

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

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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.

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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.<sup>1</sup> 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.<sup>2</sup>

However, depressive disorders are also associated with a constellation of physical or somatic symptoms.<sup>1-3</sup> 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.<sup>2,4-6</sup>

The link between depression and somatic symptoms was supported by findings from a study by Kroenke et al.,<sup>6</sup> 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.<sup>6</sup> Further, painful physical symptoms may be a predictor of more severe depression.<sup>4,7</sup> 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.<sup>2,5,8</sup>

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,<sup>9</sup> and depressed patients are 4 times as likely to suffer headaches and 5 times as likely to suffer backaches compared with nondepressed individuals.<sup>9,10</sup> 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<sup>4,6,8</sup>; 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)<sup>11,12</sup>; to keep in mind the large proportion of depressed patients who report physical symptoms as their primary concern<sup>5</sup>; to recognize the potential for depression among these patients; and to keep in mind that the

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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.<sup>13</sup> 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<sup>14</sup> and duloxetine,<sup>15,16</sup> and the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine,<sup>17</sup> 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.<sup>18,19</sup> For example, depletion of NE and 5-HT via administration of the alkaloid reserpine has been shown to induce depressive symptoms.<sup>13,19</sup> Studies have demonstrated that when NE synthesis is blocked, depressed patients who have achieved remission with noradrenergic treatments experience relapse.<sup>20</sup> Similarly, depletion of 5-HT can result in relapse for depressed patients who have been stabilized on treatment with SSRIs.<sup>20</sup> In addition, evidence of changes in brain receptors of suicide victims, such as up-regulation of 5-HT<sub>2A</sub> receptors<sup>18,21</sup> and increased density of  $\alpha_2$  and  $\beta_2$  receptors,<sup>18,19,21,22</sup> 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,<sup>23,24</sup> 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.<sup>25</sup> 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.<sup>2</sup>

Experimental studies in animals have attempted to discern the specific receptors that may be involved by evaluating the effects of  $\alpha$  and 5-HT antagonists on

antidepressant-induced analgesia, but have found mixed results.<sup>26</sup> Recent findings suggest that  $\alpha_1$ -adrenoceptors and 5-HT<sub>2</sub><sup>27</sup> and 5-HT<sub>3</sub> receptors are involved in antinociceptive mechanisms of antidepressant action, while the  $\alpha_2$ -adrenoceptors and 5-HT<sub>1A</sub> receptors are involved minimally or not at all.<sup>26</sup> These results are consistent with the findings of earlier research, which reported similar reductions in analgesic effects when receptor-blocking agents were introduced.<sup>26,28,29</sup> In contrast, other findings have suggested a role for  $\alpha_2$ -adrenoceptors in antidepressant analgesia,<sup>26,30,31</sup> such as evidence of the efficacy of clonidine (an  $\alpha_2$  agonist) in the relief of neuropathic and cancer pain.<sup>26,32,33</sup> Some reports suggest that 5-HT<sub>1A</sub> and 5-HT<sub>3</sub> receptors may be involved in 5-HT-induced pain.<sup>26,34,35</sup> 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<sup>36–38</sup> 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<sup>39</sup>; 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.<sup>36,40</sup>

For example, findings suggest that selectively modulating 5-HT neurotransmission may be particularly useful in managing symptoms of general distress, irritability/aggression, and anxiety.<sup>36,41</sup> 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.<sup>41–45</sup> 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.<sup>41–45</sup> 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.<sup>43,46,47</sup>

By contrast, noradrenergic neurotransmission has been linked to anhedonia, lack of motivation, and loss of interest.<sup>36,39</sup> 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.<sup>41,48</sup> 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.<sup>41,49-51</sup>

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,<sup>3,52,53</sup> 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.<sup>52</sup>

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:  $\mu$ ,  $\delta$ ,  $\kappa_1$ , and  $\kappa_3$ ; mirtazapine:  $\mu$  and  $\kappa_3$ ).<sup>54</sup> Other investigations have demonstrated inhibition of analgesic effects of antidepressants upon administration of naloxone, an opioid antagonist.<sup>55</sup> 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.<sup>55</sup> 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.<sup>56</sup>

Thus, although complex interactions between neurotransmitter systems<sup>36-38</sup> 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.<sup>51</sup> 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).<sup>49,50</sup> 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.<sup>51</sup>

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.<sup>57</sup> 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%,  $p < .001$ ).<sup>57</sup> 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 ( $p < .001$ ).<sup>58</sup> 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<sup>59</sup> 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).<sup>60,61</sup> Findings in some trials of TCAs have shown that improvement in physical symptoms parallels improvement in depressed mood.<sup>62</sup> However, other evidence suggests that the effects of antidepressants on pain and somatic symptoms are independent of the drugs' effects on psychological symptoms.<sup>53,60,61</sup>

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

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<sup>70</sup> and with humans,<sup>71</sup> as well as in clinical trials of several pain states. Randomized, placebo-controlled trials have demonstrated the efficacy of venlafaxine in preventing migraine headaches<sup>72</sup> and in relieving

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

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,<sup>56</sup> and some clinical evidence suggests that the SSRI may provide pain relief similar to amitriptyline in patients with musculoskeletal pain<sup>84</sup> and may be useful in the treatment of such conditions as fibromyalgia<sup>85</sup> or chronic headache.<sup>60</sup> There are also data to suggest that paroxetine or citalopram may be effective in treating diabetic neuropathy.<sup>86,87</sup> In a study of amitriptyline and citalopram, however, citalopram did not demonstrate a significant analgesic effect in patients with chronic tension headaches.<sup>67</sup> Additionally, reports from open or uncontrolled studies and case reports suggest that other non-SSRI antidepressants, such as mirtazapine,<sup>88</sup> bupropion SR,<sup>89,90</sup> or trazodone,<sup>91</sup> 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).<sup>58</sup> 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.<sup>92</sup> 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).<sup>7,93</sup> 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.<sup>7,93,94</sup>

### 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.<sup>51,95</sup> 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,<sup>96</sup> and a study of fluoxetine in patients with fibromyalgia found the SSRI to be well tolerated.<sup>85</sup> In general, the dual-acting antidepressants (i.e., SNRIs) have tolerability profiles comparable to those of SSRIs.<sup>94,97,98</sup> In addition, these antidepressants are also well tolerated among patients who present with baseline anxiety or somatic symptoms<sup>7,99</sup> and among those who suffer from chronic painful conditions.<sup>60,76</sup> 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.<sup>100</sup> 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.<sup>100</sup>

### 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,<sup>101,102</sup> comparable to the disability associated with chronic illnesses like diabetes, rheumatoid arthritis, and hypertension.<sup>103</sup> 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).<sup>104-107</sup> Evidence demonstrates that depressive and anxiety disorders are associated with higher rates and costs of health care utilization compared with the general population.<sup>108,109</sup> In fact, projections suggest that by 2020, depression will represent the second-largest global disease burden.<sup>110</sup>

The costs associated with depression and anxiety result in the significant economic burden with these disorders.<sup>103,111</sup> 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.<sup>111</sup> 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).<sup>111</sup> 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%.<sup>103,112</sup> A 10-year update of the 1990 data using the same methodological framework<sup>9</sup> 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.<sup>103</sup>

### 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.<sup>113-115</sup> As mentioned above, treatment with an SNRI improves the likelihood of achieving remission (as defined by standardized symptom rating criteria) compared with SSRI treatment.<sup>57,58</sup> 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.<sup>116</sup> 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;  $p = .0001$ ).<sup>116</sup> 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.<sup>117</sup> 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).<sup>118,119</sup>

### 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.<sup>120-122</sup> Although the SSRIs typically have higher acquisition costs, these are consistently outweighed by lower treatment costs.<sup>123</sup>

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.<sup>120,124</sup> 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.<sup>124</sup> In addition, total 6-month health care expenditures with SNRIs versus SSRIs as first-line therapy were comparable.<sup>120</sup> Moreover, there were cost advantages to SNRI treatment in certain subgroups. Specifically, the SNRI venlafaxine was associated with significantly lower inpatient expenditures than SSRIs<sup>120</sup> and had a lower cost per successfully treated patient and cost per symptom-free day compared with SSRIs and TCAs.<sup>108,125</sup>

## 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).

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