. In one study of active case management of depression,[84] when measured at 1 year, 45% of the patients who were in practices that actively managed cases were in remission, compared with 28% of patients in usual care.

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 utilization. Major depression is highly comorbid with both anxiety disorders and medical conditions and greatly worsens patient outcomes in medical illnesses, both in the short-term and long-term, over multiple decades. 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.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), clonazepam (Klonopin and others), desipramine (Norpramin 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), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil, Pexeva, and others), phentermine (Adipex-P and others), pramipexole (Mirapex), protriptyline (Vivactil), ramelteon (Rozerem), sertraline (Zoloft), sildenafil (Revatio, 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, all augmentation strategies discussed in this report are off-label. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

REFERENCES

1. Kupfer DJ. Long-term treatment of depression. J Clin Psychiatry 1991;52(5, suppl):28–34
2. Thase ME. Comparing the methods used to compare antidepressants. Psychopharmacol Bull 2002;32(suppl 1):1–17
3. Judd LL, Paulus MJ, Schettler PJ, et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? Am J Psychiatry 2000;157:1501–1504
4. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995;25: 1171–1180
5. Thase ME, Simons AD, McGeary J, et al. Relapse after cognitive behavioral therapy of depression: potential implications for longer courses of treatment. Am J Psychiatry 1992; 149:1046–1052
6. Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. J Clin Psychiatry 1998;59:608–619
7. Lustman PJ, Anderson RJ, Freedland KE, et al. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000;23:934–942
8. de Groot M, Anderson R, Freedland KE, et al. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619–630
9. Frasure-Smith N, Lesperance R, Talajic M. Depression following myocardial infarction: impact on 6-months survival. JAMA 1993;270:1819–1825
10. Penninx BW, Beekman AT, Honig AT, et al. Depression and cardiac mortality: results from a community-based longitudinal study. Arch Gen Psychiatry 2001;58:221–227
11. Vaccarino V, Kasl SV, Abramson J, et al. Depressive symptoms and risk of functional decline and death in patients with heart failure. J Am Coll Cardiol 2001;38:199–205
12. Judd LL, Akiskal HS, Paulus MP. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. J Affect Disord 1997;45:5–18
13. Judd LL, Akiskal HS, Maser JD, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J Affect Disord 1998;50:97–108
14. Simon GE. Long-term prognosis of depression in primary care. Bull World Health Organ 2000;78:439–445
15. Melartin TK, Rytsälä HJ, Leskelä US, et al. Severity and comorbidity predict episode duration and recurrence of DSM-IV major depressive disorder. J Clin Psychiatry 2004;65: 810–819
16. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19:179–200
17. Fava M, Hoog SL, Judge RA, et al. Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia. J Clin Psychopharmacol 2002;22:137–147
18. Londborg PD, Smith WT, Glaudin V, et al. Short-term cotherapy with clonazepam and fluoxetine: anxiety, sleep disturbance, and core symptoms of depression. J Affect Disord 2000;61:73–79
19. Wellbutrin (bupropion). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 2006
20. Celexa (citalopram). St. Louis, Mo: Forest Laboratories, Inc; 2005. Available at http://www.fda.gov/cder/foi/label/2005/020822s29lbl.pdf. Accessed Jan 30, 2006
21. Prozac [package insert]. Indianapolis, Ind: Eli Lilly and Company; 2005. Available at: http://pi.lilly.com/prozac.pdf. Accessed Jan 30, 2006
22. Remeron (mirtazapine). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 2002
23. Serzone (nefazodone). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 2002
24. Paxil [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2005. Available at: http://us.gsk.com/products/assets/us_paxil.pdf. Accessed Jan 30, 2006
25. Zoloft (sertraline). New York, NY: Pfizer Inc; 2004. Available at http://www.fda.gov/cder/foi/label/2005/019839s053S054lbl.pdf. Accessed January 30, 2006
26. Effexor (venlafaxine). Philadelphia, Pa: Wyeth Pharmaceuticals, Inc; 2005. Available at: http://www.wyeth.com/content/ShowLabeling.asp?id=99. Accessed Feb 20, 2006
27. Nolen WA, Haffmans PM, Bouvy PF, et al. Hypnotics as current medication in depression: a placebo-controlled, double-blind comparison of flunitrazepam and lormetazepam in patients with major depression, treated with a (tri)cyclic antidepressant. J Affect Disord 1993;28: 179–188
28. Cohn JB. Triazolam treatment of insomnia in depressed patients taking tricyclics. J Clin Psychiatry 1983;44:401–406
29. Asnis GM, Chakraburtty A, DuBoff EA, et al. Zolpidem for persistent insomnia in SSRI-treated depressed patients. J Clin Psychiatry 1999;60:668–676
30. Fava MF, Buysse DJ, Rubens R, et al. Eszopiclone co-administered with fluoxetine or

insomnia associated with major depressive disorder (MDD): effects on sleep and depression. Presented at the 45th Annual Meeting of the New Clinical Drug Evaluation Unit (NCDEU); June 6–9, 2005; Boca Raton, Fla. Session II-92
31. Dolberg OT, Hirschmann S, Grunhaus L. Melatonin for the treatment of sleep disturbances in major depressive disorder. Am J Psychiatry 1998;155:1119–1121
32. Nierenberg AA, Adler LA, Peselow E, et al. Trazodone for antidepressant-associated insomnia. Am J Psychiatry 1994;151:1069–1072
33. Fava M, McCall WV, Krystal A, et al. Eszopiclone co-administered with fluoxetine in patients with insomnia co-existing with major depressive disorder. Biol Psychiatry. In press
34. Fava M. Daytime sleepiness and insomnia as correlates of depression. J Clin Psychiatry 2004;65(suppl 16):27–32
35. Fava M. Symptoms of fatigue and cognitive/executive dysfunction in major depressive disorder before and after antidepressant treatment. J Clin Psychiatry 2003;64 (suppl 14):30–34
36. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry 2005;66:85–93
37. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry 2002;63:357–366
38. Michelson D, Amsterdam JD, Quitkin FM, et al. Changes in weight during a 1-year trial of fluoxetine. Am J Psychiatry 1999;156: 1170–1176
39. Sussman N, Ginsberg DL, Bikoff J, et al. Effects of nefazodone on body weight: a pooled analysis of selective serotonin reuptake inhibitor- and imipramine-controlled trials. J Clin Psychiatry 2001;62:256–260
40. Fava M, Judge R, Hoog S, et al. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. J Clin Psychiatry 2000;61: 863–867
41. Weihs KL, Houser TL, Batey SR, et al. Continuation phase treatment with bupropion SR effectively decreases the risk of relapse for depression. Biol Psychiatry 2002;51:753–761
42. Mallinckrodt C, Tran PV, Detke MJ, et al. Minimal effect of the antidepressant duloxetine on body weight. In: New Research Abstracts of the 154th Annual Meeting of the American Psychiatric Association; May 18–23; Philadelphia, Pa. Abstract NR441
43. Bolling MY, Kohlenberg RJ. Reasons for quitting serotonin reuptake inhibitor therapy: paradoxical psychological side effects and patient satisfaction. Psychother Psychosom 2004;73: 380–385
44. Fava M, Rankin MA, Wright EC, et al. Anxiety disorders in major depression. Compr Psychiatry 2000;41:97–102
45. Melartin TK, Rytsala HJ, Keskela US, et al. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. J Clin Psychiatry 2002;63:126–134
46. Sanderson WC, Beck AT, Beck J. Syndrome comorbidity in patients with major depression or dysthymia: prevalence and temporal relationships. Am J Psychiatry 1990;147:1025–1028
47. Zimmerman M, McDermut W, Mattia JI. Frequency of anxiety disorders in psychiatric outpatients with major depressive disorder. Am J Psychiatry 2000;157:1337–1340
48. Zimmerman M, Mattia JI. Psychiatric diagnosis in clinical practice: is comorbidity being missed? Comp Psychiatry 1999;40:182–191
49. Zimmerman M, Chelminski I. Clinician recognition of anxiety disorders in depressed outpatients. J Psychiatr Res 2003;37:325–333
50. Zimmerman M, Chelminski I. Screening for anxiety disorders in depressed patients. J Psychiatr Res. In press
51. Zimmerman M, Mattia JI. The Psychiatric Diagnostic Screening Questionnaire: development, reliability and validity. Comp Psychiatry 2001; 42:175–189
52. Kessler RC, Nelson CB, McGonagle KA, et al. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. Br J Psychiatry 1996;168(suppl 30):17–30
53. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
54. Coryell W, Endicott J, Andreasen NC, et al. Depression and panic attacks: the significance of overlap as reflected in follow-up and family study data. Am J Psychiatry 1988;145:292–300
55. Brown C, Schulberg HC, Pigerson HG. Factors associated with symptomatic improvement and recovery from major depression in primary care patients. Gen Hosp Psychiatry 2000;22:242–250
56. Fava M, Uebelacker LA, Alpert JE, et al. Major depressive subtypes and treatment response. Biol Psychiatry 1997;42:568–576
57. Brown C, Schulberg HC, Madonia MJ, et al. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am J Psychiatry 1996;153:1293–1300
58. Levitt AJ, Joffe RT, Brecher D, et al. Anxiety disorders and anxiety symptoms in a clinic sample of seasonal and nonseasonal depressives. J Affect Disord 1993;28:51–56
59. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder [Revision]. Am J Psychiatry 2000;157(suppl 4):1–45
60. Zimmerman M, Posternak M, Friedman M, et al. Which factors influence psychiatrists' selection of antidepressants? Am J Psychiatry 2004;161:1285–1289
61. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the Development and Validation of a Structured Diagnostic Psychiatric Interview. J Clin Psychiatry 1998;59 (suppl 20):22–33
62. Kessler RC, McGonagle KA, Swartz M, et al. Sex and depression in the National Comorbidity Survey, I: lifetime prevalence, chronicity, and recurrence. J Affect Disord 1993;29:85–96
63. Clinical Practice Guideline Number 5: Depression in Primary Care, vol 1. Detection and Diagnosis. Rockville, Md: US Dept Health Human Services, Agency for Health Care Policy and Research; 1993
64. Pignone MP, Gaynes BN, Rushton JL, et al. Screening for depression in adults: a summary of the evidence for the US Preventive Services Task Force. Ann Intern Med 2002;136:765–766
65. Pfizer Inc. Patient Health Questionnaire (PHQ-9). Available at: http://www.pfizer.com/pfizer/phq-9/index.jsp. Accessed Jan 26, 2006
66. Zung WWK. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63–70
67. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
68. Kessler D, Lloyd K, Lewis G, et al. Cross sectional study of symptom attribution and recognition of depression and anxiety in primary care. BMJ 1999;318:436–439
69. Katon W, Von Korff M, Lin E, et al. Distressed high utilizers of medical care: DSM-III-R diagnoses and treatment needs. Gen Hosp Psychiatry 1990;12:355–362
70. Roy-Byrne PP, Stang P, Wittchen HU, et al. Lifetime panic-depression comorbidity in the National Comorbidity Survey: association with symptoms, impairment, course and help-seeking. Br J Psychiatry 2000;176:229–235
71. Cohen-Cole SA, Kaufmen KG. Major depression in physical illness: diagnosis, prevalence, and antidepressant treatment (a ten-year review: 1982–1992). Depression 1993;1:181–204
72. Musselman DL, Betan E, Larsen H, et al. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. Biol Psychiatry 2003;54:317–329
73. Musselman DL, Evans DL, Nemeroff CB. The relationship to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry 1998;55:580–592
74. Lieberman A. Depression in Parkinson's disease—a review. Acta Neurol Scand 2006;113:1–8
75. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry 2003;54:216–226
76. Evans DL, Charney DS. Mood disorders and medical illness: a major public health problem. Biol Psychiatry 2003;54:177–180
77. Dantz B, Ashton AK, D'Mello DA, et al. The scope of the problem: physical symptoms of depression. J Fam Pract 2003;Dec(suppl):S6–S8
78. Tylee AT, Freeling P, Kerry S. Why do general practitioners recognize major depression in one woman patient yet miss it in another? Br J Gen Pract 1993;43:327–330
79. Young AS, Klap R, Sherbourne CD, et al. The quality of care for depressive and anxiety disorders in the United States. Arch Gen Psychiatry 2001;58:55–61
80. Druss BG, Schlesinger M, Allen HJM Jr. Depressive symptoms, satisfaction with health care, and 2-year work outcomes in an employed population. Am J Psychiatry 2001;158:731–734
81. Simon GE, Revicki D, Heiligenstein J, et al. Recovery from depression, work productivity, and health care costs among primary care patients. Gen Hosp Psychiatry 2000;22:153–162
82. Lin EH, Von Korff M, Lin E, et al. The role of the primary care physician in patient's adherence to antidepressant therapy. Med Care 1995;33:67–74
83. Von Korff M, Goldberg D. Improving outcomes in depression. BMJ 2001;323:948–949
84. Katzelnick DJ, Simon GE, Pearson SD, et al. Randomized trial of a depression management program in high utilizers of medical care. Arch Fam Med 2000;9:345–351

For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 501–502.

