The Brain-Body Connection and the Relationship Between Depression and Pain CME

Author: J. Sloan Manning, MD

Complete author affiliations and disclosures are at the end of this activity.

Release Date: December 17, 2002; **Valid for credit through December 17, 2003**

Target Audience

This activity is intended for psychiatrists, primary care physicians, mental health professionals, and healthcare professionals.

Goal

The goal of this activity is to provide clinicians with an understanding of the neurobiological foundation and approach to the treatment of depression and pain.

Learning Objectives

Upon completion of this self-study activity, participants will be able to:

1. Review strategies for evaluating depression in the context of pain.
2. Recognize the physical symptoms of depression.
3. Delineate the impact of the serotonin and norepinephrine systems in depression and pain.

Credits Available

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Pharmacists - up to 0.5 contact hour(s) (0.05 CEUs);
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This activity is supported by an educational grant from Eli Lilly.

Contents of This CME Activity

The Brain-Body Connection and the Relationship Between Depression and Pain

Background*

Most primary care clinicians have an intuitive sense that depression and somatization are often comorbid states. Generalists have historically resisted temptations to view individuals in dualistic terms and understand that the brain is connected to the rest of the body, either "hard-wired"

through the central nervous system or "soft-wired" through neurohormonal pathways. In many cases, illness cannot be easily dissected into mental vs somatic categories. This instinctive wisdom is continually borne out in scientific investigation and has important implications for the strategies we use to assess, diagnose, and treat patients.

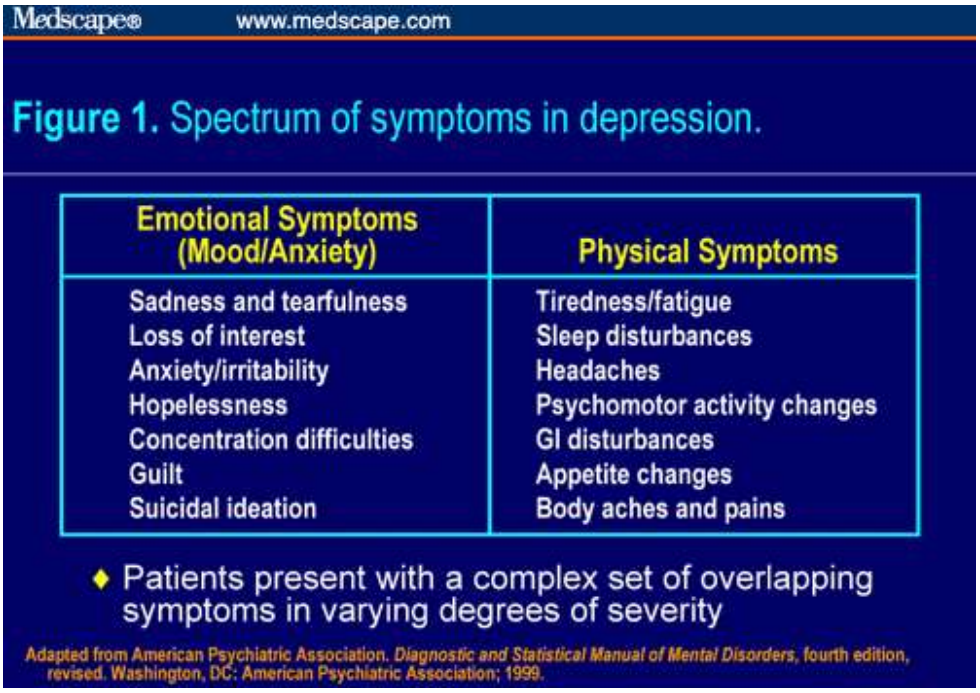
Major depression is highly prevalent and a major cause of disability. The World Health Organization expects that by 2020, depression will rank second only to ischemic heart disease in terms of disability. Depression also influences the morbidity and mortality of a number of somatic illnesses. The list grows steadily but is headlined by research documenting significantly higher mortality in depressed patients post acute myocardial infarction. Depression and chronic pain share synaptic monoamine underpinnings. Recent research suggests that addressing this connection is important in achieving robust responses to treatment. In particular, antidepressants that affect more than one monoamine system (eg, dual reuptake inhibitors of serotonin and norepinephrine) seem to possess a greater ability to both affect chronic pain states and demonstrate higher rates of symptom remission in randomized studies of major depression.

This article will provide documentation of the shared clinical domains of mood and pain. It will discuss current conceptualizations of central nervous system pathophysiology in relationship and review recent clinical investigations in the area.

*This summary mentions off-label uses for some medications. These may describe clinical uses for medications that have not been approved by the US Food and Drug Administration.

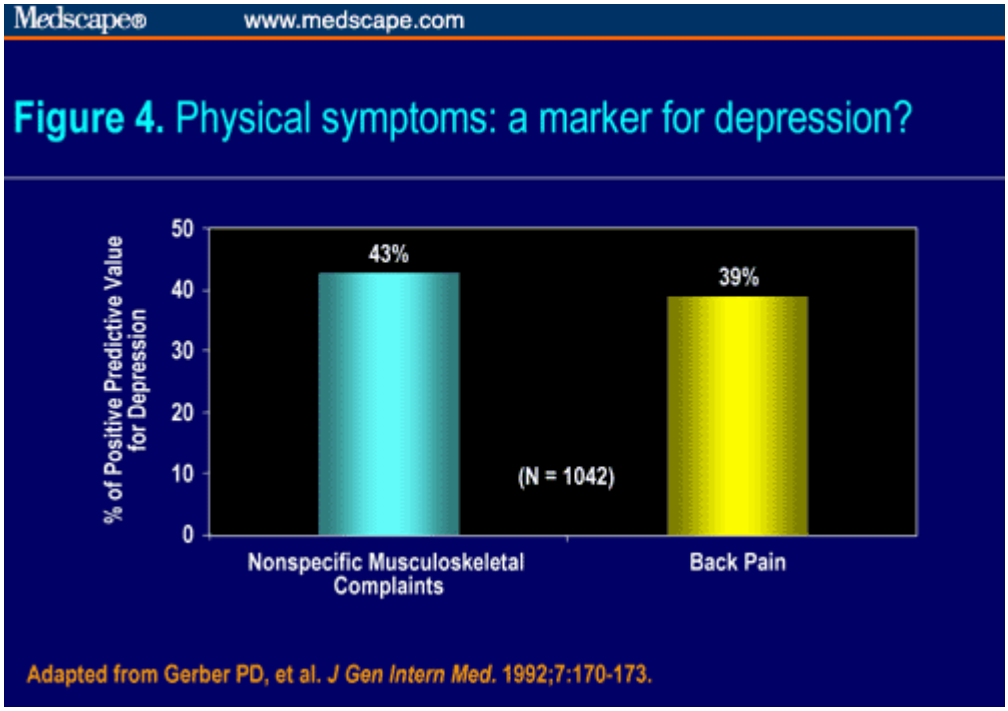
Emotional and Somatic Presentations of Depression

Although the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) emphasizes emotional symptoms such as sadness and anhedonia, the criteria for major depression include physical symptoms (fatigue, sleep aberrations, appetite changes). It is important to note that the physical symptoms associated with depression extend to other areas beyond the DSM-IV, notably pain and gastrointestinal complaints. One study of irritable bowel syndrome showed markedly higher rates in depressed patients vs controls (Figure 1).[1]



The pain associated with depression is commonly represented by headache, back pain, or nonspecific musculoskeletal complaints. In fact, in one study of 1146 patients with major depression, physical symptoms were the chief or exclusive complaint for 69% of those identified.[2] Anxiety is often comorbid with depressed mood and, in terms of patients affected, is roughly as common as physical symptoms. There is some gender variability in the spectrum of these complaints.[3,4]

Physical symptoms may have predictive value in depression screening, with one investigation finding back pain and nonspecific musculoskeletal pain significantly predictive (43% and 39%, respectively). Both patients and physicians may so emphasize these physical presentations that the diagnosis of depression can be delayed or missed altogether. Kirmayer and colleagues[5] documented that highly somatic presentations of depression were missed more often than those with significant psychosocial contexts (Figure 4).



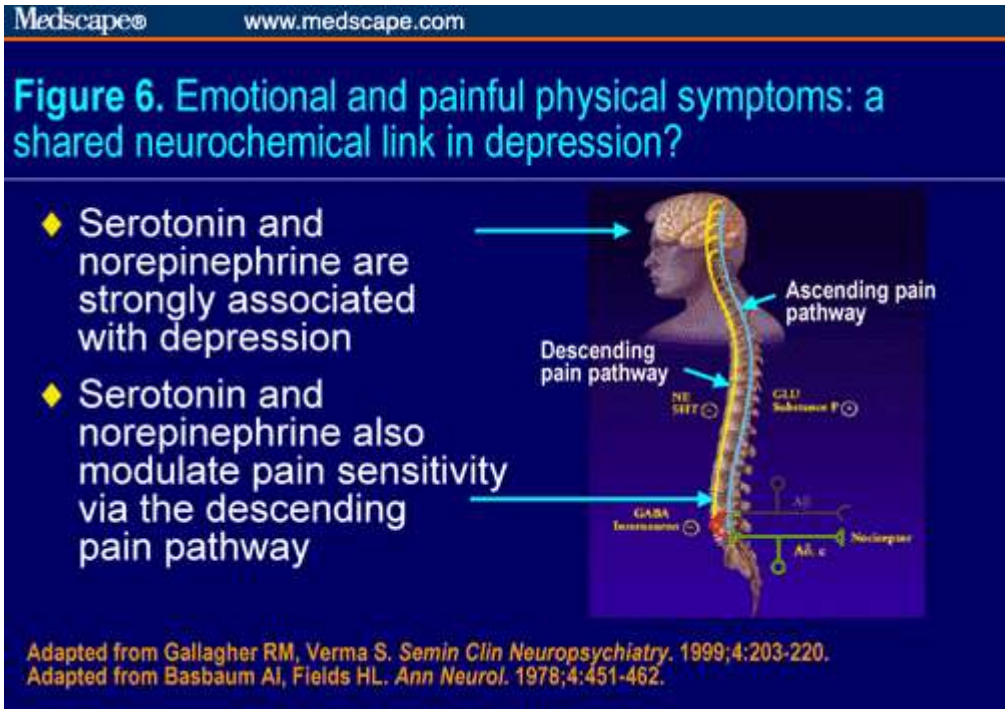
This may be due to interference from symptoms attributable to previously diagnosed comorbid illness (eg, diabetes, asthma, arthritis) or to new somatic diagnoses created to account for individual presentations of depression. Regardless, it is important to realize that depression may "amplify" the intensity or distress attributable to an existing complaint or serve as the basis for any one of a number of pseudonymous diagnoses -- aliases for depression that may be specialty specific. Therefore, any patient with symptoms out of proportion to objective findings, chronic or "functional" pain, irritable bowel syndrome, disequilibrium, "hypoglycemic" episodes of undetermined cause, "hormone imbalances," fibromyalgia, and the like should be considered fertile ground for the diagnosis of depression.

The Mind-Body Connection

Although the mechanisms through which the mind and body interact are not completely understood, there is growing evidence of the connection and its importance in clinical practice, especially in patients who have depression comorbid with somatic illness. Outcomes research documents a growing number of these interactions. Depressed diabetics tend to have poorer

blood glucose control.[6] Stroke victims suffering from depression (a very common situation) do more poorly in rehabilitation programs.[7] Depression after an acute myocardial infarction is associated with higher mortalities independent of the severity of cardiovascular function.[8] Depression appears to reduce the life expectancy of older adults.[9] Hospitalized patients with comorbid depression are less likely to survive life-threatening illnesses.[10]

The relationship between depression and pain may focus on shared monoamine synaptic pathways in the central nervous system. Both serotonin and norepinephrine appear to be important in both (Figure 6).[11]



Other neurotransmitters may be involved. Descending modulatory pathways mediated by serotonin, norepinephrine, and gamma amino butyric acid may be used to limit the intensity of pain signals arriving in the brain from the body via spinal pathways. Disruptions in this pathway or in the limbic system (controlling mood) may have the ability to influence or even disrupt the other. Although speculative, this may account for the numbers of patients developing depression in response to chronic pain or for depression acting as a "soil" for the development of chronic pain states in patients with known vulnerability to mood disorders.

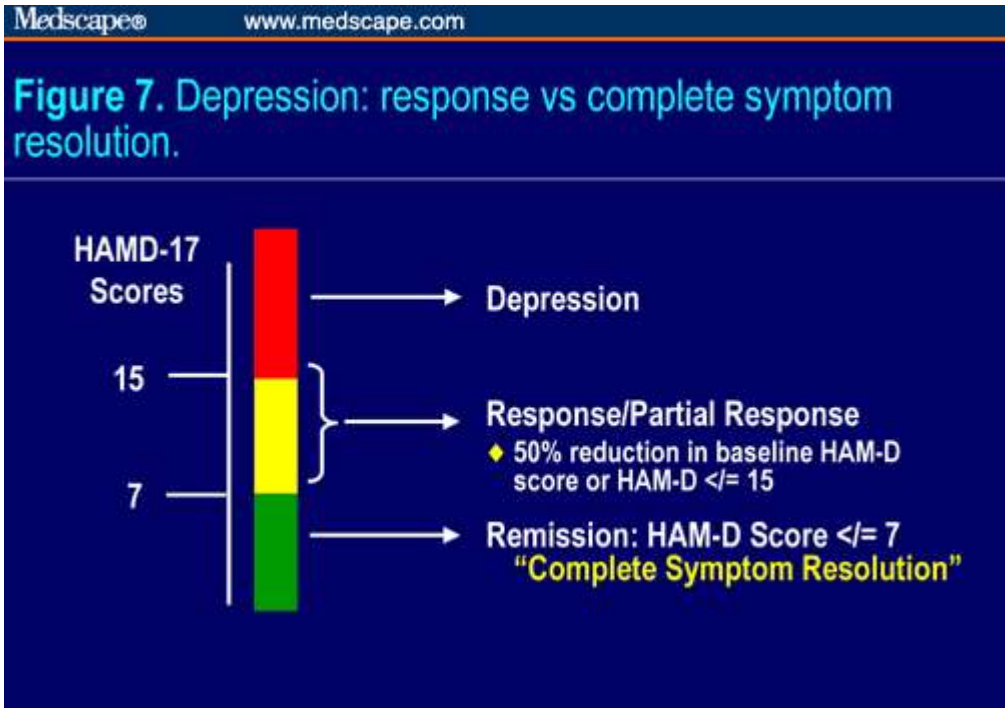
Other theories of interaction have also been suggested. One such theory emphasizes dysregulations in the hypothalamic-pituitary-adrenal (HPA) axis and reductions in brain-derived neurotrophic factor (BDNF). Changes in BDNF in depressed patients are the subject of current research. BDNF levels in the hippocampus are reduced by increased levels of endogenous glucocorticoids often seen in depressed patients. BDNF appears to retard neuronal atrophy under stress, and a loss of such protection may inhibit accommodation and response to stress that involves both neuron preservation and neurogenesis. Antidepressants may increase levels of BDNF as a key part of their mechanism of action.

Treatment Remission and the Role of Comorbid Physical Complaints

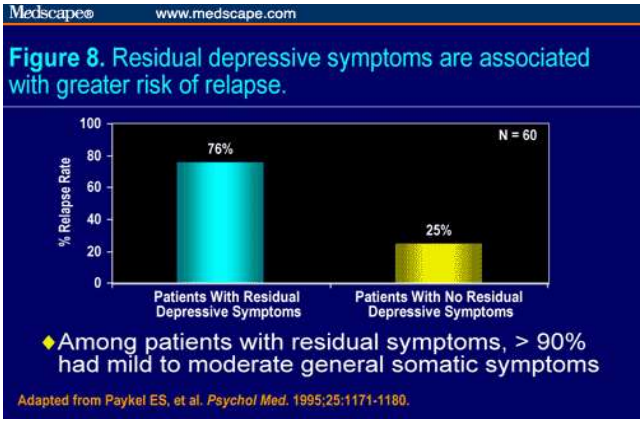
The goal of depression treatment is robust, sustained response -- complete and sustained remission of depression symptoms. Ideally, such remissions will lead to recovery of normal

functioning or, in the case of early-onset depressions, the acquisition of new life skills and mastery. Remission may be measured by the standard depression scales used to measure illness severity. Hamilton Depression Scale ratings of less than 8 are used to define remission in randomized, controlled trials. However, such scales may be cumbersome to use in day-to-day practice. Clinicians should be vigilant to inquire about the full range of emotional and physical symptoms of depression when following their patients. Anything more than trivial symptoms should prompt the consideration of further clinical intervention.

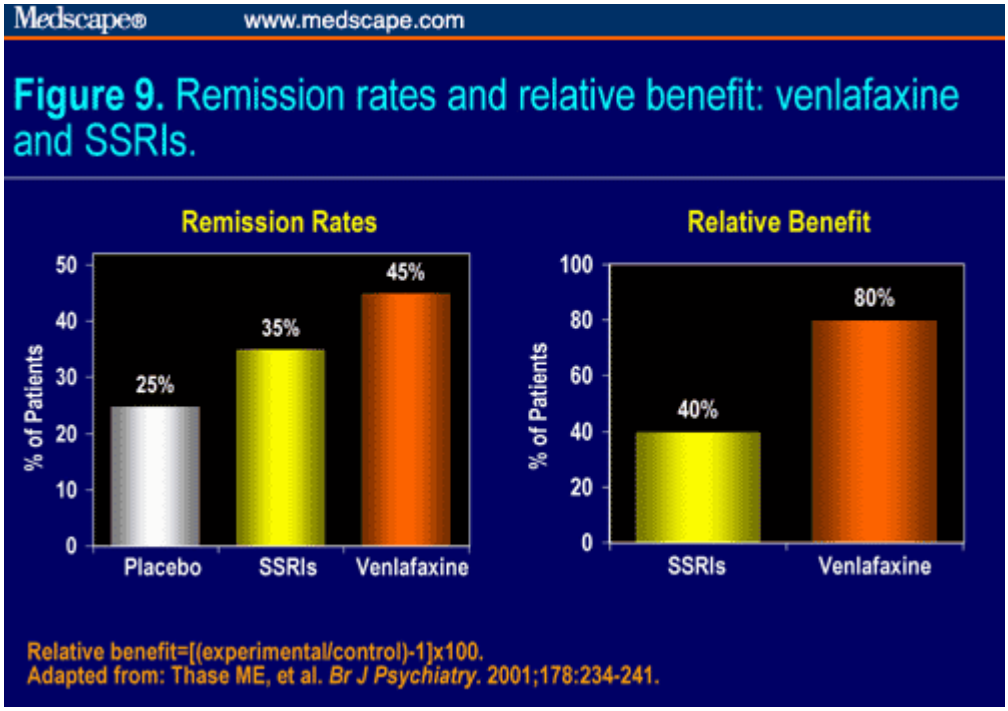
Other features of a less-than-complete response to antidepressant therapy are persistently high utilization of telephone triage, walk-in appointments, or emergency rooms as well as work absences and interpersonal difficulties. Failure to achieve this robust level of symptom remission is associated with disability, failure to achieve normal social functioning,[12] and risk of relapse (Figure 7).[13]



Additionally, in Paykel's study, 90% of partial responders had ongoing mild to moderate somatic symptoms, raising the question of whether persistent physical symptoms are evidence of partial response (Figure 8).



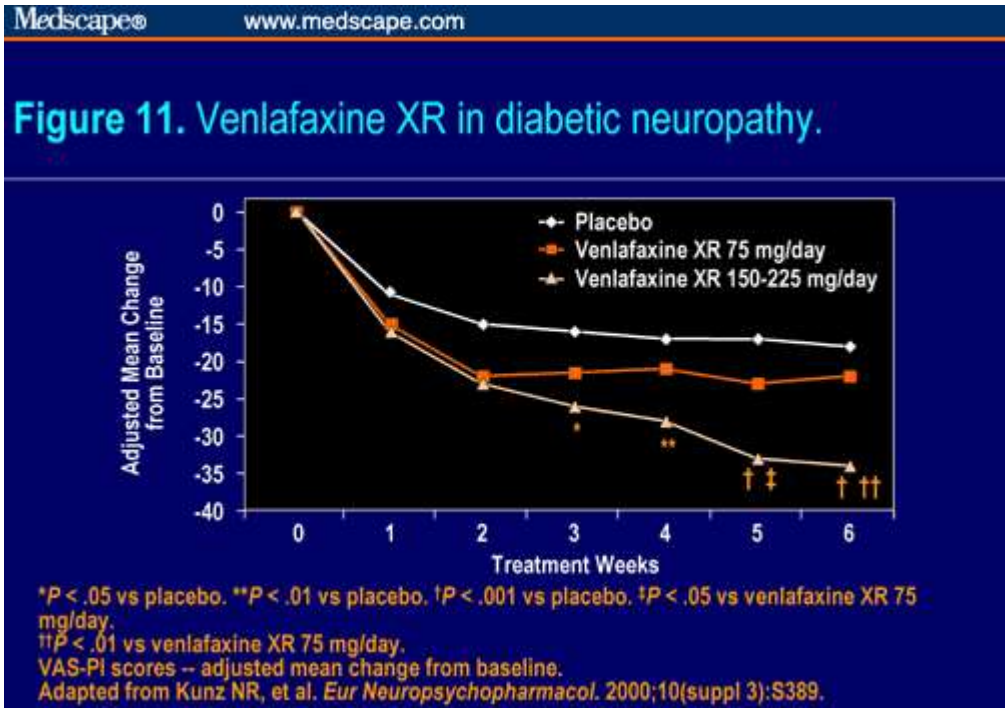
Recent investigations are beginning to differentiate currently available antidepressants based on their ability to induce remission when used as monotherapy. Dual reuptake agents such as tricyclic antidepressants (TCAs), venlafaxine (at doses of 150 mg/day or higher), mirtazapine, and monoamine oxidase inhibitors appear to best selective serotonin reuptake inhibitors (SSRIs) in this regard. In one large meta-analysis, venlafaxine at daily doses of 150 mg or greater was associated with higher remission rates than SSRIs (45% vs 35%, respectively) (Figure 9).[14]



The Danish University Antidepressant Group found similar results when comparing citalopram and paroxetine with clomipramine.[15]

Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI) scheduled to be available for clinical use in the near future, shows similar promise for higher remission rates.[16] Duloxetine appears to possess dual reuptake inhibition at its starting dose of 60 mg daily. Remission rates in Detke's single-dose study were significantly higher than those for placebo (31.4% vs 14.8%, $P <$ .003), with a high relative benefit of duloxetine over placebo of 112%. The odds ratio of duloxetine inducing remission compared with placebo was 2.6 -- similar to the values seen with higher-dose venlafaxine in Thase's meta-analysis.

Further evidence of the power of dual reuptake inhibition agents is seen in their superiority to single reuptake agents in modulating physical symptoms and usefulness in pain states. Vrethem and colleagues[17] compared amitriptyline (SNRI) with maprotiline (norepinephrine only), finding amitriptyline superior in reducing pain symptoms (66% vs 42%). Amitriptyline may be especially effective because of its ability to affect both serotonin and norepinephrine at low doses.[18] Fishbain[19] reported that dual-acting agents are superior to SSRIs in the treatment of headache with dual acting agents, demonstrating improvement in 78% of clinical trials reviewed vs 53% with serotonin-only modulating agents. Similar results were found in fibromyalgia patients, with 100% of studies of dual reuptake agents offering symptomatic relief vs 33% of studies using SSRIs. Diabetic neuropathy pain is significantly reduced by venlafaxine given at SNRI level doses (150-225 mg daily), but not by lesser doses (Figure 11).[20]



Duloxetine showed significant superiority to placebo in improving overall pain (back, shoulder, pain while awake, and interference of pain with daily activity) independent of impact on depression symptoms (Figure 12).

Dual Reuptake Antidepressants as a Rational Initial Strategy

Over the last decade, clinicians largely abandoned the use of TCAs to gain the safety and tolerability advantages of the SSRIs in depression management. Though some SSRIs also have the advantage of a reduced need for dose titration, clinicians need to be aware that optimization or amplification of dose beyond the usual or target doses of antidepressants remains a good initial strategy in patients who are nonresponsive or only partially responsive, but tolerating the selected antidepressant well. Some clinicians have also become familiar with antidepressant combination strategies that are attempts to recruit therapeutic mechanisms beyond serotonin reuptake inhibition (eg, SSRI-bupropion, SSRI-TCA combinations). Combination strategies, however, may induce additional adverse effects -- a major reason TCAs were abandoned in the first place.

Dual reuptake inhibition antidepressants deserve consideration as the new agents of first choice in depression management. They demonstrate significantly higher remission rates vs single reuptake agents (eg, SSRIs), the ability to affect physical symptoms common in depressed patients, and efficacy in patients with chronic pain states (eg, neuropathy). Newer dual reuptake inhibitors such as venlafaxine extended-release and duloxetine are as well tolerated as single reuptake agents in clinical trials and could replace SSRIs in many, if not most, depressed patients, when these additional benefits are factored into clinical decision making. Efficacy in anxious states is less completely explored for dual reuptake agents, but venlafaxine is indicated for generalized anxiety disorder and shows efficacy in other anxious states. Duloxetine has also been shown to effectively reduce anxious symptoms in depressed patients.[21]

Case Examples

Two case examples may serve to underline the principles covered so far.

Case 1: Miss Liz

Miss Liz presented as a 58-year-old female initially thought to suffer from somatization disorder. Over a period of 6 months, she asked to be worked into the appointment schedule, complaining of generalized muscle aches, abdominal cramping previously evaluated and judged to be benign or "functional," mixed tension/migraine headaches, and insomnia. When clinical depression was suggested as a likely source of her symptoms, she would always point to her psychosocial stress as the sole cause. Her mother-in-law, suffering from Alzheimer's dementia, had come to live with her and had effectively been abandoned to Liz's care by other family members. This left Liz with significant feelings of resentment directed at her husband and his siblings. Liz's history revealed numerous bouts of anxiety and depression, none of which had been treated medically except for the occasional as-needed use of lorazepam. Recommendations to consider a course of antidepressant therapy were always met with the same response -- "Dr. Manning, my mother-in-law who has Alzheimer's lives with me. If you were in the same situation, you'd be depressed, too."

Over a period of months, persistent efforts at education eventually led to a course of nortriptyline, chosen for its effectiveness in depression and pain. She increased her dose from 25 mg daily to 75 mg daily over 2 weeks and remarked at her 1-month follow up, "I don't know what it is, but I have a whole new attitude toward life." She was assertively confronting her husband and in-laws about her home situation and was successful in getting them to transfer their mother to a more supportive living environment.

Miss Liz is an example of depression presenting chiefly or exclusively with somatic symptoms. Her initial negative reaction to the diagnosis of depression was overcome with education and alliance building. This led to successful management of her illness.

Case 2: Molly

Molly presented with back and right leg pain secondary to a motor vehicle accident (MVA) 5 years previous. She required a cane to walk and reported electric shock sensations in her leg in addition to her aching pain. Injections of steroids and local anesthetics from a pain clinic had only been marginally effective for symptom flare ups. Her depressed mood accentuated her pain symptoms -- or vice versa -- it was hard to tell sometimes. She had a history of 3 major depressions prior to the MVA but had been relatively symptom free for 10 years until the MVA seemed to trigger the current episode.

At her presentation, Molly was receiving the SSRI paroxetine (40 mg/day), gabapentin (300 mg 3 times a day) and extended release oxycodone (20 mg twice a day). Despite this regimen, she reported back stiffness and pain that radiated into her right leg and both a depressed and anxious mood. At the initial interview, she remarked, "I don't think anything else can be done."

A re-evaluation of her regimen suggested several potential changes. Gabapentin, although helpful for neuropathic pain, may require considerable dose titration to achieve efficacy and a total daily dose of 900 mg per day was felt to represent an inadequate trial. Molly was instructed to increase her dose as tolerated to 600 mg 3 times a day. Paroxetine, an effective antidepressant in other scenarios, was felt to be a less focused agent for someone with significant chronic pain. It was cross-titrated with venlafaxine extended-release over 3 weeks to a final dose of 225 mg daily to take advantage of SNRI effects at that dose level. The dose of extended release oxycodone remained 20 mg twice a day.

Following these changes, Molly reported significantly less pain and depression. Although complete elimination of her pain may not be achievable, she noted, "I'm living better with my leg." The only side effects were modest and transient sedation and mild lower extremity edema. The rationale behind this clinical strategy used the emerging literature on pain and mood, enhancing effects on the descending modulating pathway to improve physical symptoms while taking advantage of the improvements in depression remission afforded by SNRI antidepressants.

Conclusion

Evidence of the relationship between physical symptoms -- especially pain -- and depression is growing. At the same time, dual reuptake inhibitors of serotonin and norepinephrine are showing evidence of improved remission rates over SSRIs in the management of depression and the ability to improve pain symptoms. This broad spectrum of activity and efficacy may be put to good clinical use in primary care, where the mind-body connection is demonstrated in day-to-day practice.

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Authors and Disclosures

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Beyond Depression: The Somatic/Affective Interface CME

Authors: Alan F. Schatzberg MD, Martin L. Korn MD

Complete author affiliations and disclosures are at the end of this activity.

Release Date: December 23, 2002; **Valid for credit through December 23, 2003**

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Introduction

Depression has traditionally been viewed as a syndrome with an affective core accompanied by associated problems such as sleep, appetite, decreased concentration, loss of interest, fatigue, and suicidal behaviors. Yet somatic symptoms are often present and may be the primary presenting problem in some individuals. These physical symptoms are wide ranging and include complaints such as headache, constipation, back pain, chest pain, dizziness, musculoskeletal complaints, and weakness. The lack of recognition of depression in the face of physical symptoms has resulted in the tendency by medical practitioners to misdiagnosis and undertreat depression. Alternatively, the lack of attention by the psychiatrist to physical symptoms in the depressed individual has resulted in neglect of this important area. In both cases, optimal treatment and functioning of the individual are compromised unless both areas are included in the overall treatment.

The monoamines serotonin (5-HT) and norepinephrine (NE) are both involved in the pathogenesis of pain. Antidepressants that act through these neurotransmitters have been shown to be useful in the treatment of pain, even in the absence of depression. The serotonin reuptake inhibitors (SSRIs) appear to have some, although limited, role in the relief of pain. This limited utility may be due to the single mode of action of these medications. There is now mounting evidence that combined dual-acting 5-HT and NE reuptake inhibitors are more effective in inducing remission in depression. This enhanced spectrum of activity may extend to the relief of somatic symptoms as well.

Somatic Symptoms and Depression

Depressed patients often present to the primary care physician with physical manifestations rather than dysphoric mood. In a study by Kirmayer and colleagues,[1] 70% to 80% of patients with significant depressive symptoms manifested somatic symptoms as well.

In a study of 150 depressed inpatients,[2] pain complaints were present in 92% of patients at intake as measured on the self-report 90-item Symptom Checklist. Complaints of headache and chest pain were more common in women, whereas complaints of myalgia and numbness were more frequently reported in men. Pain complaints were associated with increased depression and anxiety as measured. Complaints were not related to age, suicide attempts, or the severity of depression as rated by the psychiatrist.

In an international study of medical clinics conducted in 14 countries on 5 continents,[3] somatic symptoms were common in each of the centers. A total of 45% to 95% of patients (average, 69%) with major depression presented only with somatic symptoms. Unexplained physical symptoms were reported by half of the depressed patients, and 11% of the participants denied any symptoms of depression. Although cultural differences were related to the nature of the somatic presentation, the absence of an ongoing relationship with a primary physician also played a significant role. Females in all of the centers tended to report more somatic symptoms than men; however, this difference appeared to be related to the number of symptoms reported and was inversely related to the degree of social impairment.[4] The sex difference was diminished when social roles, such as marital status, occupational role, and number of children, were included in the analysis. In a study comparing somatic symptoms in primary care settings in Japan compared with the United States,[5] the rate of somatic presentation was increased in Japan. The reported symptoms also differed in the 2 countries. Japanese patients reported more abdominal symptoms, headaches, and neck pain.

The number of physical symptoms reported by primary care patients is related to the presence of psychiatric disorders. In a study by Kroenke and colleagues,[6] the presence of any physical symptom increased the likelihood that a mood or anxiety disorder was present by 2- to 3-fold. The rate of anxiety and depressive disorders was related to the number of symptoms. The rates were as follows: 0 to 1 somatic symptoms, 2%; 2 to 3 symptoms, 12%; 4 to 5 symptoms, 23%; 6 to 8 symptoms, 44%; and 9 or more symptoms, 60%. The presence of an anxiety disorder showed a similar increase as follows: 0 to 1 somatic symptoms, 1%; 2 to 3 symptoms, 7%; 4 to 5 symptoms, 13%; 6 to 8 symptoms, 30%; and 9 or more symptoms, 48%. The extent of functional impairment was also related to the number of physical complaints.

In patients with a preponderance of physical symptoms, affective disorders are often missed. Posse and Hallstrom[7] found that the recognized frequency of depression in a primary care setting was 1.8% in a sample of 442 patients. Sixty-two individuals with high somatic scores were assessed for the presence of an affective disorder. Forty-one of the 62 patients were found to have a mood disorder, including major depression (n=2), dysthymia (n=26), and adjustment disorder with depressed mood (n=9). Depression was highest in patients with musculoskeletal disorders. There is also a high rate of psychiatric disorders in patients with syncope.[8] The rate of recurrence of syncope at 1 year was 35% in patients with a psychiatric disorder compared with 15% in those without these difficulties. Psychiatric syndromes were not recognized in 60% of patients with syncope.

Patients with depression or anxiety use healthcare services at a much higher rate. In a study by Katon and colleagues,[9] 767 high users of healthcare services were identified. The diagnoses of these patients were major depression, 23.5%; dysthymic disorder, 16.8%; generalized anxiety

disorder, 21.8%; and somatization disorder, 20.2%. Two thirds of the sample reported a lifetime history of major depression. There is a high rate of depression in patients presenting with unexplained physical symptoms. Compared with women with breast lumps, women presenting with breast pain of unknown origin recalled more childhood emotional abuse and were more depressed and anxious.[10] Treatments targeted to patients with comorbid somatic and psychological symptoms have shown some effectiveness. Koike and associates[11] found that "quality improvement programs" decreased the rate of probable depressive disorders at both 6 and 12 months. The interventions included more effective screening and case management services and greater access to psychotherapeutic interventions. There are several other studies[12-14] that have demonstrated the effectiveness of intervention programs in primary care settings. The effect of these intervention programs is often modest, however, and a significant proportion of patients continues to experience depressive disorders even with the added interventions. For example, in the study by Koike and colleagues,[11] 43.1% of patients at 6 months and 45.2% of patients at 12 months enrolled in the enriched treatment program were diagnosed as having probable depressive disorders.

The Functional Role of Pain

Despite the noxious quality of pain symptoms, painful somatic sensations are essential to survival. Pain serves as a warning signal for the organism to identify and avoid a potentially harmful situation. If pain sensations are significantly impaired, as in some congenital disorders or in hypoanalgesic conditions such as a vascular neuropathy, the individual is at risk of significant injury.

Although sensory neurons in the periphery may be subjected to equivalent painful stimuli, multiple factors influence and regulate the perception of pain. The response to the stimuli is therefore highly variable and modified by cognitive, affective, social, and attentional factors. Serious injuries, for example, may be neglected if the individual is involved in an engrossing physical activity, such as a sport, or in the presence of imminent physical harm. In these situations, pain is only recognized after the activity is over and different modulating mechanisms come in to play. In chronic pain, however, there may be no clear adaptive advantages and pain should be minimized. One such condition is phantom limb pain that results from amputation. Phantom limb pain occurs after the loss of a limb and, since pain is not required to avoid further injury, **it** only serves to limit the adaptation to an already disabling wound.

Neuroanatomy and Neurophysiology of Pain

Understanding the neuroanatomic and neurophysiologic underpinnings of somatic symptoms and presentations helps us to understand the nature of the symptoms and the role of specific treatment interventions. Several classes of peripheral receptors are involved in the detection of painful stimuli. These receptors include thermal receptors, mechanical receptors, and polymodal receptors.[15] In contrast to the pain-specific thermal and mechanical receptors, polymodal fibers respond to several types of stimuli. The neuronal fibers emanating from these peripheral receptors synapse primarily in the dorsal horn of the spinal cord. Glutamate and neuropeptides are the principal neurotransmitters used by afferent neurons at the dorsal horn synapse. Several tracts carry the nociceptive signals to the brain. These tracts include the following:

- The spinothalamic tract is the most prominent ascending pain pathway and terminates in the thalamus.
- The spinoreticular tract terminates in the reticular formation and the thalamus.
- The spinomesencephalic tract projects to the mesencephalic reticular formation and the periaqueductal gray matter. Neurons from this tract synapse with neurons that terminate in the amygdala. The amygdala is involved in emotion and fear responses.

- The cervicothalamic tract projects to the medial lemniscus of the brainstem and to thalamic nuclei.
- The spinohypothalamic tract projects to the supraspinal autonomic control centers. It is therefore involved in the neuroendocrine and cardiovascular responses to painful stimuli.

The thalamic nuclei, where many of the pain pathways are projected, relay sensory information to both cortical and subcortical areas of the brain. Neurons in the somatosensory cortex have small receptive fields and therefore allow for localization of the painful stimuli in space. Projections to the limbic system trigger the emotional response to pain. Projections to the insular cortex help to modulate the autonomic response to pain and integrate sensory, affective, and cognitive responses to pain. Projections to the frontal lobe are involved in the cognitive interpretation and response to pain.[15]

Role of the Opiate System

The role of the opiate system in nociception has been well studied. The opiate system includes several receptors, such as the mu, delta, and kappa receptors. Several endogenous opioid peptides have been identified, including enkephalins, [Beta]-endorphins, and dynorphins. Although the opiate system is central to the regulation of pain, numerous other neurotransmitter systems are involved in the transmission and modulation of painful stimuli.

Role of Monoamines

The monoamines 5-HT, NE, and dopamine (DA) have all been shown to play a significant modulatory role in pain. In a study of the tail-flick pain paradigm in rats, intrathecal injection of morphine, 5-HT, and the NE reuptake inhibitor desipramine all appeared to induce some analgesic effects.[16] When subthreshold doses of morphine were administered, the application of 5-HT and desipramine augmented the antinociceptive properties of the opioid drug. Thus, lower doses of each of the agents may be combined to minimize adverse effects while inducing more effective analgesia. Yokogawa and colleagues[17] found that antidepressants that primarily inhibit NE reuptake (eg, nortriptyline and maprotiline) and dual reuptake inhibitors (eg, imipramine) were effective analgesics in a dose-dependent fashion. The SSRI fluvoxamine was not effective, however. Both $alpha_1$-adrenoreceptors and 5-HT2 and 5-HT3 receptors appeared to be involved in this effect. There are numerous interactions between the serotonergic and the noradrenergic system, and this may explain the overlapping or synergistic effects of these monoamines.

The centrally acting analgesic tramadol is an example of the synergistic action of 5-HT, NE, and opioid analgesics.[18,19] The pharmacological action of tramadol is related in part to the opioid receptor binding profile. However, the opioid analgesic effect is only partially blocked by the opiate antagonist naloxone. This suggests that there is also a nonopioid analgesic effect. Central neuronal synaptic levels of both 5-HT and NE occur with administration of this agent, and these monoamines appear to play a role in enhancing the therapeutic effects.

Pain-Related Disorders

There are several specific physical disorders associated with pain that appear to involve both noradrenergic and serotonergic dysfunction. Irritable bowel syndrome, for example, is one of the most common gastrointestinal disorders and symptoms include abdominal pain and discomfort. The prevalence of irritable bowel syndrome is between approximately 10% and 20% of the population[20,21] and accounts for approximately 28% of patients presenting in gastrointestinal practice.[22] Psychological factors often play a prominent role in the disorders, and the rate of psychiatric disorders is high in these patients. It is unclear, however, whether the psychological factors are the primary problem and the gastrointestinal complaints secondary or, conversely, whether chronic pain is primary and affective symptoms secondary.[23]

Multiple mechanisms are involved in the pathogenesis of irritable bowel disorder and involve the central, autonomic, and enteric nervous systems. NE, 5-HT, and DA serve to modulate the motor, sensory, and secretory activities of the gastrointestinal system.[24] There are several anatomical connections between areas of the limbic system involved in emotions and the gastrointestinal tract. These connections help to account for the psychological factors, such as anxiety, that influence gastrointestinal functioning and sensations.[25] Cortical areas involved in sensation and cognition also influence gastrointestinal functioning as has been demonstrated with a variety of imaging techniques, including positron emission tomographic scans, functional magnetic resonance imaging, and transcranial stimulation.[26] Since peripheral and central effects of serotonergic are present, several agents, including 5-HT receptor agonists and antagonists, are targeted directly at the gastrointestinal system.[22,27] Antidepressants have been used in this disorder; however, newer dual-acting agents, which appear to alleviate pain more effectively, have not been adequately investigated.

The serotonergic system has been repeatedly implicated in the pathophysiology of headache. The triptans, selective 5-HT1B/1D agonists, are some of the most widely used and effective antimigraine agents.[28] In addition, the SSRIs fluoxetine[29] and sertraline[30] have been shown to be effective in the relief of migraine. However, there is increasing evidence that the noradrenergic system plays a role in the pathophysiology of this disorder. When the dual reuptake inhibitor amitriptyline was compared with the SSRI citalopram, only amitriptyline was efficacious.[31] In a meta-analysis of 44 studies, the efficacy of tricyclic antidepressants (TCAs), SSRIs, and 5-HT antagonists was analyzed.[32] Each of the agents was found to be efficacious for both migraine and tension headache. In a retrospective study, the effectiveness of the dual reuptake inhibitor venlafaxine was studied in patients with migraine (n=114) and tension-type headaches (n=56).[33] Most subjects had been resistant to other medications. The median dose of venlafaxine was 150 mg, and the average length of the study was 6 months. There was a significant decrease in types of headaches. Lastly, the $alpha_2$-adrenergic agonist tizanidine, an agent that inhibits the release of NE centrally and in the spinal cord, was shown to be more effective than placebo in chronic daily headaches.[34] Considering the involvement of both 5-HT and NE in the pathogenesis of headache, dual-acting agents may have a significant clinical advantage, and further research is necessary to determine the role of these broader-spectrum agents.

In a study of the treatment of neuropathic pain by Sindrup and Jensen,[35] the effectiveness of TCAs was compared with the SSRIs. The number of patients required to identify one patient with more than 50% improvement in pain was the measure of effectiveness. The number of patients required for the dual-action tricyclics was 1.4, whereas the single-action SSRIs required 6.7 patients. In the treatment of central pain, the number of patients required was 2.5 for tricyclics. The SSRIs were found to be ineffective treatment of this symptom. Atkinson and associates[36] also found that the SSRIs were ineffective in the treatment of back pain. They compared the NE reuptake blocker maprotiline, paroxetine, and placebo. Patients randomized to maprotiline demonstrated significantly more improvement (45%) compared with both paroxetine (26%) and placebo (27%). In a review of 5 studies of antidepressants in postherpetic neuralgia, both amitriptyline and desipramine were found to be helpful in pain control.[37] The SSRIs zimelidine and paroxetine were not effective in postherpetic neuralgia. The author suggested that the NE reuptake effect is the most important factor in symptom control.[37] In a study by Kunz and colleagues,[38] extended release venlafaxine demonstrated efficacy in the amelioration of pain from diabetic neuropathy. The authors pointed out that since the presence of depression was an exclusion criterion, symptom improvement can only be attributed to an analgesic rather than an antidepressant effect.

Optimizing Treatment of Depression

Despite the major advances in the treatment of depression, depression still remains a significant healthcare burden. As more sophisticated treatments evolve, the probability of achieving greater therapeutic results has increased.

Role of Monoamines in Depression

Both 5-HT and NE treat the core symptoms of depression, and the therapeutic efficacy of serotonergic agents is approximately equal to that of noradrenergic agents. In a meta-analysis of 1500 patients, Nelson[39] found that the response rate was equivalent in patients treated with SSRIs (61.4%) or NE reuptake inhibitors (59.5%). However, since these neurotransmitters have differing functions in the central nervous system, there may be differing therapeutic effects that are not detected by the typical rating scales used in studies. For example, NE is involved to a greater extent in the regulation of motivation, energy, interest, and concentration. Alternatively, 5-HT regulates impulsivity, appetite, and sexual function.

Although antidepressants are often classified by their structural similarities (eg, tricyclics or monoamine oxidase inhibitors) or year of introduction (eg, first or second generation), it is often more fruitful to group them by the neurotransmitters affected by the medications.[40] The antidepressants may be clustered into 4 categories as follows[40]:

1. Selective NE reuptake blockers. The TCAs desipramine, nortriptyline, and protriptyline are potent NE reuptake inhibitors. Reboxetine, a yet-to-be released, structurally unique compound, is also a potent NE reuptake inhibitor.
2. Selective serotonergic reuptake blockers. Among the SSRIs are escitalopram, citalopram, fluoxetine, paroxetine, and sertraline.
3. NE and 5-HT reuptake blockers. Included are several of the TCAs, such as amitriptyline and imipramine, and the monoamine oxidase inhibitors, such as phenelzine and tranylcypromine. More recent examples include the specific serotonin and noradrenergic reuptake inhibitors. This class includes venlafaxine and duloxetine. The latter compound has not yet been marketed.
4. Miscellaneous compounds. Several agents are weak monoamine reuptake inhibitors. They work through a variety of mechanisms, including the receptor stimulation or antagonism in addition to the reuptake blockade. These agents work through a variety of other mechanisms, and the reasons for their antidepressant potency are less well delineated. Examples include bupropion and nefazodone.

Mechanisms of Monoamine Action

Since there are multiple mechanisms that result in an antidepressant response, the particular mechanisms responsible for alleviation of symptoms have been difficult to discern. Originally, it was hypothesized that a deficiency in monoamines was responsible for depressive reactions. Therefore, by increasing the amount of monoamines at the synaptic cleft, the deficiency could be remedied.[41,42] Since the TCAs acted by the potent reuptake of NE and/or 5-HT and the monoamine oxidase inhibitors increased the monoamines via inhibition of degradative enzymes, this hypothesis was supported.

Yet there were aspects of this theory that could not explain the observed responses. Increased release of monoamines at the synaptic cleft resulted in subsensitivity of the postsynaptic receptors through down-regulation. It was therefore unclear that simply increasing the monoamines would result in an overall increase in postsynaptic transmission of the neuronal impulse. In addition, reuptake inhibition and decreased enzyme degradation occurred shortly after administration of the medications. The antidepressant response, however, did not occur in full for several weeks. Lastly, some of the agents did not act primarily through reuptake inhibition, and these other mechanisms had to be accounted for to develop a more comprehensive theory. Long-term down-regulation of the beta-adrenoceptor receptors was hypothesized to be a central factor[43]; however, this occurs with administration of several, but not all, antidepressants. For example, noradrenergic agents such as desipramine, protriptyline, and phenelzine induce down-regulation, whereas SSRIs do not.[40]

Clinical Evidence of Monoamine Specificity

There are several lines of evidence that indicate that the serotonergic and noradrenergic systems have specific effects. There are several disorders or behaviors that involve one of the monoamines more than the others. Clinically, there are several disorders that are particularly responsive to agents that affect either NE or 5-HT.

Suicidal behavior and, in particular, impulsive suicide are associated with low levels of 5-hydroxyindoleacetic acid (5-HIAA).[44] Impulsive aggression has also been associated with low levels of cerebrospinal fluid 5-HIAA.[45] Serotonergic but not noradrenergic agents are effective in the treatment of obsessive-compulsive disorder.[46]

Alternatively, noradrenergic or dopaminergic agents help to ameliorate symptoms associated with attention-deficit/hyperactivity disorder (ADHD).[47] Stimulant medications, which form the mainstay of treatment of the disorder, block the reuptake of the catecholamines NE and DA and also stimulate their release.[48] The noradrenergic tricyclic desipramine has been shown to be effective in ADHD even when comorbid depression is not present[49] or when stimulant therapy has not been effective.[50] The dual-acting noradrenergic and dopaminergic agent bupropion has also shown to be effective in children,[51] adolescents,[52] and adults.[53] SSRIs, however, have not been shown to be efficacious in ADHD.

The dual noradrenergic and dopaminergic reuptake agent bupropion has been shown to be effective in smoking cessation.[54] This antismoking effect has usually been ascribed to the catecholamine reuptake properties. The noradrenergic TCA desipramine has also been shown to increase abstinence rates in smokers.[55,56]

Emotional experiences may be divided into negative and positive affects. Negative affects include anger, irritability, sadness, guilt, and worry. Positive affects include pleasure, happiness, enthusiasm, interest, surprise, and creativity. A medication may differentially affect some of these realms of emotional experience. Opbroek and associates[57] found that patients treated with SSRI who experienced sexual dysfunction also experienced blunted emotional responses. These individuals reported a diminished ability to cry and decreased creativity, surprise, and anger. They were also less concerned about the feelings of others. Scores of emotional blunting were not associated with decreased depression scores but were positively correlated with sexual dysfunction ($r = 0.64$; $P < .05$).

Experimental Evidence for Monoamine Specificity

To test the specificity of antidepressant agents, a series of monoamine depletion studies were conducted. Tryptophan is an essential amino acid that is the precursor to 5-HT. By administration of a drink deficient in tryptophan and rich in competing large neutral amino acids, levels of 5-HT could be rapidly and dramatically reduced. Delgado and colleagues[58] found that the drink lowered total and free plasma tryptophan levels by 87% and 91%, respectively. The decrease in 5-HT levels also occurs centrally as indicated by decreased levels of spinal fluid 5-HIAA, the primary metabolite of 5-HT.[59] The effect is specific to 5-HT, because the DA metabolite homovanillic acid and the noradrenergic metabolite 3-methoxy-4-hydroxy-phenylglycol were not affected. The tryptophan-free drink causes relapses in patients treated with serotonergic but not noradrenergic agents. Delgado and associates[60] administered the drink to patients responsive to the SSRI fluoxetine or the noradrenergic reuptake inhibitor desipramine. Eight of 15 of the fluoxetine-treated patients experienced disease relapse compared with only 1 of the 15 desipramine-treated patients.

The risk of recurrence of major depression may be predicted with tryptophan depletion.[61] Patients with previous major depressive episodes who were medication free for >/= 3 months and healthy controls were examined. The risk of relapse during the subsequent year was significantly greater in subjects who became depressed after the depletion. The sensitivity of the test was 78% and the specificity was 80%. The depressive effect induced by the tryptophan-free drink has been shown to occur in a dose-response relationship. Previously depressed individuals administered a full dose of 102 g became more depressed than those administered a quarter strength dose of 25 g in a study by Moreno and colleagues.[62] Healthy controls had minimal mood changes.

Alternatively, catecholamine depletion may be rapidly induced through the administration of the tyrosine hydroxylase inhibitor alpha-methylparatyrosine (AMPT). Tyrosine hydroxylase is the rate-limiting enzyme in the production of NE and DA. AMPT produced a significant increase in depression in patients treated with the noradrenergic agents desipramine or mazindol but not in patients treated with the serotonergic agents fluoxetine or sertraline.[63] When a dual-acting agent such as mirtazapine is administered, depression may be partially induced by depletion of either 5-HT or catecholamines.[64] AMPT did not result in increased depression in drug-free, depressed patients, however.[65] Yet, self-report measures of "tired" were increased, whereas measures of "energetic" were diminished in patients administered AMPT.

Synergy of Dual-Acting Agents

Measuring Monoamine Selectivity

To determine the selectivity of the agents, the ability of the drug to competitively inhibit binding of biogenic amines in an in vivo synaptosome preparation is calculated.[66,67] The kinetic parameter inhibition constant (or K_i) is calculated, and the inverse of the K_i provides a measure of potency of the agent. The selectivity of an agent is determined by the ratio of the K_i to inhibit one amine (eg, 5-HT) compared with another (eg, NE). Equal selectivity is determined by the extent that the ratio approaches 1. Drugs that have 20-fold or more selectivity for a particular amine do not inhibit the other amine at therapeutic doses.[68,69] TCAs, such as maprotiline, desipramine, protriptyline, and nortriptyline, are much more selective for NE than for 5-HT. The TCAs, including imipramine, clomipramine, and amitriptyline, possess dual mechanisms of action with selectivity ratios less than 6. The serotonin and NE reuptake inhibitor venlafaxine also demonstrates a dual mechanism of action,[69] as does duloxetine. Duloxetine is much more balanced in its 5-HT/NE ratio compared with venlafaxine. Although the SSRIs are often considered to be equivalent in their mechanisms of action, there are differences among the agents. Paroxetine, for example, is more potent at blocking serotonin than are sertraline and fluoxetine.[67]

Remission Vs Response

Traditionally, the standard of the effectiveness of antidepressant treatment has been the rate of response, defined as a 50% reduction in depression scores on scales such as the Hamilton Depression Rating Scale (HAM-D) or in the Montgomery-Asberg Depression Rating Scale. Although complete remission of symptoms is more difficult to achieve, it is the ultimate goal of treatment and therefore should be considered the standard of care. Remission is often defined as a final score of </= 7 on the 17-item HAM-D, a final score of </= 10 on the 21-item HAM-D, or a score of 1 on the Clinical Global Impression Scale.[70,71]

Inability to achieve a complete remission has long-term consequences. Paykel and colleagues[72] found that individuals with major depression with residual symptoms of 8 or more on the 17-item HAM-D had a much higher rate of an early relapse compared with complete remitters (76% vs 25%). In a 10-year naturalistic study, patients who had residual symptoms had a much higher rate of relapse compared with those who were symptom free.[73] The rate of relapse to a

subsequent major depressive episode was 3 times faster in the partially responsive cohort. Residual symptoms were a stronger predictor of relapse than was a history of previous major depressive episodes. The effect was not secondary to antidepressant dose or comorbid conditions.

Optimizing Outcome: Dual Neurotransmitter Effects

There are numerous studies that indicate that dual-action agents that affect both 5-HT and NE are therapeutically superior to single-action agents. This is most evident when remission rather than response is considered to be the study standard. Nelson[74] found that the addition of serotonergic fluoxetine and noradrenergic desipramine was superior to monotherapy with desipramine alone in depressed inpatients. The remission rates among patients undergoing combination therapy were 71% compared with only 6% in those treated with desipramine alone. The combination of the NE reuptake inhibitor reboxetine to the SSRI was found to augment the treatment response in treatment-resistant patients. The therapeutic effects of a medication are also related to the percentage of the drug that is protein bound compared with the fraction that is free. Venlafaxine has a relatively large unbound fraction, which may help to explain the increased therapeutic effect as well

Although the tolerability of TCAs is less than the SSRIs, several studies have documented a significant clinical advantage of the dual-action TCAs. Anderson[75] conducted a meta-analysis of 10,706 patients enrolled in 102 randomized studies. There was no overall difference between the TCAs and SSRIs when hospitalized and nonhospitalized patients were included. However, in hospitalized patients alone, those taking TCAs demonstrated greater improvement. In another meta-analysis of 21 double-blind studies comparing TCAs with SSRIs,[76] the improvement with TCAs was significantly greater than with SSRIs. When the more rigorous intention-to-treat criteria were used, however, no differences were found. Patients treated with SSRIs complained more often of gastrointestinal adverse effects, whereas those taking TCAs complained more of sedation, dizziness, and anticholinergic symptoms.

The dual-action TCA clomipramine (150 mg/d) was shown to be clinically superior to the SSRI paroxetine (30 mg/d) in 120 patients with major depression, although the adverse effect burden was greater with clomipramine.[77] The improved therapeutic effect of clomipramine was noted by the second week of treatment. Similarly, in a study of 150 depressed patients, clomipramine (150 mg/d) was found to be superior to the SSRI citalopram (40 mg/d) in patients with "endogenous" major depression.[78] In patients with "nonendogenous" depression, no difference was observed between the 2 agents. In all patients, 60% of patients taking clomipramine demonstrated a complete response compared with 30% of those taking paroxetine after 5 weeks of treatment. Alternatively, Feighner and Boyer[79] found that paroxetine was superior to imipramine as measured by the HAM-D. In another study, the dual-action agent mirtazapine was compared with fluoxetine.[80] The dose of mirtazapine ranged from 15 to 60 mg/d (mean, 36.5 mg/d), and the dose of fluoxetine was 20 to 40 mg/d (mean, 19.6 mg/d). Mirtazapine was found to be superior in efficacy starting at week 3.

The dual-acting agent venlafaxine has also been shown to be more efficacious compared with single-acting agents in a variety of studies. Poirier and Boyer[81] found that venlafaxine (200-300 mg/d) was more effective than paroxetine (30-40 mg/d) in a cohort of inpatients and outpatients. The response rate was 51.9% for venlafaxine-treated patients and 32.7% for paroxetine-treated patients. In a study by Rudolph and Feiger,[82] venlafaxine was compared with fluoxetine and placebo in depressed outpatients. The remission rates were 37% for venlafaxine, 22% for fluoxetine, and 22% for placebo. Venlafaxine was statistically superior to both fluoxetine and placebo. Venlafaxine was also shown to be superior to fluoxetine in hospitalized patients with depression.[83] Mehtonen and colleagues[84] compared venlafaxine with sertraline in an 8-week, double-blind, randomized study. The initial dosages were 37.5 mg twice daily for venlafaxine and 50 once daily for sertraline. After 15 days the dose of venlafaxine could be increased to 75 mg

twice daily and the dose of sertraline to 50 mg twice daily. The response rate was statistically greater in the venlafaxine-treated cohort compared with the sertraline-treated group at week 8 (83% vs 68%). Remission rates at week 8 were noted in 68% of patients taking venlafaxine and 45% of patients taking sertraline. Thase and associates[85] analyzed data from 8 randomized, double-blind studies comparing venlafaxine with the SSRIs fluoxetine, paroxetine, and fluvoxamine as well as placebo. The overall remission rates, defined as a HAM-D score of </= 7, was 45% for those taking venlafaxine, 35% for those taking SSRIs, and 25% for those taking placebo. The difference between venlafaxine and SSRIs was noted by the second week, whereas the difference between the SSRIs and placebo reached significance by the fourth week.

Duloxetine is a yet-to-be released, potent dual 5-HT and NE reuptake inhibitor. The compound has a more balanced 5-HT/NE ratio compared with venlafaxine (Table).[86] Because of the higher 5-HT/NE ratio of venlafaxine, the NE reuptake properties of this agent are generally not evident until a dose of 150 mg/d is achieved. Detke and colleagues[87] conducted a double-blind, placebo-controlled study in patients with major depression. The dose of duloxetine was 60 mg/d. The onset of action of duloxetine was rapid, with a significant difference starting at 2 weeks. The remission rate was significantly higher for patients taking duloxetine (44%) compared with those taking placebo (16%). Duloxetine also reduced overall painful symptoms significantly more than placebo. The extent of back and shoulder pain and the amount of time with pain were reduced by the drug. In a study by Goldstein and colleagues,[88] duloxetine was compared with placebo and fluoxetine in an 8-week, double-blind, placebo-controlled study. A total of 173 patients with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of major depression were included. The dose of duloxetine was increased from 20 mg twice daily to 60 mg twice daily in a forced dose escalation design. The dose of fluoxetine was 20 mg/d. The response and remission rates were 64% and 56% for duloxetine, 52% and 30% for fluoxetine, and 48% and 32% for placebo, respectively. Compared with placebo, duloxetine was superior at 8 weeks with regard to both response and remission rates. Duloxetine was numerically but not significantly superior to fluoxetine on these measures.

Table. 5-HT/NE Reuptake Ratios*

Agent	Ratio
Imipramine	5.2
Duloxetine	9.4
Venlafaxine	30.3
Fluoxetine	146.0
Paroxetine	330.0
Sertraline	794.4
Citalopram	1052.6

*Table adapted from Bymaster FP, Detke M, Hemrick-Luecke SK, et al, 2002[85]

Summary and Conclusions

Somatic symptoms play a prominent role in the depressed individual. Because of theoretical and practice biases, there is a strong tendency for the medical practitioner to focus on somatic rather than emotional aspects of function and disease. Similarly, the psychiatrist is strongly biased toward identifying the emotional and affective aspects of functioning to the neglect of the physical. These biases have resulted in an unfortunate separation of the 2 domains. Yet, it is clear that the

somatic-affective split is unwarranted and does not result in optimal care for the patient with both these aspects of function.

Antidepressants have been shown to be useful in the treatment of pain even in the absence of depressive disorders. This therapeutic effect is related, in part, to the monoamines 5-HT and NE. These neurotransmitters, in turn, act on and are influenced by the myriad of other central neurotransmitters and receptors. Through synergistic action, the therapeutic potential of one neurotransmitter may be enhanced by another neurotransmitter. There is emerging evidence that the dual-acting agents that alter 5-HT and NE function are more efficacious in the treatment of depression and the alleviation of pain symptoms compared with single-acting agents.

Therefore, of necessity, our clinical conception of depression must be expanded beyond the affective realm. Similarly, the tendency to isolate specific neurotransmitter functions and effects must be challenged and the complex synergistic neurotransmitter/receptor interactions explored. In this way, both our clinical perspective and our therapeutic range of effectiveness will be extensively broadened. Through these expanded vantage points, patients may be helped to achieve a higher level of function.

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Authors and Disclosures

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Disclosure: The author will discuss the investigational drug duloxetine and the off label use of various drugs for the treatment of pain.

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Registration for CME credit, the post test and the evaluation must be completed online.