



Pretest and Objective

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This educational activity is eligible for CME credit through August 31, 2006. The latest review of this material was June 2004.

Educational Objective

After studying the ACADEMIC HIGHLIGHTS, you will be able to:

- Identify the effects that physical symptoms may have on the course and outcome of depression, and compare treatment strategies.

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

1. According to the DSM-IV, physical pain is a criterion of major depressive disorder.

- a. True
- b. False

Pretest answer and Posttest on page 176.

Disclosure of Off-Label Usage

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In this *ACADEMIC HIGHLIGHTS*, issues pertinent to physical symptoms and depression in primary care patients are discussed by experts. Dr. Maurice Ohayon sketches the prevalence and overlap of physical symptoms, chronic pain, and depression in a random sample; Dr. Bruce Arnow discusses chronic pain, comorbidity, and medical utilization; Dr. Pedro Delgado makes the case for early and aggressive treatment of depression; Dr. Vivien Burt explores treatment options; and Dr. Ruta Nonacs focuses on populations especially susceptible to depression with physical symptoms. The interface between the emotional (mind) and the physical (body) is commonly overlooked in practice but may be particularly clinically relevant in primary care, where many depressed patients first seek treatment for pain and other physical symptoms.

—Larry Culpepper, M.D., M.P.H.
Editor in Chief

The Primary Care Companion to The Journal of Clinical Psychiatry

ACADEMIC HIGHLIGHTS

Recognizing and Treating the Physical Symptoms of Depression in Primary Care

This *ACADEMIC HIGHLIGHTS* section of The Primary Care Companion to The Journal of Clinical Psychiatry presents the highlights from the teleconference “Recognizing the Physical Symptoms of Depression,” which was held March 16, 2004. The teleconference and this *ACADEMIC HIGHLIGHTS* were independently developed pursuant to an unrestricted educational grant from Eli Lilly and Company. This report was prepared by Physicians Postgraduate Press, Inc.

This teleconference was chaired by **Alan F. Schatzberg, M.D.**, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, Calif. The faculty were **Bruce A. Arnow, Ph.D.**, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Calif.; **Vivien K. Burt, M.D., Ph.D.**, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles; **Pedro L. Delgado, M.D.**, Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, Ohio; **Ruta M. Nonacs, M.D., Ph.D.**, Department of Psychiatry, Harvard Medical School, Cambridge, Mass.; and **Maurice M. Ohayon, M.D., D.Sc., Ph.D.**, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Calif.

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The mind-body connection has important implications for treatment and outcome in mental illness. In recent years, much attention has been paid to depression as a pathologic emotional state incorporating physical causes and consequences. In this teleconference, chaired by Alan F. Schatzberg, M.D., participants discussed the intersection of emotional and physical symptoms—notably chronic pain—in major depressive disorder (MDD).

Does Depression Hurt? Epidemiology of Physical and Depressive Symptoms

Maurice M. Ohayon, M.D., D.Sc., Ph.D., began by stating that although physical symptoms are common in depression, their etiology within the disorder is little understood. Physical symptoms of depression have been known to include those such as sleep or appetite disturbances, but physical pain, although not stated as a symptom of depression according to the DSM-IV classification of MDD, is also frequently reported by patients with depression. To illustrate the association between pain and MDD, Dr. Ohayon shared the results of a large 5-year study of depression and physical pain.¹ A detailed account of the results was published in the *Archives of General Psychiatry* in 2003.

Dr. Ohayon explained that the study sample comprised 18,980 subjects ranging in age from 15 to 100 years and representing the general popula-

tions of 5 European countries. The Sleep-EVAL System administered to the subjects is a series of questions based on DSM-IV criteria, the International Classification of Sleep Disorders, and the International Classification of Diseases. In addition to classifying subjects who met criteria for major depression, the system identified subjects who, although they reported no clear psychiatric disorder, did have depressive symptoms such as sadness or depression, hopelessness, or loss of interest in things that had formerly given them pleasure. Responses to the Sleep-EVAL survey were categorized into sociodemographic information, sleep habits, physical health, and sleep and mental disease symptoms.

Chronic painful physical conditions (limb pain, backaches, joint/articular pain, gastrointestinal pain or diseases,

and headaches) were considered present if the pain had led to a medication consultation or to the use of medication to ease the pain, had interfered with normal functioning, or had lasted for at least 6 months.

Pain With Depressive Symptoms

Dr. Ohayon distinguished subjects with some symptoms of depression from those with MDD. Symptoms of depression were reported by 16.5% of subjects, of whom 27.6% also reported at least 1 chronic painful physical condition. Subjects who reported at least 1 depressive symptom were more likely than subjects with no depressive symptoms to report each of the painful physical conditions queried. The difference was statistically significant ($p < .001$) for all painful physical conditions except headache.

Dr. Ohayon drew attention to several interesting points found in the study, namely that the more depressive symptoms were reported, the greater was the association between depressive symptoms and chronic painful physical conditions. Subjects who felt sad or depressed were more likely to report chronic painful physical conditions than those who experienced hopelessness, anhedonia, or loss of interest. Those with fatigue or loss of energy tended to report numerous chronic painful conditions. Limb pain was more frequently reported by subjects who also had symptoms of insomnia or hypersomnia, fatigue or loss of energy, and feelings of worthlessness or guilt. Subjects with fatigue or

loss of energy reported more gastrointestinal disorders.

Pain With Major Depressive Disorder

Of the subjects who participated in the interview, 4% had a diagnosis of MDD. At least 1 chronic painful physical condition was mentioned by 43.4% of these subjects. Subjects with MDD were 5 times more likely to report backaches, 4 times more likely to report headaches, 3 times more likely to report limb pain, and 2 times more likely to report gastrointestinal problems or joint/articular diseases than the rest of the sample. Furthermore, most subjects with MDD (61.6%) reported having either a chronic painful physical condition or a nonpainful medical condition. Although appetite or weight changes, fatigue, insomnia or hypersomnia, and feelings of worthlessness or guilt were frequently associated with pain alone, about 88% of subjects with MDD reported having somatic symptoms, such as fatigue or appetite disturbance.

Conclusion

The associations between depression, chronic pain, and somatic symptoms strongly suggest that patients who present to primary care with chronic painful physical conditions should be evaluated for depression as well as medical illness.

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nance of physical complaints in an environment where the discovery and treatment of physical illness is the mandate.

Prevalence and Burden of Depression and Comorbid Pain in Primary Care

Although prevalence rates vary due to differing methodologies, estimates^{2,3} of the rate of MDD in primary care hover around 10% of patients. Data collected using the Primary Care Evaluation of Mental Disorders indicate that 12% of patients in primary care have MDD.⁴ Recent estimates of the prevalence of chronic pain range from 38%⁵ to 46%⁶ of patients. The variability of epidemiologic information is clear in estimates of the 2 conditions occurring together: estimates range from 15% to 100% for the prevalence of chronic pain among patients who present with depression, and from 1.5% to 100% for the prevalence of depression among patients who present with chronic pain.⁷

Comorbidity among psychiatric illnesses is common and may occur without any definable relationship between the comorbid disorders. However, Dr. Arnow pointed out that as data from Dr. Ohayon demonstrated and as other presenters in the symposium will assert, there is evidence for an important—if still nebulous—relationship between MDD and chronic pain. In a study of primary care patients with depression, Bair et al.⁸ found that a total of 69% reported chronic pain. Of these, 30% reported moderate pain, and 14% reported severe pain.

Chronic pain and depression, even when they occur separately, are known to decrease health-related quality of life and to increase somatic preoccupation and anxiety. The impact of comorbid chronic pain and depression on these variables remains unexplored in the literature. The personal burden of comorbid chronic pain and depression translates into a societal one as anxious, depressed patients living with pain become high utilizers of medical

Review of Comorbid Depression and Painful Physical Symptoms

Bruce A. Arnow, Ph.D., introduced his topic by stating that relatively few studies have examined the extent to which depression and chronic pain are associated in primary care settings, where a majority of patients with these conditions first present for treatment. However, the available literature does

indicate that comorbidity of depression and chronic pain is common in general health care. Most patients with depression are treated not in psychiatric but in primary care settings.¹ Even so, the successful recognition and diagnosis of depression in primary care is complicated by the predomi-

care. Indeed, primary care patients with recognized depression alone have been shown to generate more medical costs than their nondepressed counterparts.⁹⁻¹¹

Comorbid chronic pain may also moderate clinical response to antidepressant treatment. In a primary care study,⁸ 24% of patients who had been assigned to 1 of 3 selective serotonin reuptake inhibitors (SSRIs)—fluoxetine, paroxetine, or sertraline—for depression had a poor depression treatment response. Multivariate odds ratios indicated that severity of pain was a strong predictor of poor depression and health-related quality of life outcomes at 3 months. Clearly, medications that can address both the physical and the emotional symptoms of depression seem desirable for achieving remission. More research is needed.

Conclusion

Dr. Arnow concluded that chronic pain and MDD are highly comorbid in

primary care. The patient burden associated with comorbid depression and chronic pain is greater than that associated with MDD alone. Further, patients with comorbid depression and chronic pain use more medical services (and therefore incur higher medical costs) than patients with depression alone. Some evidence suggests that chronic pain may moderate antidepressant response, but more research is needed.

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Serotonin and Norepinephrine: Navigating the Broad Range of Symptoms

Pedro L. Delgado, M.D. began by pointing out that physical symptoms are common in a variety of psychiatric disorders. Research¹ has shown that, overall, psychiatric patients report physical symptoms and bodily pains with far greater frequency than healthy controls. Depression is a chronic illness, and like other chronic illnesses encountered in primary care, much of its burden is linked to its recurrent nature. Increasing evidence suggests that the prevention of recurrences—and by extension, of the consequences of multiple episodes—may be as important as acute treatment. Dr. Delgado drew an analogy between depression and diabetes, which must be aggressively treated to prevent the development of, for example, ocular or renal disease. Prolonged depression must also be aggressively treated, to avoid consequences that may include brain injury.

The Dangers of Depression: Chronicity, Recurrence, and Brain Injury

Seventy-five to 90% of patients with MDD experience more than 1 episode.² As episodes of depression recur over time, they tend to increase in frequency and become more resistant to treatment. Number of previous depressive episodes may predict the likelihood of rapid relapse following treatment; Keller and Boland³ found that 12 weeks after recovery, patients who had experienced 0 to 3 previous depressive episodes had about a 10% chance of recurrence, compared with an approximately 45% chance of recurrence for patients who had experienced 3 or more previous episodes. After 3 or more depressive episodes, more than 90% of patients are likely to suffer a recurrence of the illness within 5 years. Some data suggest that, via a process called *kindling*—a term bor-

rowed from epilepsy study and applied also in discussion of withdrawal syndromes—the brain “warms” to the depressive state, so that each successive depressive episode is more easily provoked than the last.⁴

Further, the longer an episode of depression lasts, the more likely it is that residual symptoms will persist beyond recovery.⁵ Judd and colleagues showed that among patients whose depressive episode had a duration from onset to recovery of 0 to 6 months, only 6.1% were likely to have residual symptoms, while residual symptoms were likely in 43.9% of patients whose depressive episode lasted for more than 2 years. Thus, longer depressive episodes are associated with a diminished likelihood of full remission, which in turn is predictive of relapse. Increasingly, there is evidence to suggest that prolonged depression and multiple depressive episodes increase the likelihood of damage

to the brain, including loss of hippocampal volume. Dr. Delgado pointed to considerable work⁶⁻⁹ demonstrating that recurrent major depression causes brain injury as reflected in smaller hippocampal volume in patients than in controls, that smaller hippocampal volume may result in cognitive deficits, and that these changes in brain volume may not be completely reversible.

The Serotonin and Norepinephrine Connection

Dr. Delgado explained that serotonin and norepinephrine are part of the body's endogenous analgesic system, modulating regulation of pain as well as emotional states, and are involved in the etiology of some of the physical and emotional symptoms of depression. These neurochemicals appear to have overlapping yet somewhat divergent roles to play in MDD.

In addition to acutely affecting neurochemicals responsible for depressive symptoms, some antidepressants appear to induce neurogenesis—or growth of neurons in the brain—which may exert a defense against brain injury caused by prolonged and recurrent major depression.¹⁰ Such regrowth of cells is currently being investigated as one of the potential mechanisms underlying antidepressant effects and why such effects take several weeks to manifest. A recent rodent study by Santarelli et al.¹¹ showed that the SSRI fluoxetine administered over 10 to 28 days increased the formation of new neurons in the hippocampus in an apparently time-dependent manner. When the researchers compared the effects of the dual-action antidepressant imipramine—which works on both serotonin and norepinephrine—with the effects of fluoxetine in a mouse genetically modified to lack serotonin-1A (5-HT_{1A}) receptors, they found that fluoxetine failed to induce neurogenesis. However, imipramine did induce neurogenesis in these modified mice. Such findings have led experts to speculate that dual-action antidepressants are likely to have advantages over singly selective agents in neuroprotection.

To illustrate the effects of dual-action antidepressants on managing chronic pain—even pain that is not associated with depression—Dr. Delgado referred to studies^{12,13} conducted on individuals with diabetic neuropathy. Kunz et al.¹² found that high doses of the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine were more effective than low doses or placebo at reducing pain in this population. Goldstein and colleagues¹³ reported that the dual action agent duloxetine, too, was more effective than placebo in managing pain and exerted its effect in a dose-dependent manner. Both of these dual-action medications appear to have a unique and powerful effect on pain sensitivity that is attributable to reuptake inhibition of both serotonin and norepinephrine.

Conclusion

Dr. Delgado reiterated that a neurodegenerative-like process may proceed from chronicity and recurrence in MDD. The cyclical, almost self-perpetuating aspects of depression highlight the need for early and aggressive intervention to prevent damaging consequences.

The emotional and physical symptoms of depression appear to be modulated in part by serotonin and norepinephrine. Thus, dual-action antidepressants may have advantages over selective agents by treating a wider array of symptoms, thereby leading to more complete recovery in patients treated with these agents. Dr. Delgado concluded that treatment must be aimed not only at symptoms but also at underlying changes in brain structure and function that may be increasingly hard to reverse over time and may be associated with observed patterns in chronic depression.

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The Course to Remission: Strategies to Improve Outcomes

Vivien K. Burt, M.D., Ph.D., began by reminding her colleagues that while many advances have been made in the treatment of depression, there remains much work to be done in optimizing outcome for patients with this disabling disorder. Current pharmacologic treatments for depression have a relatively slow onset of action, resulting in a $\geq 50\%$ improvement in the patient's

score on the Hamilton Rating Scale for Depression (HAM-D) 4 to 6 weeks after initiation. Dr. Burt warned that treatment does not guarantee remission; about a third of patients with depression remain symptomatic 2 years after the onset of the disorder.^{1,2} Even patients who are deemed clinical responders frequently fall short of complete remission. Those who remain chronically depressed remain impaired. They tend to be high utilizers of health care as well as abusers of alcohol and other substances, which exacts not only a personal but also a societal toll. Patients who respond to treatment but do not achieve remission are also at high risk of experiencing a relapse of depression.² Any residual depressive symptoms are markers of continuing danger for the patient.

Dr. Burt drew attention to a persisting view of depression that focuses on emotional symptoms to the exclusion of other symptom domains. In fact, depressive illness involves not only mood symptoms but also physical symptoms such as chronic pain. However, the physical discomfort of depression often goes unaddressed by treating clinicians. This may be especially true in primary care, where physical illness may be sought as the cause of physical symptoms that are actually associated with depression.

Targeting Serotonin and Norepinephrine in Depression Treatment

Dr. Burt turned to the theory that dual-reuptake inhibitor antidepressants may increase the likelihood of achieving remission by simultaneously treating both the emotional and the physical symptoms of depression. Because there is no single neurotransmitter responsible for the various symptoms of depression, treatment is evolving toward antidepressants with broad spectrums of action, such as agents that increase both serotonin and norepinephrine in the brain. Indeed, specific clinical evidence indicates that modulation of serotonin and norepinephrine together yields better clinical results

than modulation of either neurotransmitter alone. Dr. Burt called attention to a meta-analysis³ of 25 studies that found tricyclic antidepressants (TCAs) to be more effective than SSRIs. This analysis further found TCAs that inhibited reuptake of both serotonin and norepinephrine to be more effective than TCAs that inhibited reuptake of norepinephrine alone. However, TCAs should be avoided by some patients due to side effects such as the risk of QTc prolongation.

A study published by Nelson and colleagues⁴ concluded that an SSRI (fluoxetine) administered in combination with a potent norepinephrine reuptake inhibitor (desipramine) was more effective in providing remission from MDD than either selective agent alone. Approximately 54% of patients who received fluoxetine and desipramine in combination achieved remission of symptoms, compared with about 7% of patients who received only fluoxetine. None of the patients who received only desipramine reached remission, although half of them displayed a partial response. Polypharmacy can be eliminated and similar results can be attained by treating depression with 1 dual-action agent, such as an SNRI.

Data from diverse sources suggest that dual-reuptake inhibitor antidepressants may be more effective than single-acting agents. A meta-analysis by Thase et al.⁵ pooled the results of 8 studies to compare the SNRI venlafaxine with 1 of 3 SSRIs and placebo. Remission rates for all treatment conditions increased over time during the studies; however, remission rates among patients receiving venlafaxine exceeded those in all other treatment groups early in the study. Nonetheless, more than half of the patients had not reached remission by study endpoint, including those who had been treated with venlafaxine.

The superiority of dual-action agents in depression treatment has been supported by numerous data. In a comparison of the SNRI venlafaxine with the dual-action agent mirtaz-

apine,⁶ there were no statistically significant differences between the 2 dual reuptake inhibitors in remission rates. A separate meta-analysis of head-to-head trials of mirtazapine and the SSRIs fluoxetine and paroxetine found that mirtazapine was statistically significantly more effective than the SSRIs at nearly all time points.⁶ A study presented by Thase and colleagues⁷ used data from 6 randomized, double-blind, placebo-controlled clinical trials to compare the SNRI duloxetine, which is not yet approved by the U.S. Food and Drug Administration (FDA), with SSRIs and placebo. Pooled analysis of remission rates favored duloxetine (43.0%) over the SSRIs (38.3%) and placebo (28.4%). Other data^{8,9} too have shown greater improvement in depressive, anxious, and painful physical symptoms with duloxetine than with a comparator SSRI or placebo.

Turning to a discussion of side effects, Dr. Burt mentioned that some dual-action agents do not affect the 2 neurochemicals equally. For example, at lower doses venlafaxine works primarily on serotonin; it requires a dose of at least 150 mg/day to achieve dual-reuptake inhibition. However, at high doses venlafaxine may exert adverse cardiovascular side effects such as hypertension.¹⁰ Mirtazapine, which appears to have efficacy comparable to that of venlafaxine⁶ and a more rapid onset of action than the SSRIs,¹¹ also has adverse effects—in particular, increased appetite, weight gain, and somnolence¹⁰—that may limit its usefulness. The as-yet unapproved dual-action agent duloxetine has the benefit of exerting considerable and relatively balanced dual-reuptake inhibition at low doses but may cause nausea.¹²

Psychotherapy

Dr. Burt reminded her colleagues not to neglect the role of psychotherapy in enhancing the efficacy of pharmacologic treatment. Although more randomized, placebo-controlled, double-blinded, long-term studies are needed,

there are firm data^{13,14} to indicate that pharmacotherapy and psychotherapy in combination or sequentially are more effective than either treatment alone. It is important that clinicians use all the tools at their disposal to achieve optimal outcome—i.e., remission of symptoms—for every patient with depression.

Conclusion

Remission is the goal to which treating clinicians must aspire. Because serotonin and norepinephrine are shared biochemical mediators of depressive and painful or other physical symptoms in MDD, the newer generation dual-action agents are likely to have advantages over singly selective agents in the treatment of depression. A drug's efficacy in treating a broad spectrum of symptoms associated with depression may increase the likelihood of remission. Finally, the role of psychotherapy should not be neglected. There is a great need for more data examin-

ing the role of psychotherapy in enhancing response to medications and promoting remission.

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Looking Beyond the Symptoms of Depression: Considerations for Special Populations

Ruta M. Nonacs, M.D., Ph.D., focused her presentation on populations especially at risk for major depressive disorder: women and the elderly. Although reasons for the preponderance of depression in these populations remain largely unknown, it is theorized that biological and psychosocial factors conspire to increase these populations' vulnerability to the illness.

Women and Depression

Dr. Nonacs introduced the topic by citing epidemiologic and other studies that indicate women are at greater risk than men for MDD¹ and other mood disorders in which depression figures strongly: dysthymia,² seasonal affective disorder,³ and bipolar II disorder.⁴ Additionally, depending upon reproductive status, women are vulnerable to premenstrual dysphoric disorder and postpartum depression. In addition to prevalence, the presentation of major

depressive disorder differs by sex; women are more likely than men to experience anxious mood, physical and/or painful symptoms, and atypical symptoms such as hyperphagia and hypersomnia.⁵ Clinical experience indicates that atypical depression, compared with other depressions, is more chronic and refractory to treatment. Further, depressed men and women tend to present with different comorbidities: alcohol and substance abuse in men versus anxiety and eating disorders in women.⁶ Having outlined these differences between men and women with depression, the presentation turned to the question of whether treatment response differs by sex as well.

Treatment Response: Are Men and Women Different?

Ample evidence exists for sex-specific differences in the efficacy and

tolerability of antidepressant drugs (Table 1).⁷ For instance, the predominance of atypical features in depression among women may have implications for treatment. Atypical depression responds less well to serotonergic agents like SSRIs than does premenstrual dysphoric disorder or postpartum depression^{8–10}; the symptoms of atypical depression instead respond preferentially to monoamine oxidase inhibitors (MAOIs).¹¹ Although MAOIs are quite effective in treating women with major depressive disorder, they are not recommended as first-line treatment due to their side effect profiles and requisite dietary restrictions, and many clinicians prefer to avoid them.

Although both serotonin and norepinephrine play a role in the depressive, anxious, and painful physical symptoms common to MDD, data¹² indicate that TCAs tend to be less effective

Table 1. Antidepressant Response Differs With Sex and Age of Patient

MAOIs > SSRIs in atypical depression
SSRIs effective in premenstrual dysphoric disorder
SSRIs effective in postpartum depression
TCA < SSRIs in premenopausal women with depression
TCA = SSRIs in postmenopausal women with depression
SNRIs effective in men, pre- and postmenopausal women

Abbreviations: MAOI = monoamine oxidase inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

tive in women than they are in men. Dr. Nonacs cited a study by Kornstein and colleagues¹³ that examined differences in response to a TCA (imipramine) and an SSRI (sertraline) between 235 male and 400 female depressed outpatients. Male and female patients were diagnosed with chronic depression or depression superimposed on dysthymia. Nonetheless, gender differences in response to drug treatment were marked, with men responding better to the TCA and women responding better to the SSRI. Compared with men, women taking the TCA experienced a slower response to the drug and more adverse effects, which can lead to discontinuation of treatment. Dr. Nonacs drew attention to the finding that, among the women enrolled by Kornstein et al., age exerted an effect upon likelihood of drug response. Premenopausal women were more likely to respond to the SSRI than to the TCA, whereas postmenopausal women responded to the 2 drugs in similar numbers. This finding raises the important question of hormonal status as a factor in antidepressant response among women. Indeed, estrogen acts as a natural antidepressant¹⁴ and, although data are conflicting, some studies have suggested that estrogen may improve response to SSRIs in postmenopausal women.¹⁵ As yet, however, the possible role of natural estrogen or estrogen replacement therapy in antidepressant response remains unclear.

There have been few studies of gender differences in response to dual-action agents in the treatment of depression. Existing data, however, suggest that there is virtually no gender difference in response to the commonly-used dual-action agent venlafaxine, an SNRI. For instance, a meta-analysis by Entsuah and colleagues⁶ compared remission rates between men and women who received venlafaxine, an SSRI, or placebo. Results indicated that men and women, regardless of age, had comparable rates of both response and remission in each of the treatment conditions; importantly, both men and women were more likely to achieve remission by week 8 if assigned to venlafaxine.

In summary, the presentation showed restated that clinically relevant differences exist between depression in men and in women. Depressed women are more likely than depressed men to present with anxious and/or physical symptoms. Individual nuances such as the female patient's age and the type of depression with which she presents should inform the careful clinician's choice of antidepressant therapy. SSRIs tend to be effective in treating premenstrual dysphoric disorder and postpartum depression but not atypical depression. MAOIs and SNRIs tend to be effective in treating major depressive disorder in premenopausal women; however, MAOIs are not recommended as first-line treatment due to risk of adverse events. TCAs are both less effective and less tolerable in premenopausal women than they are in postmenopausal women and in men. Postmenopausal women tend to respond well also to SSRIs but appear most likely to achieve an optimal response (i.e., remission) with an SNRI.

Depression and the Elderly

The presentation of late-life depression with painful symptoms may be complicated by numerous physical symptoms associated with aging, medical comorbidity, or cognitive dysfunction. To safely and successfully

treat depression in elderly patients, the clinician must be mindful of older persons' heightened risks of adverse events and drug-drug interactions, in part due to their reduced rate of metabolism and drug clearance. Data^{16,17} summarized in the presentation indicated that SSRIs and TCAs tend to be effective in treating late-life depression, although SSRIs may be better tolerated by the elderly. On the basis of available studies,^{6,18,19} however, the presentation suggested that dual-action agents, such as venlafaxine or duloxetine, once available, may be used as first-line treatment for late-life depression with painful symptoms.

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- Drug names:** desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).
- Faculty Disclosure:** In the spirit of full disclosure and in compliance with all Accreditation Council for Continuing Medical Education (ACCME) Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows:
Dr. Schatzberg is a consultant and speaker for Abbott, Aventis, Bristol-Myers Squibb, Corcept, Eli Lilly, Forest, GlaxoSmithKline, Innapharma, Janssen, Merck, Novartis, Organon, Pharmacia, Solvay, Somerset, and Wyeth; has received grants from Bristol-Myers Squibb, Eli Lilly, and Wyeth; and has equity in Corcept, Cypress Biosciences, Elan, Merck, and Pfizer. **Dr. Arnov** is an employee of Stanford University School of Medicine and has received grant/research support from Eli Lilly, Pfizer, and the National Institutes of Health (NIH). **Dr. Burt** is a consultant for and has received grant/research support from Eli Lilly and is on the speakers/advisory boards for Eli Lilly, GlaxoSmithKline, AstraZeneca, and Pfizer. **Dr. Delgado** has received grant/research support from the National Institute of Mental Health (NIMH), Eli Lilly, GlaxoSmithKline, Organon, Wyeth, and Forest and is on the speakers/advisory boards for Eli Lilly, GlaxoSmithKline, Organon, and Wyeth. **Dr. Nonacs** is on the speakers/advisory board for GlaxoSmithKline. **Dr. Ohayon** is a consultant for Organon and Aventis and has received honoraria from Eli Lilly and Pfizer.
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For the CME Posttest for this article, see pages 176–177.



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1. **Physical symptoms are _____ in depression, and their etiology within the disorder is _____ understood.**
 - a. Uncommon, fully
 - b. Common, fully
 - c. Uncommon, little
 - d. Common, little
2. **As many as _____ % of primary care patients with depression have been shown to report chronic pain, many of whom describe it as severe or moderate.**
 - a. 9
 - b. 16
 - c. 69
 - d. 96
3. **Long depressive episodes are associated with all of the following *except*:**
 - a. Persistent residual symptoms
 - b. Diminished likelihood of full remission
 - c. Increased hippocampal volume
 - d. Relapse
4. **Research suggests that remission rates are _____ in patients treated with dual-action agents compared with patients treated with single-action agents.**
 - a. Lower
 - b. Higher
 - c. The same
 - d. Negligible
5. **All of the following are more likely to occur in depressed women than depressed men *except*:**
 - a. Anxious symptoms
 - b. Physical symptoms
 - c. Age and hormonal status affecting response to treatment
 - d. Alcohol abuse

Answer to Pretest: 1. b



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