Depression and Physical Symptoms: The Mind-Body Connection

This ACADEMIC HIGHLIGHTS section of 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 teleconference was chaired by ***Alan F. Schatzberg****, M.D., Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 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 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 received equity from Corcept, Cypress Biosciences, Elan, Merck, and Pfizer.* ***Dr. Arnow*** *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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Treating depression and addressing the many factors that influence whether or not remission is achieved were the focus of a teleconference chaired by Alan F. Schatzberg, M.D. At the heart of each presentation was the connection between the brain and the body. Although somatic symptoms, such as fatigue or changes in sleep or eating patterns, have long been associated with depression, chronic physical pain as described in recent research has not. The roles of specific pathways for serotonin (5-HT) and norepinephrine (NE) in regulating both emotional and painful physical symptoms were described, as well as the effect of recurrent depression on the brain and recent findings regarding the efficacy of the newer dual-action antidepressants. Evidence was also presented regarding both psychosocial and physiological factors that influence treatment response in certain populations.

Does Depression Hurt? Epidemiology of Pain and Depression

Maurice M. Ohayon, M.D., D.Sc., Ph.D., began by stating that physical symptoms are often present in patients with depression, but that the pain-depression interaction is not fully understood. Physical pain, although not stated as a symptom of depression according to the DSM-IV classification of major depressive disorder (MDD), is frequently reported by patients with depression. To illustrate the association between pain and MDD, Dr. Ohayon shared the results of a large cross-sectional study involving telephone interviews using the Sleep-EVAL System. A detailed account of the results was published in the *Archives of General Psychiatry* in 2003.[1]

Method

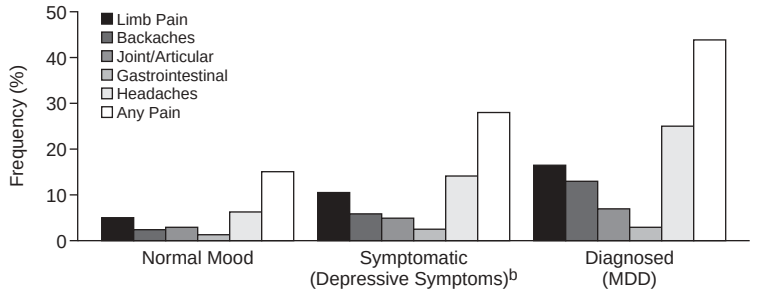
Dr. Ohayon explained that the study sample represented the general populations of 5 European countries (the United Kingdom, Germany, Italy, Portugal, and Spain) and was conducted between 1994 and 1999.[1] A total of 18,980 subjects ranging in age from 15 to 100 years participated in the study.

The Sleep-EVAL System is composed of standard questions and diagnostic pathways covering mental disorders as classified by the DSM-IV, the International Classification of Sleep Disorders, and the International Classification of Diseases. In addition to classifying those who meet criteria for major depression, the system identifies subjects who did not report a psychiatric disorder but who were identified as having depressive symptoms, such as feelings of sadness or depression, or 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 mental disease symptoms.

Chronic painful physical conditions (limb pain, backaches, joint/articular pain, gastrointestinal [GI] pain or diseases, and headaches) were included if the pain led to a medical consultation

or the use of a medication (over-the-counter or prescribed) or if the pain interfered with the normal functioning of the individual. Pain also must have been present for at least 6 months. Figure 1 shows the relationship between these various physical symptoms and depressive pathology described below.

Figure 1. Chronic Painful Physical Symptoms and Depressive Pathology in a Random European General Population (N = 18,980)[a]



[a]Data from Ohayon and Schatzberg.[1] [b]Depressive symptoms were defined as the presence of at least 1 of the following 3 key symptoms: feeling sad or depressed, loss of hope, and loss of interest or lack of pleasure. Abbreviation: MDD = major depressive disorder.

Table 1. Association Between Medical Conditions and Chronic Painful Physical Conditions (CPPC)[a]

	Depressive Symptoms[b] (N = 3140)		Diagnosed MDD (N = 748)[c]	
Description	N	%	N	%
Nonpainful medical disorder	520	16.6	136	18.2
Painful physical condition	576	18.3	216	28.9
Nonpainful medical condition but CPPC	292	9.3	108	14.5
No medical condition/no CPPC	1752	55.8	288	38.4

[a]Data from Ohayon and Schatzberg.[1] [b]Subjects had at least 1 depressive symptom (feeling sad or depressed, loss of hope, and loss of interest or lack of pleasure). [c]Includes 76 subjects with a mood disorder owing to a general medical condition. Abbreviation: MDD = major depressive disorder.

Pain With Depressive Symptoms

Dr. Ohayon distinguished subjects with depressive symptoms from those with a diagnosis of MDD. Symptoms of depression were reported by 16.5% of subjects (95% CI = 16.0% to 17.1%). Of these, 27.6% also reported at least 1 chronic painful physical condition (see Figure 1). For example, 10.5% of subjects who reported at least 1 depressive symptom also mentioned limb pain compared with 4.9% of subjects with no depressive symptoms who mentioned limb pain. Similarly, 4.9% of subjects with depressive symptoms mentioned joint/articular diseases while only 2.9% of subjects without depressive symptoms mentioned joint/articular diseases. A nearly 2-to-1 ratio was seen in subjects with backaches: 5.7% of subjects with depressive symptoms compared with 2.5% of subjects without depressive symptoms. GI disturbances were mentioned by 2.4% of subjects with depressive symptoms compared with 1.3% without, and headaches were mentioned by 14.0% of subjects with depressive symptoms compared with 6.3% without.

Dr. Ohayon pointed out several interesting findings among subjects with depressive symptoms:

- Subjects who reported feeling sad or depressed were more likely to report chronic painful physical conditions than those who reported feeling hopeless or those who mentioned loss of interest or lack of pleasure.
- Subjects who mentioned fatigue or loss of energy tended to report all types of chronic painful conditions.
- Limb pain was more frequently reported by subjects with 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 GI diseases.
- The more depressive symptoms reported, the greater the association with chronic painful physical conditions.

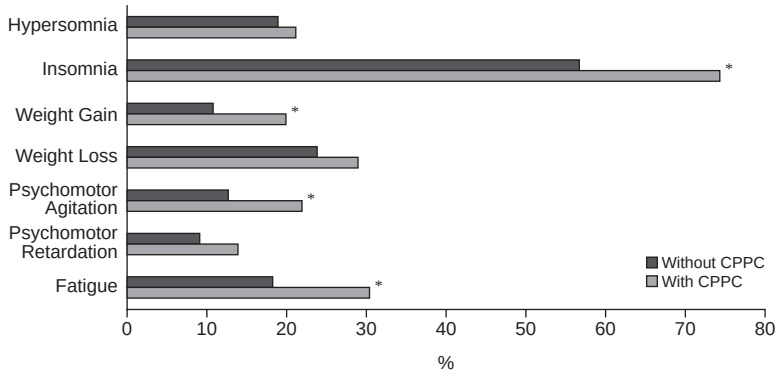
Pain With Major Depressive Disorder

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 (see Figure 1). 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 GI diseases or joint/articular diseases than those with normal mood. Furthermore, most subjects with diagnosed MDD (61.6%) reported having either a chronic painful physical condition or a nonpainful medical condition (Table 1). Dr. Ohayon shared 2 interesting observations about subjects who had a diagnosis of MDD:

- A change in weight or appetite, psychomotor agitation, fatigue or loss of energy, or difficulty concentrating or making decisions was observed more frequently in subjects who reported chronic painful physical conditions than in those without pain.
- Insomnia was mentioned more frequently by subjects who reported chronic painful physical conditions than by those without pain.

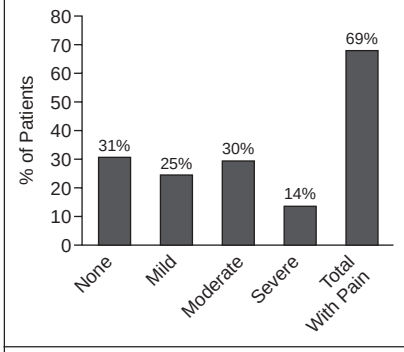
Overall, about 88% of subjects with MDD reported having somatic symptoms, such as sleep or fatigue and appetite disturbances (Figure 2).

Figure 2. Physical Symptoms in Major Depressive Disorder[a]



[a]Data from Ohayon and Schatzberg.[1] Abbreviation: CPPC = chronic painful physical conditions. *p < .05.

Figure 3. Chronic Pain Among Primary Care Patients With Depression[a]



[a]Data from Bair et al.[12] Severity of pain as assessed by the bodily pain subscale of the SF-36 Health Survey.

Conclusions

Dr. Ohayon summarized his presentation by stating that patients seeking consultation for a chronic painful physical condition should be evaluated for depression. Findings from this study and from a similar study in a California population (M.M.O., manuscript submitted) indicate that nearly half of all individuals with MDD have a chronic painful physical condition. The implications of these findings point to a need for further investigation of the relationship between depression and pain.

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Review of Depression With Comorbid Painful Physical Symptoms

Bruce A. Arnow, Ph.D., presented findings regarding the association between chronic pain and MDD in primary care and data on the clinical burden of comorbid depression and chronic pain. He asserted that despite the frequent coexistence of depression and chronic pain, the magnitude and implications of that relationship are still unclear. Since most patients with depression are treated in primary care settings,[1] treating the presentation of somatic complaints in these patients often takes precedence over identifying and treating depression.[2] The prevalence of MDD in primary care has been reported to range between 7% and 12%,[3–6] and the prevalence of chronic pain reported in this setting is much higher, ranging between 38%[7] and 46%.[8]

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.[9] The more severe the pain, the greater the association with depressive symptoms. Similarly, patients who are depressed and have pain complain more about pain and exhibit greater impairment. Few studies of the prevalence of pain in patients presenting with depression and, conversely, the prevalence of depression in patients presenting with pain have been carried out in primary care settings. In the general population, however, Dr. Arnow reiterated Dr. Ohayon's finding[10] that 43.4% of subjects with MDD reported having at least 1 chronic painful physical condition compared with 16.1% of subjects without MDD. Among subjects with chronic pain, 10% had diagnosed MDD compared with only 2.7% who had MDD without pain. A relationship appears to exist, and treating both the depression and the pain presents a challenge to clinicians.

Outcomes of Comorbid Pain and Depression

The concept of clinical comorbidity[11] raises the question of whether the presence of comorbid depression and pain would require a different course of treatment than either malady alone. Dr. Arnow cited findings from a recent study[12] that indicated comorbid chronic pain may moderate antidepressant treatment response. Patients with depression (N = 573) were randomly assigned to treatment with fluoxetine, paroxetine, or sertraline. More than two thirds of patients reported a painful condition at baseline that ranged from mild or moderate to severe on the SF-36 Health Survey bodily pain subscale (Figure 3). Treatment response showed no differences among the 3 selective serotonin reuptake inhibitors (SSRIs). However, after 3 months of treatment, 24% of patients had a poor response. An analysis of the odds ratio for poor response showed 1.5 (95% CI = 0.8 to 3.2) for mild pain, 2.0 (95% CI = 1.1 to 4.0) for moderate pain, and 4.1 (95% CI = 1.9 to 8.8) for severe pain.

Medical Utilization

Another consideration in treating comorbid depression and chronic pain is the cost. Patients with depression in primary care settings are generally high

utilizers of health care services in the form of increased office visits and extra procedures.[13] One group that contributes to high medical utilization is patients who were sexually abused as children,[14] particularly women.[14–17] Several studies[18–20] have found a relationship between childhood sexual or physical abuse and the presence of depression in patients with high levels of medical utilization. As adults, these patients are frequently seen in the emergency department for pain-related complaints.[19,20] Patients who are frequently seen for chronic pain may benefit from a referral to a psychiatrist; as discussed earlier, treating comorbid chronic pain and depression with SSRIs alone may result in a poor response.

Conclusions

Dr. Arnow reiterated that patients who report somatic symptoms often also report symptoms of depression, and vice versa. The question remains whether these 2 conditions together are associated with a different course of illness than either alone and, if so, how that affects the course of treatment and response to treatment.

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Serotonin and Norepinephrine: Navigating the Broad Range of Symptoms

Pedro L. Delgado, M.D., underscored the importance of treating depression to remission and preventing recurrence by stating that unremitted depression and physical pain may result in progressive and cumulative damage to the brain. Hippocampal volume is reduced in MDD, and the change in volume may not be reversible. Since depression and physical pain are believed to be regulated by serotonin (5-HT) and norepinephrine (NE), both neurotransmitters are likely involved in the therapeutic effects of antidepressants as well as in the mechanisms that may impact neurodegeneration and neuroplasticity in the brain. Dual-action antidepressants that incorporate both 5-HT and NE reuptake inhibition have been shown to be effective in not only preventing neurodegeneration, but also treating a wide array of physical symptoms, thereby leading to more complete recovery in patients suffering from the emotional and physical pain of chronic depression.

Effects of Recurrence

Dr. Delgado offered that in depression, it is important to prevent recurrence because the consequences of multiple episodes of depression may lead to physical symptoms such as unexplained body aches and pains, headaches, GI disturbances, fatigue, and loss of energy, and injury to the brain. Because of these untoward possibilities, Dr. Delgado stated that it may be more necessary to prevent recurrence than to treat an acute episode of depression. Further, some evidence[1,2] suggests that each new episode of depression tends to occur sooner and have a more severe, treatment-resistant course than the preceding episode. Dr. Delgado identified persistent symptoms,[1,3] length of illness,[3,4] and multiple episodes[5,6] as predictors of recurrence. Recurrent depressive episodes appear to increase the likelihood of neurochemical changes in the brain, including loss of hippocampal volume in patients with depression who have had multiple episodes.[7]

Neurobiology

Dr. Delgado focused on the specific pathways for 5-HT and NE in the brain and spinal cord that appear to be involved in regulating the emotional and painful physical symptoms of depression. Serotonergic and noradrenergic neurotransmitters from the brain stem ascend into the brain and mediate numerous emotional and physical func-

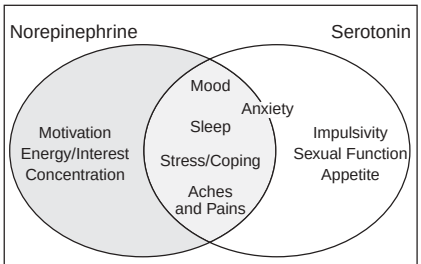
tions and descend down the spinal cord where they suppress painful input from the body. These neurotransmitters are the key modulatory transmitters and seem to be part of the body's endogenous analgesic system. Thus, antidepressants may exert their therapeutic action not only in depression but also in some pain conditions via the 5-HT system.[8]

Serotonergic and noradrenergic pathways overlap, and many human functions impacted by depression seem to be affected by both pathways. However, in certain areas, these transmitter systems have a slightly divergent set of effects (Figure 4).[9] The noradrenergic system may be involved in motivation, while the serotonergic system may be more involved in aspects of behavior.

Along with the acute effects of antidepressants on serotonergic and noradrenergic function, Dr. Delgado pointed out that some antidepressants can actually induce neurogenesis in the brain. Since neurons in the hippocampus are diminished in depressed patients, neurogenesis may explain why it takes several weeks for antidepressant action to emerge. Neurogenesis effects shown in laboratory animals suggest that 5-HT and NE pathways may act independently of each other to mediate antidepressant response. Dr. Delgado referred to a recent study by Santarelli et al.[10] in which the SSRI fluoxetine did not induce neurogenesis in genetically modified mice lacking 5-HT_{1A} receptors. The dual-action antidepressant imipramine was, however, capable of inducing neurogenesis in these mice. Dr. Delgado speculated that imipramine was able to induce neurogenesis in mice without 5-HT_{1A} receptors because it affects neurogenesis via the norepinephrine pathway as well as the serotonin pathway.

Data from neurotransmitter depletion studies[11–17] further support the view that 5-HT and NE pathways behave independently. These studies showed that the therapeutic effects of SSRIs in patients whose depression had responded to treatment could be transiently reversed by rapid depletion of 5-HT but not by depletion of NE. Conversely, the therapeutic effects of an NE reuptake inhibitor could be transiently reversed by depletion of NE but not by depletion of 5-HT.

Figure 4. Model Neurotransmitter Specificity[a]



[a]Based on Healy and McMonagle.[9]

Managing Pain With Antidepressants

Both the mood effects shown in depressed patients and neurogenesis effects shown in laboratory animals suggest that 5-HT and NE pathways may act independently of each other but potentially converge on common mechanisms. A study in animals,[18] for example, has shown that the SSRI paroxetine combined with the selective NE thionisoxetine had a much more potent effect than either drug alone on reducing pain. Such findings have led experts to speculate that dual-action antidepressants are likely to have advantages over singly selective agents in neuroprotection. The clinical evidence suggests that dual action not only has a more robust antidepressant effect that more frequently leads to remission of depressive symptoms compared with singly selective agents, but also has advantages for analgesia. To illustrate the effects of dual-action antidepressants on managing pain, Dr. Delgado referred to 2 studies[19,20] of patients with diabetic neuropathy. High doses of venlafaxine were more effective than low doses or placebo at reducing pain in this population,[19] and duloxetine decreased pain sensitivity in patients with diabetic neuropathy in a dose-dependent fashion as well.[20] Findings from both of these studies suggest that venlafaxine and duloxetine share a proclivity for reducing pain and confirm the animal data that medications with dual action have a unique and powerful effect on pain sensitivity.

Summary

Dr. Delgado emphasized that a growing body of evidence suggests that antidepressants that inhibit the reuptake of both 5-HT and NE have the best chance to reduce most symptoms of depression by targeting the multiple pathways that mediate them in the brain and spinal cord. These neurotransmitters appear to be involved both in the therapeutic effects of antidepressants on somatic and psychiatric symptoms of depression and as mechanisms that potentially impact neurodegeneration and neuroplasticity in the brain.

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Plotting the Course to Remission: Balanced Strategies to Improve Outcomes

Vivien K. Burt, M.D., Ph.D., acknowledged that although advancements in the treatment of depression have been made, work remains to be done to adequately treat this disabling disorder. She reviewed dual-reuptake inhibition antidepressants and psychotherapy as treatment strategies that show promise in achieving remission in depression.

Depression: Current Outcomes

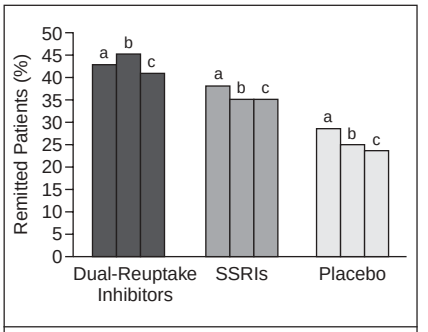
Dr. Burt stated that with current pharmacologic treatments, depressive patients tend to achieve partial symptom relief between 2 and 4 weeks after the administration of standard therapeutic doses. When treatment is successful, full response, as measured in research terms by 50% or more improvement in scores on the Hamilton Rating Scale for Depression (HAM-D), is typically reached after 4 to 6 weeks of treatment. Furthermore, almost a quarter[1] to a third[2] of treated patients with depression remain symptomatic 2 years after the onset of their disorder. For those patients who respond but do not achieve remission (defined in research as ≤ 7 score on the HAM-D), the risk of experiencing a relapse of depression ranges from 50% to 80%.[2] The failure of treatment modalities to effectively treat depression may lead to patients remaining chronically depressed, which exacts a personal and national toll for economic burden and poor productivity.

Dr. Burt offered that despite its elusiveness in the treatment of depression, remission is the goal to which clinicians need to aspire. She suggested that depression treatments thus far have fallen short of eliciting remission because they target the emotional, or mood-related, symptoms of depression. Pain and anxiety have not been addressed by treatments, despite evidence that these symptom domains are part of depression.

Targeting Serotonin and Norepinephrine for Remission

Because some depressive symptoms are mediated by one neurotransmitter more than another, dual-action inhibitor antidepressants that modulate 5-HT and NE may treat a broad range of symptoms at once, including emotional, physical, and anxious symptoms. Dr. Burt suggested that targeting all 3 depressive symptom domains may lead to remission of depression because patients experience more symptom relief.

Figure 5. Pooled Analysis Depression Remission Rates of Dual-Reuptake Inhibitors, SSRIs, and Placebo



[a]Data from Thase et al.[8] [b]Data from Thase et al.[9] [c]Data from Nemeroff et al.[10] $p < .001$ for all comparisons. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Remission. Dr. Burt offered that data[3–7] from diverse sources, including meta-analytic studies as well as individual clinical trials, suggest that dual-action inhibitor antidepressants may be more effective depression treatments than single-action inhibitors. A randomized, double-blind, controlled study by Nelson and colleagues[7] recently tested this hypothesis. Inpatients who had nonpsychotic unipolar major depression and HAM-D scores of at least 18 were randomly assigned to the dual-action agent desipramine at therapeutic doses, single-action fluoxetine at 20 mg/day, or a combination of both agents. After 6 weeks, the desipramine-fluoxetine combination was significantly more likely to result in remission, as assessed by the Montgomery-Asberg Depression Rating Scale (MADRS), than either agent alone.

Dr. Burt also presented the findings of several pooled analyses[8–10] in which the remission rates of dual-reuptake agents were compared with those of SSRIs and placebo in randomized, double-blind trials. With remission defined as a score ≤ 7 on the HAM-D-17, remission rates were similar across studies within each treatment group (Figure 5). Dr. Burt noted that in the meta-analysis of duloxetine,[8] in a subset of patients with a baseline

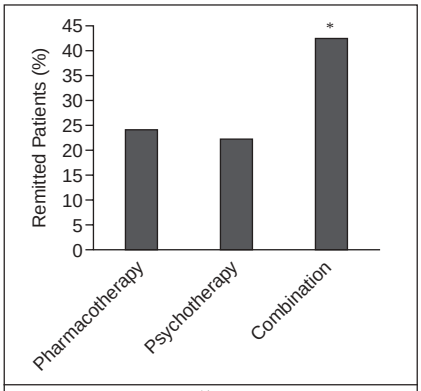
HAM-D-17 score ≥ 19, remission rates for duloxetine-treated patients were statistically significantly greater than those for SSRI- and placebo-treated patients. She further mentioned that in the Thase et al.[9] meta-analysis of venlafaxine, patients treated with venlafaxine actually reached remission 1 to 2 weeks earlier than patients treated with SSRIs or placebo. Dr. Burt noted that despite these higher rates of remission, over half of patients treated with dual-reuptake agents were not in remission at study endpoint across studies.

Broad Symptom Relief. To support the suggestion that dual-action antidepressants relieve the broad symptom range of depression, Dr. Burt cited a 9-week, randomized, double-blind, placebo-controlled trial[11] that assessed the efficacy of duloxetine in depression and its associated physical symptoms. In addition to being significantly more effective than placebo for emotional symptoms ($p < .001$), duloxetine, 60 mg/day, was significantly superior to placebo in reducing overall pain throughout most of the study ($p < .05$).

Next, she reviewed the effect of duloxetine on the anxiety symptoms associated with depression as assessed in a meta-analysis by Dunner et al.[12] Anxiety severity was assessed with items 10–13, 15, and 17 on the HAM-D-17 in 4 studies as well as the Hamilton Rating Scale for Anxiety (HAM-A) in 2 studies. Duloxetine was superior to SSRIs and placebo in treating anxiety symptoms.

Side Effects. After concluding her discussion of the efficacy of dual-action antidepressants, Dr. Burt briefly reviewed the safety and tolerability of these agents. The newer dual-action agents have, in general, more benign side effects than the tricyclic antidepressants. However, venlafaxine may exert adverse cardiovascular side effects, in particular hypertension, at higher doses, which are required to achieve dual-reuptake inhibition. Mirtazapine, a dual-action agent with remission rates similar to venlafaxine,[13] may cause increased appetite, weight gain, and somnolence, while the most common side effect of duloxetine appears to be nausea.

Figure 6. Remission Rates of Depressed Patients Treated With Pharmacotherapy, Psychotherapy, or Both[a]



[a]Data from Keller et al.[14]
*$p < .001$ vs. monotherapies.

The Role of Psychotherapy to Enhance Treatment Efficacy

Dr. Burt emphasized that psychotherapy should not be neglected in striving for remission of depression. A number of promising studies have been published,[14,15] but more randomized, placebo-controlled, blinded, long-term studies of the role of psychotherapy in enhancing response and improving remission rates are needed.[16]

Keller and others[14] randomly assigned 681 treatment-refractory, chronically depressed outpatients to antidepressant pharmacotherapy, psychotherapy (16 to 20 sessions), or both for 12 weeks. Approximately one half of patients who completed the study responded in each monotherapy group, while over three quarters of patients responded in the combination treatment group ($p < .001$). Remission rates were significantly higher for the combination group ($p < .001$) (Figure 6).

Frank and colleagues[15] randomly assigned women with recurrent unipolar major depression to receive either combination psychotherapy and pharmacotherapy at the outset of treatment or to receive psychotherapy initially and have pharmacotherapy added if remission did not occur. In this study, which was actually a distillation of 2 studies comprising a total sample size of 339, the remission rate was 66% for outset combination therapy versus 79% for those who received psychotherapy and then had pharmacotherapy added. This significant ($p = .02$) difference suggests that offering antidepressant therapy to patients with chronic depression who do not remit with psychotherapy alone may be a highly effective treatment strategy. Despite the improved recurrence rate, however, this strategy has the drawback of having a slower onset of action, at least for some patients.

Summary

Dr. Burt concluded by saying that remission, the goal of depression treatment, is an unmet need for depressed patients. The newer generation dual-action antidepressants appear to have advantages over SSRIs for the remission of depression, and balanced and potent dual-reuptake inhibition may offer improved efficacy with fewer side effects. Psychotherapy for depression treatment should be considered for its ability to enhance response and promote remission.

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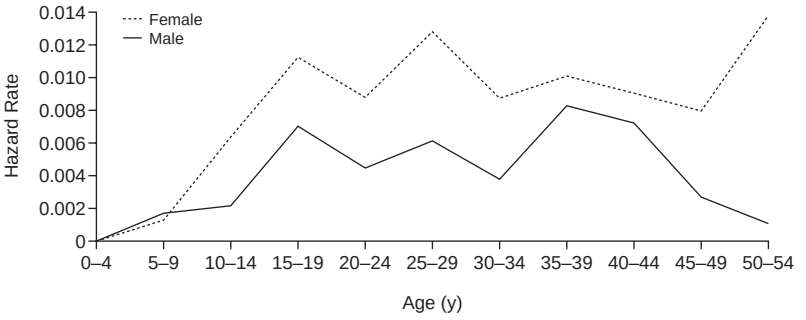
Looking Beyond the Symptoms of Depression: Considerations for Special Populations

In her presentation, Ruta M. Nonacs, M.D., Ph.D., emphasized that not all treatments for major depression will work for everyone. Two populations at high risk for poor response to antidepressant treatments are women and the elderly. Women respond to treatment differently than men, and their symptoms and side effect profiles are often dissimilar. Elderly patients may not respond well because of somatic symptoms, cognitive dysfunction, medical comorbidity, reduced metabolism and clearance, and drug-drug interactions. Many factors, both psychosocial and physiological, affect care considerations in both of these populations. Recognizing that these groups have differing responses to treatment than others and that transitions over the life span may affect treatment needs and response can help psychiatrists to better optimize treatment in individual patients.

Figure 7. Affective Disorders in Women: Risk for Depression by Age and Sex[a]



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

Women and Depression

Dr. Nonacs, citing data from the U.S. National Comorbidity Survey,[1] stated that the risk of depression among women is consistently greater than for men across the life span (Figure 7).[2] More so in women than in men, depression tends to be precipitated by stressful life events and seasonal changes. Reproductive events also appear to play an important role; women are more vulnerable to depression during the postpartum and perimenopausal periods and may also have cyclical mood changes, such as premenstrual syndrome or premenstrual dysphoric disorder (PMDD). Further, the presentation of MDD 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.[3,4] Women tend to have longer episodes of depression, and these tend to be more chronic and recurrent than episodes experienced by men.[5] Women are more likely to have an anxiety and/or eating disorder comorbid with depression, whereas men are more likely to abuse alcohol or other substances and are at a greater risk for suicide. Given that depression has a different course in women than in men, perhaps it follows that women respond differently than men to treatment.

Treatment Response in Women

Dr. Nonacs presented evidence from several studies on sex-specific differences in the efficacy and tolerability of the different classes of antidepressants. While women with PMDD and postpartum depression respond well to SSRIs,[6,7] the symptoms of atypical depression instead respond preferentially to monoamine oxidase inhibitors (MAOIs).[6–8] Although MAOIs are effective in treating women with MDD,[9] they are not recommended as first-line treatment because of their side effect profiles and requisite dietary restrictions.

TCAs tend to be less effective in women than in men.[5,10,11] A post hoc analysis of the gender differences in response to a TCA (imipramine) and an SSRI (sertraline) by Kornstein and colleagues[5] supports this claim. This double-blind randomized, controlled trial compared the effects of these agents among 235 men and 400 women with DSM-III-R chronic major depression or major depression superimposed on dysthymia. 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 and more adverse effects from the drug.

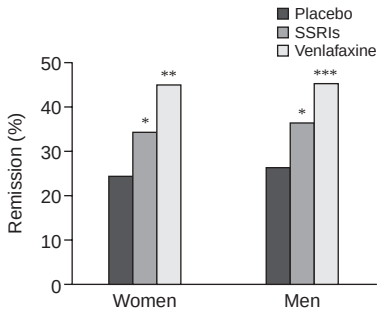
Dr. Nonacs noted that among the women in this study,[5] age exerted an

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 antidepressant[12] and, although data are conflicting, some studies have suggested that estrogen may improve response to SSRIs in postmenopausal women.[13] As yet, however, the possible role of natural estrogen or estrogen replacement therapy in antidepressant response remains unclear.

Few studies of gender differences in response to newer dual-action agents in the treatment of depression have been conducted. Entsuah and colleagues[14] conducted a meta-analysis of remission rates between men and women who received venlafaxine (a serotonin-norepinephrine reuptake inhibitor [SNRI]), an SSRI, or placebo. Regardless of age, men and women had comparable rates of response and remission in each of the treatment conditions, and both men and women receiving venlafaxine achieved higher rates of remission with venlafaxine than with an SSRI or placebo (Figure 8).

To summarize, Dr. Nonacs restated that clinically relevant differences exist between men and women with MDD. Women are more likely than men to present with anxiety or somatic symptoms. Biological and psychosocial changes during the course of a woman's life are factors to consider before making treatment decisions. Further, women and men respond differently to the same treatment. SSRIs appear to be effective in treating PMDD and postpartum depression but not atypical depression. MAOIs and SNRIs appear to be effective in treating MDD in premenopausal women. TCAs are both less effective and less tolerable in premenopausal women than they are in postmenopausal women and men. In addition, postmenopausal women appear most likely to achieve remission with an SNRI.

Figure 8. Gender Differences in Remission Rates After 8 Weeks of Treatment



Reprinted with permission from Entsuah et al.[14]
*p < .05 vs. placebo. **Venlafaxine vs. placebo, p ≤ .001; vs. SSRIs, p ≤ .001. ***Venlafaxine vs. placebo, p ≤ .001; vs. SSRIs, p ≤ .04.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Elderly Patients With Depression

Dr. Nonacs next turned her attention to another special population at risk for depression: the elderly. The prevalence of depression in the elderly is presumed to be quite high, and data from one study indicated that as many as 10% of people over the age of 60 years warrant some type of intervention for depression.[15] Consistent prevalence estimates, however, are difficult to quantify. Differences in study design and methodology in studying depression among elderly in the community at large, patients receiving acute care, and residents of long-term care facilities have rendered prevalence estimates that range from 51% to 94%.[16] In addition, the presentation of late-life depression may be complicated by numerous physical symptoms associated with aging, medical comorbidity, or cognitive dysfunction. Dr. Nonacs stated that psychiatrists must be mindful of the heightened risks of adverse events and drug-drug interactions, in part due to reduced metabolism rates and drug clearance, when prescribing treatment for elderly patients with depression.

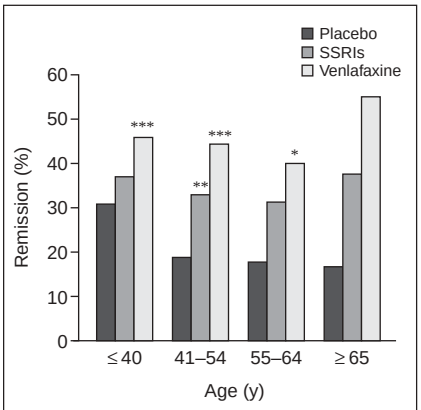
Treatment Response in the Elderly

Dr. Nonacs presented evidence from several studies on the efficacy and tolerability of the different classes of antidepressants in the elderly. Beginning with SSRIs and TCAs, Dr. Nonacs cited a comparative meta-analysis[17] of the SSRI paroxetine against active TCA controls amitriptyline, clomipramine, and doxepin and the tetracyclic mianserin. Paroxetine was found to be as effective as the comparison agents, and patients receiving paroxetine had less frequent and less severe anticholinergic effects and sedation. Paroxetine was effective against anxiety, and some data indicated reduced cardiotoxicity than with the other agents.

Another meta-analysis[15] allowed that TCAs, SSRIs, and MAOIs are effective for treating depression in the elderly. However, concern about adverse events and drug-drug interaction is highlighted by a recent finding[18] that SSRIs increase the risk of upper GI tract bleeding, especially when used concurrently with nonsteroidal anti-inflammatory drugs or low-dose aspirin. The risk of upper GI bleeding was not attributed to non-SSRI antidepressants.

Lastly, Dr. Nonacs introduced comparisons of antidepressants from different classes to dual-action agents, which perhaps show the most promise for treating depression in an elderly population. A comparison[19] of the dual-action agent mirtazapine to a TCA (amitriptyline) and an SSRI (paroxetine) in 115 elderly patients with DSM-III major depressive episode yielded comparable reductions in HAM-D scores and MADRS scores during a 6-week investigation. However, greater reductions in HAM-D scores favoring mirtazapine were seen in a double-blind comparison[20] with paroxetine. In addition, mirtazapine had a positive impact on multiple symptoms including sleep, appetite, and anxiety. Referring again to the meta-analysis by Entsuah et al.,[14] Dr. Nonacs said that patients receiving the dual-action agent venlafaxine exhibited a more rapid onset of action and had a greater likelihood of remission than patients receiving SSRIs across age groups (Figure 9). Perhaps because of

Figure 9. Remission Rates After 8 Weeks of Treatment, by Age[a]



[a]Reprinted with permission from Entsuah et al.[14] Remission across all age groups for venlafaxine vs. SSRIs, $p < .05$. *$p \leq .01$ vs. placebo. **$p \leq .001$ vs. placebo. ***Venlafaxine vs. placebo, $p \leq .001$; vs. SSRIs, $p \leq .01$. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

the small number of patients in the elderly group, differences between the active treatment groups that were similar in timing and magnitude to those seen in the other age groups failed to reach statistical significance.

Although duloxetine has not been approved by the U.S. Food and Drug Administration, data[21] have found duloxetine (60 mg/q.d.) to be effective in both response and remission in patients older than 55 years as well as effective in reducing painful physical symptoms that accompany depression. Further study of duloxetine in this population is warranted.

The ultimate goal in treating depression, Dr. Nonacs concluded, is to achieve complete remission of depressive symptoms. Elderly patients respond differently to antidepressant treatment than younger patients for a variety of reasons, including the numerous physical symptoms often associated with aging, medical comorbidity, or cognitive dysfunction. Elderly patients are at greater risk for adverse events and drug-drug interactions, in part due to reduced metabolism rates and drug clearance. Although SSRIs and TCAs have proven effective in this population, SSRIs appear to be better tolerated. On the basis of available data, however, Dr. Nonacs suggested that dual-action agents, such as venlafaxine or duloxetine (once available) be used as first-line treatment for late-life depression.

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Drug names: *amitriptyline (Elavil and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan, Zonalon, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).*

Disclosure of off-label usage: *The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented that is outside U.S. Food and Drug Administration (FDA)–approved labeling. Duloxetine is not approved by the FDA for use in the United States. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.*

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