SNRIs Versus SSRIs: Mechanisms of Action in Treating Depression and Painful Physical Symptoms

Norman Sussman, M.D.

Patients with depression frequently experience painful somatic symptoms, which may be the only symptoms reported to the physician. In addition, patients with chronic painful medical illnesses frequently suffer comorbid depression. Antidepressants have been used successfully to treat psychological and physical symptoms of depression as well as chronic pain in nondepressed patients. Although the precise mechanisms by which antidepressants relieve symptoms of depression and pain are not clearly understood at this time, evidence suggests that serotonin and norepinephrine are involved in both. Antidepressants that act via modifying both serotonergic and noradrenergic neurotransmission may have an advantage compared with antidepressants that primarily affect only one of these neurotransmitter systems, particularly in patients with both depression and painful physical symptoms.

(Primary Care Companion J Clin Psychiatry 2003;5[suppl 7]:19–26)

Most clinicians are quite familiar with the psychological symptoms of major depression: depressed mood, hopelessness, suicidal thoughts, decreased interest/productivity, decreased libido, and feelings of guilt or worthlessness.[1] These symptoms typically have received the majority of emphasis in classifying depressive disorders and must be present in some combination to firmly establish a diagnosis. In addition, psychological symptoms generally receive the most attention in evaluating antidepressant efficacy in clinical trials or in practice.[2]

However, depressive disorders are also associated with a constellation of physical or somatic symptoms.[1–3] Some of these symptoms are included as criteria in assessment instruments such as the Hamilton Rating Scale for Depression (HAM-D) (i.e., sleep disturbances, appetite changes, fatigue/low energy). Symptoms that are less specific to depression but are commonly reported include specific (e.g., back pain, chest pain, headaches) or nonspecific pains, muscle tension, sleep disturbances, changes in appetite, gastrointestinal disturbances, and fatigue.[2,4–6]

The link between depression and somatic symptoms was supported by findings from a study by Kroenke et al.,[6] which found a correlation between the number of physical symptoms that are reported by a patient and the likelihood of a mood/anxiety disorder. Specifically, the findings indicated that as the number of physical symptoms increased, so did the likelihood of a psychiatric diagnosis.[6] Further, painful physical symptoms may be a predictor of more severe depression.[4,7] Physical symptoms, then, are an important consideration in the diagnosis and treatment of depression. In fact, it is these symptoms and not necessarily complaints of depressed mood that are most frequently cited by patients as the primary reason that they chose to seek medical care.[2,5,8]

In addition to somatic symptoms directly related to depressive disorders, there is a high degree of association between depression and other pain states. For example, 22% to 45% of depressed patients also suffer from diagnosed fibromyalgia,[9] and depressed patients are 4 times as likely to suffer headaches and 5 times as likely to suffer backaches compared with nondepressed individuals.[9,10] Whether there is a causal relationship between depression and these conditions has not yet been determined. Nevertheless, major depression and chronic pain states are frequently intertwined.

It is important for clinicians, particularly primary care clinicians, to be aware of the association between the presence of physical symptoms and the likelihood of a mood/anxiety disorder[4,6,8]; to understand that there is considerable overlap between various pain states and depression (i.e., that patients who suffer chronic pain states frequently experience comorbid depression and vice versa)[11,12]; to keep in mind the large proportion of depressed patients who report physical symptoms as their primary concern[5]; to recognize the potential for depression among these patients; and to keep in mind that the

From the Department of Psychiatry, New York University School of Medicine, New York.

Supported by funding from Wyeth Pharmaceuticals, Philadelphia, Pa.

Dr. Sussman has been a consultant for GlaxoSmithKline and Wyeth and has received honoraria from Pfizer, Wyeth, GlaxoSmithKline, Organon, and Forest.

Corresponding author and reprints: Norman Sussman, M.D., Department of Psychiatry, New York University School of Medicine, 150 E 58th Street, 27th floor, New York, NY 10155 (e-mail: sussman01@aol.com).

goal of treatment is remission of all symptoms—both physical and emotional.

NEUROBIOLOGY

Depression

Although the precise pathophysiologic underpinnings of depression remain unclear, evidence suggests that the monoamine neurotransmitters serotonin (5-HT) and norepinephrine (NE) play an important role in mediating depressive symptoms.[13] The antidepressant efficacy of agents such as the monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs) supports a role for 5-HT in depression. Similarly, the antidepressant efficacy of dual-acting agents (i.e., those that affect both 5-HT and NE neurotransmission), including several TCAs, the serotonin-norepinephrine reuptake inhibitors (SNRIs) venlafaxine[14] and duloxetine,[15,16] and the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine,[17] implicate NE in depression.

In addition to observations from clinical trials of antidepressant treatment, findings from other areas of research are consistent with the role of 5-HT and NE in depression.[18,19] For example, depletion of NE and 5-HT via administration of the alkaloid reserpine has been shown to induce depressive symptoms.[13,19] Studies have demonstrated that when NE synthesis is blocked, depressed patients who have achieved remission with noradrenergic treatments experience relapse.[20] Similarly, depletion of 5-HT can result in relapse for depressed patients who have been stabilized on treatment with SSRIs.[20] In addition, evidence of changes in brain receptors of suicide victims, such as up-regulation of 5-HT_{2A} receptors[18,21] and increased density of α_2 and β_2 receptors,[18,19,21,22] supports the involvement of both 5-HT and NE, respectively.

Pain and Somatic Symptoms

The neurobiology of pain relief is complex and, as it relates to antidepressants, remains unclear. While evidence demonstrates the pain-relieving effects of antidepressants, particularly those that act via serotonergic and noradrenergic pathways,[23,24] the precise mechanisms of these analgesic effects are unknown. It has been suggested that serotonergic and noradrenergic projections from the brainstem are involved in the spinal pathways that modulate painful physical symptoms and that dysfunction of these pathways due to depression may lead to increased perceptions of these symptoms.[25] In addition, it has been suggested that depression and pain are mediated through a common pathway and that the balance of 5-HT and NE influences the perception of painful symptoms.[2]

Experimental studies in animals have attempted to discern the specific receptors that may be involved by evaluating the effects of α and 5-HT antagonists on antidepressant-induced analgesia, but have found mixed results.[26] Recent findings suggest that α_1-adrenoceptors and 5-HT_2[27] and 5-HT_3 receptors are involved in antinociceptive mechanisms of antidepressant action, while the α_2-adrenoceptors and 5-HT_{1A} receptors are involved minimally or not at all.[26] These results are consistent with the findings of earlier research, which reported similar reductions in analgesic effects when receptor-blocking agents were introduced.[26,28,29] In contrast, other findings have suggested a role for α_2-adrenoceptors in antidepressant analgesia,[26,30,31] such as evidence of the efficacy of clonidine (an α_2 agonist) in the relief of neuropathic and cancer pain.[26,32,33] Some reports suggest that 5-HT_{1A} and 5-HT_3 receptors may be involved in 5-HT–induced pain.[26,34,35] Thus, although specific mechanisms have not yet been confirmed, evidence from multiple studies supports the roles of 5-HT and NE in modifying the perception of pain.

ANTIDEPRESSANT MECHANISM OF ACTION: SINGLE-ACTING VERSUS DUAL-ACTING

The complex nature of interactions between neurotransmitter systems[36–38] may limit the accuracy of predictions of an antidepressant's ability to successfully treat a given patient's symptoms based on its mechanism of action. However, it has been suggested that serotonergic and noradrenergic antidepressants have differential efficacy in patients with a particular combination of symptoms or subtype of depression[39]; that is, antidepressants that selectively target 5-HT might be more effective in treating patients with a given symptomatic profile, while those that target NE neurotransmission might be more suited to patients with a different symptomatic profile.[36,40]

For example, findings suggest that selectively modulating 5-HT neurotransmission may be particularly useful in managing symptoms of general distress, irritability/aggression, and anxiety.[36,41] Some studies that compared primarily serotonergic (e.g., SSRIs) and primarily noradrenergic antidepressants (e.g., maprotiline) evaluated the efficacy of these agents in relieving specific symptoms of irritability or anxiety in addition to depressive symptoms.[41–45] The results demonstrated that, while both the serotonergic and noradrenergic agents effectively ameliorated symptoms of depressed mood, primarily serotonergic agents tended to be more effective than primarily noradrenergic antidepressants in reducing irritability and anxious symptoms.[41–45] The efficacy of serotonergic antidepressants in relieving symptoms of anxiety is further supported by the efficacy of SSRIs and the SNRI venlafaxine in treating anxiety disorders.[43,46,47]

By contrast, noradrenergic neurotransmission has been linked to anhedonia, lack of motivation, and loss of interest.[36,39] Some research has suggested that patients with psychomotor retardation associated with depression

tended to respond better to a noradrenergic antidepressant compared with a serotonergic agent.[41,48] Furthermore, evidence has suggested that symptoms of severe depression or melancholia may respond more favorably to treatment with antidepressants that exhibit noradrenergic activity than with SSRIs.[41,49–51]

In addition to possible differential efficacy in treating the psychological symptoms of depression, dual- and single-acting antidepressants also may differ in their ability to relieve physical symptoms related to depression. Given that both 5-HT and NE are believed to play a role in the perception of painful physical symptoms,[3,52,53] it is possible that antidepressants that act by modulating both neurotransmitter systems may have an advantage over single-acting agents. In addition, studies suggest that antidepressants that target both 5-HT and NE neurotransmission are typically effective in relieving various types of chronic pain, while evidence for serotonergic agents is less consistent.[52]

Research has also suggested an interaction between antidepressants and opioid receptors. For example, a study evaluating venlafaxine and mirtazapine found that both agents significantly potentiated antinociceptive effects through interactions with multiple opioid receptors (venlafaxine: μ, δ, κ_1, and κ_3; mirtazapine: μ and κ_3).[54] Other investigations have demonstrated inhibition of analgesic effects of antidepressants upon administration of naloxone, an opioid antagonist.[55] Additional data suggest that dual-acting antidepressants (e.g., TCAs) may produce analgesic effects as a result of both direct and indirect interaction with opioid systems.[55] Experimental studies in animals also suggested that the pain-relieving effects of fluoxetine are mediated not only by serotonergic neurotransmission, but by modulation of central opioid pathways as well.[56]

Thus, although complex interactions between neurotransmitter systems[36–38] impair the ability to reliably attribute effects on various symptoms to a specific antidepressant or type of antidepressant, it is conceivable that dual-acting agents (e.g., TCAs, SNRIs) may represent a more broadly effective treatment option compared with SSRIs in treating the physical symptoms of depression.

EFFICACY: SNRIs VERSUS SSRIs

Depression/Remission

It has been clearly established that antidepressants that are used today are effective in treating depression in general, regardless of whether they primarily affect serotonergic or noradrenergic neurotransmission or both. However, it has been suggested that there may be differences in efficacy among certain patient populations.[51] For example, studies of depressed inpatients by the Danish University Antidepressant Group reported superior efficacy of the TCA clomipramine compared with SSRIs (citalopram or paroxetine).[49,50] Additionally, findings from a meta-analysis of 23 inpatient investigations suggested that, in this patient population, at least some TCAs may be more effective than SSRIs.[51]

In light of the importance of achieving remission of symptoms in depression, it is useful to consider the relative ability of antidepressants to bring patients to remission. Although, in general, antidepressants are thought to have comparable efficacy, evidence has demonstrated significantly greater remission (HAM-D $\leq$ 7) rates with the SNRI venlafaxine compared with SSRIs.[57] In a pooled analysis of data from 8 comparative studies, patients treated with venlafaxine were significantly more likely to achieve remission compared with SSRI-treated patients (45% vs. 35%, $p < .001$).[57] These results were further supported by recent findings from a pooled analysis of data from more than 7000 depressed patients treated in more than 30 randomized controlled trials of venlafaxine and SSRIs, which revealed remission rates of 41% and 35% for venlafaxine and SSRIs, respectively ($p < .001$).[58] Preliminary results from a pooled analysis of 6 studies comparing duloxetine, an investigational compound with dual 5-HT and NE reuptake properties, with an SSRI[59] also support the hypothesis that dual-acting antidepressants may have an advantage over single-acting agents in terms of treating patients to remission.

Chronic and Neuropathic Pain

Dual-acting agents may also be preferable for the treatment of chronic painful conditions. The antidepressant activity and analgesic activity of antidepressants are thought to involve effects on common neurotransmitter systems (i.e., 5-HT and NE).[60,61] Findings in some trials of TCAs have shown that improvement in physical symptoms parallels improvement in depressed mood.[62] However, other evidence suggests that the effects of antidepressants on pain and somatic symptoms are independent of the drugs' effects on psychological symptoms.[53,60,61]

TCAs are among the most extensively investigated, most commonly used, and most consistently effective pharmacotherapeutic interventions for chronic pain and pain of neuropathic origin.[24] Several members of this class of antidepressants (e.g., amitriptyline, nortriptyline, imipramine) have been successfully used to treat painful conditions, including chronic neuropathic pain,[61] postherpetic neuralgia,[63–65] headaches,[66–68] fibromyalgia,[69] and polyneuropathy.[24]

Because venlafaxine, like TCAs, also inhibits the reuptake of 5-HT and NE, it is reasonable to expect that it would produce similar analgesic effects. Venlafaxine has, in fact, demonstrated analgesic effects in experimental models with animals[70] and with humans,[71] as well as in clinical trials of several pain states. Randomized, placebo-controlled trials have demonstrated the efficacy of venlafaxine in preventing migraine headaches[72] and in relieving

diabetic neuropathic pain,[73] painful polyneuropathy,[74] and neuropathic pain following breast cancer.[75] In addition, several case reports, retrospective reviews, and open trials have reported analgesic effects of venlafaxine in chronic headache,[76] fibromyalgia,[77,78] neuropathic back pain,[79] and other chronic or neuropathic pain states.[80–83]

The use of other antidepressants, including the SSRIs, in the treatment of chronic pain has been researched less extensively than use of the TCAs, and efficacy results have been somewhat inconsistent. Animal studies suggest an analgesic effect with fluoxetine,[56] and some clinical evidence suggests that the SSRI may provide pain relief similar to amitriptyline in patients with musculoskeletal pain[84] and may be useful in the treatment of such conditions as fibromyalgia[85] or chronic headache.[60] There are also data to suggest that paroxetine or citalopram may be effective in treating diabetic neuropathy.[86,87] In a study of amitriptyline and citalopram, however, citalopram did not demonstrate a significant analgesic effect in patients with chronic tension headaches.[67] Additionally, reports from open or uncontrolled studies and case reports suggest that other non-SSRI antidepressants, such as mirtazapine,[88] bupropion SR,[89,90] or trazodone,[91] may be useful in the treatment of pain. Further investigation would be necessary to confirm the analgesic efficacy of these antidepressants.

Physical Symptoms Associated With Depression

Given evidence that dual-acting antidepressants are generally more effective than single-acting agents in treating both psychological symptoms of depression and various chronic pain states, it is reasonable to expect that these agents might also be more effective in treating the painful and somatic symptoms that frequently accompany depression. Results of an analysis of pooled original patient data from 31 studies demonstrated that treatment with venlafaxine was significantly more effective than treatment with SSRIs (i.e., fluoxetine, paroxetine, sertraline, citalopram, and fluvoxamine) in reducing specific symptoms of depression, as assessed by individual HAM-D-21 items (i.e., anxiety-psychic, anxiety-somatic, somatic symptoms-gastrointestinal, somatic symptoms-general, hypochondriasis, and insight).[58] Additionally, compared with SSRI-treated patients, significantly more venlafaxine-treated patients achieved complete symptomatic resolution of backaches, headaches, muscle aches, loss of energy, fatigue, and heaviness in limbs, back, or head.[92] Double-blind, placebo-controlled trials of the SNRI duloxetine for the treatment of major depression have evaluated the drug's effects on painful physical symptoms associated with depression (e.g., overall pain, back pain, shoulder pain).[7,93] As would be expected in light of previous evidence with venlafaxine, these studies demonstrated significantly greater remission rates for the SNRI versus placebo, as well as significant improvement in multiple depressive symptoms, including physical symptoms.[7,93,94]

TOLERABILITY: SNRIs VERSUS SSRIs

The tolerability of pharmacotherapy is always an important consideration. However, it may be particularly important when making treatment decisions for patients who experience painful conditions or those with somatic symptoms of depression. Patients who present with these symptoms may be especially sensitive to or have a lower threshold for tolerating the potential adverse events associated with antidepressant treatment.

Evidence suggests that in outpatient populations, SSRIs and TCAs have comparable efficacy, but the SSRIs are better tolerated.[51,95] Thus, in terms of safety and tolerability, the SSRIs maintain a significant advantage over the TCAs, which may be particularly relevant when treating patients who present with somatic symptoms or pain. A study of paroxetine and fluoxetine found that these SSRIs were well tolerated among patients with baseline gastrointestinal somatic symptoms,[96] and a study of fluoxetine in patients with fibromyalgia found the SSRI to be well tolerated.[85] In general, the dual-acting antidepressants (i.e., SNRIs) have tolerability profiles comparable to those of SSRIs.[94,97,98] In addition, these antidepressants are also well tolerated among patients who present with baseline anxiety or somatic symptoms[7,99] and among those who suffer from chronic painful conditions.[60,76] Analyses of pooled original patient data from 5 short-term studies of patients with generalized anxiety disorder who reported physical symptoms at baseline demonstrated that treatment with venlafaxine extended release (XR) effectively treated not only emotional, but also physical symptoms of anxiety.[100] Further, venlafaxine XR treatment was effective regardless of the severity of baseline physical symptoms and was well tolerated among these patients, even those with a high severity of gastrointestinal complaints at baseline.[100]

HEALTH OUTCOMES AND COST-EFFECTIVENESS

Because depression and anxiety disorders are associated with chronic and pervasive psychosocial and occupational dysfunction, they are a significant cause of disability,[101,102] comparable to the disability associated with chronic illnesses like diabetes, rheumatoid arthritis, and hypertension.[103] Further, depressive symptoms have been linked to increased morbidity and mortality from all causes, including poor outcomes associated with other medical illnesses (e.g., diabetes, heart failure, stroke).[104–107] Evidence demonstrates that depressive and anxiety disorders are associated with higher rates and costs of health care utilization compared with the general population.[108,109] In fact, projections suggest that by 2020, depression will represent the second-largest global disease burden.[110]

The costs associated with depression and anxiety result in the significant economic burden with these disorders.[103,111] For example, a cost-of-illness study of 1980 U.S. data estimated that major depression resulted in 156 million days of paid work lost and total costs of $16.3 billion.[111] Of this total cost, it was estimated that direct costs (e.g., medication, hospitalization) account for about 13% ($2.1 billion), while the rest is attributed to indirect costs, e.g., mortality, reduced productivity ($14.2 billion).[111] Later studies of data from 1990 reported that the overall cost of depression in the United States was about $44 billion, of which direct costs accounted for about 28% and indirect costs accounted for the remaining 72%.[103,112] A 10-year update of the 1990 data using the same methodological framework[9] found that the economic burden of depression remained relatively stable, with overall costs of $83.1 billion in 2000 compared with $82.2 billion in 1990 (inflated to reflect 2000 dollars). As in 1990, only approximately 30% of these costs were attributed to direct medical costs, with indirect costs of morbidity and mortality accounting for more than two thirds of the total economic burden. Similar patterns of findings were reported in studies from the United Kingdom.[103]

Health Outcomes With Newer Antidepressants

Given that the economic burden of depression is largely a function of the substantial disability associated with the illness, treatments that demonstrate a clinical advantage in bringing patients to remission of symptoms have the potential to effect an overall savings in terms of both individual and societal costs of illness. Achievement of remission is associated with not only more favorable outcomes directly related to depressive symptoms (e.g., decreased risk of relapse/recurrence), but also greater improvements in psychosocial and vocational functioning.[113–115] As mentioned above, treatment with an SNRI improves the likelihood of achieving remission (as defined by standardized symptom rating criteria) compared with SSRI treatment.[57,58] It may be possible, then, that SNRIs are associated with improved health outcomes as a result.

Evidence from studies of health outcomes in depressed and anxious patients suggests that patients may experience a greater number of depression-free days when treated with the SNRI venlafaxine compared with SSRIs.[116] Analysis of pooled data from 8 controlled clinical studies showed that the median number of depression-free days with venlafaxine treatment was significantly greater compared with SSRI or placebo (18.8 vs. 13.6 vs. 7.4; $p = .0001$).[116] Not surprisingly, the increase in depression-free days translated into increased days free from depression-related work loss among patients treated with venlafaxine compared with those treated with SSRIs.[117] Finally, a longer duration of therapy has been demonstrated with SNRIs compared with SSRIs, which may lead to a better course of illness (e.g., lower likelihood of relapse/recurrence, longer time to relapse/recurrence).[118,119]

Cost-Effectiveness With SNRIs vs. SSRIs

While newer antidepressants may be preferable in terms of improved health outcomes, it is also important to weigh these advantages in light of the direct costs of the interventions. Newer antidepressants tend to be more expensive compared with those that have been on the market for several years, particularly those that are available as generics. If the cost of the treatment with the newer agents is too great, it may outweigh any potential treatment advantages.

The development of the SSRIs as a more tolerable alternative to the TCAs created interest in comparisons of cost-effectiveness between these classes of antidepressants. It has been reported that direct health care expenditures associated with initiation of SSRI treatment are similar to or less than those associated with initiation of treatment with TCAs.[120–122] Although the SSRIs typically have higher acquisition costs, these are consistently outweighed by lower treatment costs.[123]

Comparisons between costs with SNRIs and costs with SSRIs revealed that direct health care expenditures (i.e., inpatient and outpatient care costs of treatment) with the SNRI venlafaxine are comparable to those with SSRIs.[120,124] For example, in retrospective administrative database studies, direct medical expenditures were similar among patients receiving venlafaxine, SSRIs, TCAs, and other second-line therapies for depression.[124] In addition, total 6-month health care expenditures with SNRIs versus SSRIs as first-line therapy were comparable.[120] Moreover, there were cost advantages to SNRI treatment in certain subgroups. Specifically, the SNRI venlafaxine was associated with significantly lower inpatient expenditures than SSRIs[120] and had a lower cost per successfully treated patient and cost per symptom-free day compared with SSRIs and TCAs.[108,125]

CONCLUSIONS

Depression is commonly associated with physical or painful symptoms, which are important to recognize as indicators of possible mood disorders. Serotonin and norepinephrine appear to be involved in the mechanisms of both depression and pain, and these conditions may be mediated through a common pathway. Antidepressants that act via serotonergic or noradrenergic mechanisms (or both) have analgesic properties independent of their effects on mood and have been used successfully to manage the symptoms of various pain states.

It is thought that the effects of the TCAs on both 5-HT and NE convey an advantage over single-acting agents, such as the SSRIs, both in terms of antidepressant efficacy

(particularly for severely depressed patients) and in terms of analgesic potential. Historically, the TCAs have been the most consistently successful antidepressant treatment option for chronic or neuropathic pain; however, safety and tolerability concerns may limit their use. SSRIs have a more favorable safety and tolerability profile compared with the TCAs, but their analgesic potential is less extensively documented.

Newer dual-acting antidepressants (e.g., the SNRIs venlafaxine and duloxetine) appear to possess analgesic efficacy similar to that of the TCAs, but have a more favorable safety and tolerability profile. These drugs also may have an efficacy advantage over SSRIs in treating the painful physical symptoms of depression and in achieving remission of all symptoms of depression. In particular, venlafaxine has been shown to bring significantly more patients to remission of symptoms compared with SSRIs, based on analyses of data from over 30 head-to-head studies. No other modern antidepressant has demonstrated a similar record of performance.

Costs associated with newer antidepressants are generally not significantly greater than with older agents (e.g., TCAs), giving them a cost-effectiveness advantage as well. Given the high rate of somatic symptoms and comorbid painful conditions in depressed patients, dual-acting antidepressants (e.g., venlafaxine) provide clinicians with a treatment option that has tolerability comparable to that of SSRIs and a potential efficacy advantage in terms of treating the broad spectrum of depressive symptoms and achieving remission of this debilitating disorder.

Drug names: amitriptyline (Elavil, Limbitrol, and others), bupropion SR (Wellbutrin and others), citalopram (Celexa), clomipramine (Anafranil and others), clonidine (Catapres, Duraclon, and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), maprotiline (Ludiomil and others), mirtazapine (Remeron and others), naloxone (Narcan and others), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil), reserpine (Serpalan and others), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
2. Greden JF. Physical symptoms of depression: unmet needs. J Clin Psychiatry 2003;64(suppl 7):5–11
3. Stahl SM. Does depression hurt? [BRAINSTORMS] J Clin Psychiatry 2002;63:273–274
4. Gerber PD, Barrett JE, Barrett JA, et al. The relationship of presenting physical complaints to depressive symptoms in primary care patients. J Gen Intern Med 1992;7:170–173
5. Kirmayer LJ, Robbins JM, Dworkind M, et al. Somatization and the recognition of depression and anxiety in primary care. Am J Psychiatry 1993;150:734–741
6. Kroenke K, Spitzer RL, Williams JB, et al. Physical symptoms in primary care: predictors of psychiatric disorders and functional impairment. Arch Fam Med 1994;3:774–779
7. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry 2002;63:308–315
8. Simon GE, VonKorff M, Piccinelli M, et al. An international study of the relation between somatic symptoms and depression. N Engl J Med 1999; 341:1329–1335
9. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression: how did things change between 1990 and 2000? [poster] Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
10. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. Arch Gen Psychiatry 2003;60:39–47
11. Goodnick PJ. Use of antidepressants in treatment of comorbid diabetes mellitus and depression as well as in diabetic neuropathy. Ann Clin Psychiatry 2001;13:31–41
12. Greenberg PE, Leong SA, Birnbaum HG, et al. The economic burden of depression with painful symptoms. J Clin Psychiatry 2003;64:17–23
13. Hirschfeld RM. History and evolution of the monoamine hypothesis of depression. J Clin Psychiatry 2000;61(suppl 6):4–6
14. Harvey AT, Rudolph RL, Preskorn SH. Evidence of the dual mechanisms of action of venlafaxine. Arch Gen Psychiatry 2000;57:503–509
15. Chalon SA, Granier LA, Vandenhende FR, et al. Duloxetine increases serotonin and norepinephrine availability in healthy subjects: a double-blind, controlled study. Neuropsychopharmacology 2003:May 28 [Epub ahead of print]
16. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacology 2001;25:871–880
17. Haddjeri N, Blier P, de Montigny C. Acute and long-term actions of the antidepressant drug mirtazapine on central 5-HT neurotransmission. J Affect Disord 1998;51:255–266
18. Schatzberg AF. Noradrenergic versus serotonergic antidepressants: predictors of treatment response. J Clin Psychiatry 1998;59(suppl 14):15–18
19. Schatzberg AF. Pharmacological principles of antidepressant efficacy. Hum Psychopharmacol 2002;17:S17–S22
20. Delgado PL, Moreno FA. Role of norepinephrine in depression. J Clin Psychiatry 2000;61(suppl 1):5–12
21. Nordstrom P, Asberg M. Suicide risk and serotonin. Int Clin Psychopharmacol 1992;6(suppl 6):12–21
22. Cheetham SC, Katona CLE, Horton RW. Post-mortem studies of neurotransmitter biochemistry in depression and suicide. In: Horton R, Katona CLE, eds. Biological Aspects of Affective Disorders. London, England: Academic Press; 1991:192–221
23. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. J Psychiatry Neurosci 2001;26:30–36
24. Sindrup SH, Jensen TS. Pharmacologic treatment of pain in polyneuropathy. Neurology 2000;55:915–920
25. Stahl SM. The psychopharmacology of painful physical symptoms in depression [BRAINSTORMS]. J Clin Psychiatry 2002;63:382–383
26. Yokogawa F, Kiuchi Y, Ishikawa Y, et al. An investigation of monoamine receptors involved in antinociceptive effects of antidepressants. Anesth Analg 2002;95:163–168
27. Blier P, Abbott FV. Putative mechanisms of action of antidepressant drugs in affective and anxiety disorders and pain. J Psychiatry Neurosci 2001; 26:37–43
28. Walker MJ, Poulos CX, Le AD. Effects of acute selective 5-HT1, 5-HT2, 5-HT3 receptor and alpha 2 adrenoceptor blockade on naloxone-induced antinociception. Psychopharmacology (Berl) 1994;113:527–533
29. Ansuategui M, Naharro L, Feria M. Noradrenergic and opioidergic influences on the antinociceptive effect of clomipramine in the formalin test in rats. Psychopharmacology (Berl) 1989;98:93–96
30. Ghelardini C, Galeotti N, Bartolini A. Antinociception induced by amitriptyline and imipramine is mediated by alpha2A-adrenoceptors. Jpn J Pharmacol 2000;82:130–137
31. Sahebgharani M, Zarrindast M. Effect of alpha-adrenoceptor agents on imipramine-induced antinociception in nerve-ligated mice. Eur Neuropsychopharmacol 2001;11:99–104
32. Davis KD, Treede RD, Raja SN, et al. Topical application of clonidine relieves hyperalgesia in patients with sympathetically maintained pain. Pain 1991;47:309–317
33. Eisenach JC, DuPen S, Dubois M, et al, and the Epidural Clonidine Study Group. Epidural clonidine analgesia for intractable cancer pain. Pain 1995;61:391–399
34. Taiwo YO, Levine JD. Serotonin is a directly-acting hyperalgesic agent in

the rat. Neuroscience 1992;48:485–490
35. Eschalier A, Kayser V, Guilbaud G. Influence of a specific 5-HT3 antagonist on carrageenan-induced hyperalgesia in rats. Pain 1989;36:249–255
36. Nutt DJ. The neuropharmacology of serotonin and noradrenaline in depression. Int Clin Psychopharmacol 2002;17:S1–S12
37. Svensson TH. Brain noradrenaline and the mechanisms of action of antidepressant drugs. Acta Psychiatr Scand Suppl 2000;402:18–27
38. Westenberg HG. Pharmacology of antidepressants: selectivity or multiplicity? J Clin Psychiatry 1999;60:4–8; discussion 46–48
39. Shelton RC, Tomarken AJ. Can recovery from depression be achieved? Psychiatr Serv 2001;52:1469–1478
40. Montgomery SA. Is there a role for a pure noradrenergic drug in the treatment of depression? Eur Neuropsychopharmacol 1997;7:S3–S9; discussion S71–S73
41. Humble M. Noradrenaline and serotonin reuptake inhibition as clinical principles: a review of antidepressant efficacy. Acta Psychiatr Scand Suppl 2000;402:28–36
42. Aberg-Wistedt A. A double-blind study of zimelidine, a serotonin uptake inhibitor, and desipramine, a noradrenaline uptake inhibitor, in endogenous depression, 1: clinical findings. Acta Psychiatr Scand 1982;66:50–65
43. Eriksson E. Antidepressant drugs: does it matter if they inhibit the reuptake of noradrenaline or serotonin? Acta Psychiatr Scand Suppl 2000;402: 12–17
44. Eriksson E, Hedberg MA, Andersch B, et al. The serotonin reuptake inhibitor paroxetine is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. Neuropsychopharmacology 1995;12:167–176
45. van Praag HM, Kahn R, Asnis GM, et al. Therapeutic indications for serotonin-potentiating compounds: a hypothesis. Biol Psychiatry 1987; 22:205–212
46. Gelenberg AJ, Lydiard RB, Rudolph RL, et al. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. JAMA 2000;283: 3082–3088
47. Katz IR, Reynolds CF III, Alexopoulos GS, et al. Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: pooled analysis of 5 randomized placebo-controlled clinical trials. J Am Geriatr Soc 2002; 50:18–25
48. Aberg-Wistedt A. Comparison between zimelidine and desipramine in endogenous depression: a cross-over study. Acta Psychiatr Scand 1982; 66:129–138
49. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990;18:289–299
50. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. Psychopharmacology (Berl) 1986;90:131–138
51. Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. Depress Anxiety 1998; 7(suppl 1):11–17
52. Fishbain D. Evidence-based data on pain relief with antidepressants. Ann Med 2000;32:305–316
53. Mattia C, Paoletti F, Coluzzi F, et al. New antidepressants in the treatment of neuropathic pain: a review. Minerva Anestesiol 2002;68:105–114
54. Schreiber S, Bleich A, Pick CG. Venlafaxine and mirtazapine: different mechanisms of antidepressant action, common opioid-mediated antinociceptive effects: a possible opioid involvement in severe depression? J Mol Neurosci 2002;18:143–149
55. Sawynok J, Esser MJ, Reid AR. Antidepressants as analgesics: an overview of central and peripheral mechanisms of action. J Psychiatry Neurosci 2001;26:21–29
56. Singh VP, Jain NK, Kulkarni SK. On the antinociceptive effect of fluoxetine, a selective serotonin reuptake inhibitor. Brain Res 2001;915:218–226
57. Thase M, Entsuah R, Cantillon M. Venlafaxine and SSRIs in the treatment of depression: comparison among age and gender variables [abstract]. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
58. Nemeroff CN, Entsuah R, Willard LB, et al. Comprehensive pooled analysis of remission data: venlafaxine vs SSRIs. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
59. Thase M, Lu Y. Remission in placebo-controlled trials of duloxetine with an SSRI comparator [poster]. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco,Calif
60. Ansari A. The efficacy of newer antidepressants in the treatment of chronic pain: a review of current literature. Harv Rev Psychiatry 2000;7:257–277
61. Reisner L. Antidepressants for chronic neuropathic pain. Curr Pain Headache Rep 2003;7:24–33
62. Casper RC, Katz MM, Bowden CL, et al. The pattern of physical symptom changes in major depressive disorder following treatment with amitriptyline or imipramine. J Affect Disord 1994;31:151–164
63. Watson CP, Vernich L, Chipman M, et al. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. Neurology 1998;51: 1166–1171
64. Graff-Radford SB, Shaw LR, Naliboff BN. Amitriptyline and fluphenazine in the treatment of postherpetic neuralgia. Clin J Pain 2000;16: 188–192
65. Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2002;59:1015–1021
66. Descombes S, Brefel-Courbon C, Thalamas C, et al. Amitriptyline treatment in chronic drug-induced headache: a double-blind comparative pilot study. Headache 2001;41:178–182
67. Bendtsen L, Jensen R. Amitriptyline reduces myofascial tenderness in patients with chronic tension-type headache. Cephalalgia 2000;20: 603–610
68. Holroyd KA, O'Donnell FJ, Stensland M, et al. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. JAMA 2001;285:2208–2215
69. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia: a meta-analysis and review. Psychosomatics 2000;41:104–113
70. Lang E, Hord AH, Denson D. Venlafaxine hydrochloride (Effexor) relieves thermal hyperalgesia in rats with an experimental mononeuropathy. Pain 1996;68:151–155
71. Enggaard TP, Klitgaard NA, Gram LF, et al. Specific effect of venlafaxine on single and repetitive experimental painful stimuli in humans. Clin Pharmacol Ther 2001;69:245–251
72. Kathpal GS. Role of SSRIs in the management of migraine. Headache Quarterly Curr Treat Res 1998;9:265–266
73. Kunz NR. Effect of Venlafaxine Extended Release on Diabetic Neuropathic Pain [poster]. Presented at the 153rd annual meeting of the American Psychiatric Association; May 13–18, 2000; Chicago, Ill
74. Sindrup SH, Bach FW, Madsen C, et al. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology 2003; 60:1284–1289
75. Tasmuth T, Hartel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. Eur J Pain 2002;6:17–24
76. Adelman LC, Adelman JU, Von Seggern R, et al. Venlafaxine extended release (XR) for the prophylaxis of migraine and tension-type headache: a retrospective study in a clinical setting. Headache 2000;40:572–580
77. Dryson E. Venlafaxine and fibromyalgia [letter]. N Z Med J 2000;113:87
78. Dwight MM, Arnold LM, O'Brien H, et al. An open clinical trial of venlafaxine treatment of fibromyalgia. Psychosomatics 1998;39:14–17
79. Sumpton JE, Moulin DE. Treatment of neuropathic pain with venlafaxine. Ann Pharmacother 2001;35:557–559
80. Taylor K, Rowbotham MC. Venlafaxine hydrochloride and chronic pain. West J Med 1996;165:147–148
81. Songer DA, Schulte H. Venlafaxine for the treatment of chronic pain [letter]. Am J Psychiatry 1996;153:737
82. Pernia A, Mico JA, Calderon E, et al. Venlafaxine for the treatment of neuropathic pain. J Pain Symptom Manage 2000;19:408–410
83. Durand JP, Goldwasser F. Dramatic recovery of paclitaxel-disabling neurosensory toxicity following treatment with venlafaxine. Anticancer Drugs 2002;13:777–780
84. Schreiber S, Vinokur S, Shavelzon V, et al. A randomized trial of fluoxetine versus amitriptyline in musculo-skeletal pain. Isr J Psychiatry Relat Sci 2001;38:88–94
85. Arnold LM, Hess EV, Hudson JI, et al. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med 2002;112:191–197
86. Sindrup SH, Bjerre U, Dejgaard A, et al. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. Clin Pharmacol Ther 1992;52:547–552

87. Sindrup SH, Gram LF, Brosen K, et al. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 1990;42:135–144
88. Brannon GE, Stone KD. The use of mirtazapine in a patient with chronic pain. J Pain Symptom Manage 1999;18:382–385
89. Semenchuk MR, Davis B. Efficacy of sustained-release bupropion in neuropathic pain: an open-label study. Clin J Pain 2000;16:6–11
90. Semenchuk MR, Sherman S, Davis B. Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. Neurology 2001;57: 1583–1588
91. Wilson RC. The use of low-dose trazodone in the treatment of painful diabetic neuropathy. J Am Podiatr Med Assoc 1999;89:468–471
92. Entsuah R, Li Y. Venlafaxine vs SSRIs: Comparison of complete somatic symptom resolution. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
93. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res 2002;36:383–390
94. Goldstein DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. J Clin Psychiatry 2002;63:225–231
95. Moller HJ, Glaser K, Leverkus F, et al. Double-blind, multicenter comparative study of sertraline versus amitriptyline in outpatients with major depression. Pharmacopsychiatry 2000;33:206–212
96. Linden RD, Wilcox CS, Heiser JF, et al. Are selective serotonin reuptake inhibitors well tolerated in somatizing depressives? Psychopharmacol Bull 1994;30:151–156
97. Thase ME, for the Venlafaxine XR 209 Study Group. Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. J Clin Psychiatry 1997;58:393–398
98. Arias F, Padin JJ, Gilaberte I. Comparative efficacy and tolerability among different selective serotonin reuptake inhibitors and venlafaxine in a naturalistic setting. Int J Psych Clin Pract 1998;2:255–260
99. De Nayer A, Geerts S, Ruelens L, et al. Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety. Int J Neuropsychopharmacol 2002;5:115–120
100. Lydiard B, Pitrosky B, Hackett D, et al. Venlafaxine extended release (ER) is effective and well tolerated in the treatment of somatic and psychic symptoms of generalized anxiety disorder, regardless of baseline symptomatology. Presented at the 41st annual meeting of the American College of Neuropsychopharmacology; December 8–12, 2002; San Juan, Puerto Rico
101. Judd LL, Akiskal HS, Maser JD, et al. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry 1998;55:694–700
102. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. JAMA 1989;262:914–919
103. Berto P, D'Ilario D, Ruffo P, et al. Depression: cost-of-illness studies in the international literature, a review. J Ment Health Policy Econ 2000;3: 3–10
104. Murphy JM, Monson RR, Olivier DC, et al. Affective disorders and mortality: a general population study. Arch Gen Psychiatry 1987;44: 473–480
105. Lustman PJ, Anderson RJ, Freedland KE, et al. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000;23:934–942
106. Everson SA, Roberts RE, Goldberg DE, et al. Depressive symptoms and increased risk of stroke mortality over a 29-year period. Arch Intern Med 1998;158:1133–1138
107. Vaccarino V, Kasl SV, Abramson J, et al. Depressive symptoms and risk of functional decline and death in patients with heart failure. J Am Coll Cardiol 2001;38:199–205
108. Casciano R, Arikian SR, Tarride JE, et al. Antidepressant selection for major depressive disorder: the budgetary impact on managed care. Drug Benefit Trends 2000;12:6–16
109. Simon GE, Katzelnick DJ. Depression, use of medical services and cost-offset effects. J Psychosom Res 1997;42:333–344
110. Murray CJ, Lopez AD. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases. Injuries and Risk Factors in 1990 and Projected to 2020. Cambridge, Mass: Harvard University Press; 1996
111. Stoudemire A, Frank R, Hedemark N, et al. The economic burden of depression. Gen Hosp Psychiatry 1986;8:387–394
112. Greenberg PE, Stiglin LE, Finkelstein SN, et al. The economic burden of depression in 1990. J Clin Psychiatry 1993;54:405–418
113. Mintz J, Mintz LI, Arruda MJ, et al. Treatments of depression and the functional capacity to work. Arch Gen Psychiatry 1992;49:761–768
114. Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression, pt 3: psychosocial functioning before and after treatment with sertraline or imipramine. J Clin Psychiatry 1998;59:608–619
115. Simon GE, Revicki D, Heiligenstein J, et al. Recovery from depression, work productivity, and health care costs among primary care patients. Gen Hosp Psychiatry 2000;22:153–162
116. Mallick R, Chen J, Entsuah AR, et al. Depression-free days as a summary measure of the temporal pattern of response and remission in the treatment of major depression: a comparison of venlafaxine, selective serotonin reuptake inhibitors, and placebo. J Clin Psychiatry 2003;64: 321–330
117. Mallick R, Ninan PT. Depression symptomatology and work impairment in major depressive disorder: a pooled comparison of venlafaxine, SSRIs, and placebo [abstract]. Int J Neuropsychopharmacol 2002;5: S208
118. Boccuzzi SJ, Kreilick C, Wogen J, et al. Venlafaxine XR associated with longer duration of therapy and lower discontinuation rates compared with SSRIs [poster]. Presented at the Collegium Internationale Neuro-Psychopharmacologicum; June 23–27, 2002; Montreal, Ontario, Canada
119. Wan G, Boccuzzi S, Kreilick C, et al. Venlafaxine XR associated with longer duration of therapy and lower discontinuation rates compared with SSRIs [abstract]. Int J Neuropsychopharmacol 2002;5:S207
120. Wan GJ, Crown WH, Berndt ER, et al. Healthcare expenditure in patients treated with venlafaxine or selective serotonin reuptake inhibitors for depression and anxiety. Int J Clin Pract 2002;56:434–439
121. McFarland BH. Depression in managed care: costs of selective serotonin reuptake inhibitors. J Managed Care Pharm 2001;7:142–148
122. Baker AM, Russell JM, Campbell JK. Variance in treatment compliance and costs by antidepressant class: analysis in an HMO setting. Formulary 2001;36:204–210
123. Einarson TR, Arikian S, Sweeney S, et al. A model to evaluate the cost-effectiveness of oral therapies in the management of patients with major depressive disorders. Clin Ther 1995;17:136–153
124. Griffiths RI, Sullivan EM, Frank RG, et al. Medical resource use and cost of venlafaxine or tricyclic antidepressant therapy following selective serotonin reuptake inhibitor therapy for depression. Pharmacoeconomics 1999;15:495–505
125. Doyle JJ, Casciano J, Arikian S, et al. A multinational pharmacoeconomic evaluation of acute major depressive disorder (MDD): a comparison of cost-effectiveness between venlafaxine, SSRIs and TCAs. Value Health 2001;4:16–31