

# Single-Action Versus Dual-Action Antidepressants

Rakesh Jain, M.D.

Selective serotonin reuptake inhibitors (SSRIs) have become the most popular antidepressants over the last decade, largely because they have a better side effect profile than the medications that were widely used previously, the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs). The SSRIs mostly have one main mechanism of action, inhibition of serotonin reuptake. A few of the TCAs are single action but many are dual action, acting mainly on the neurochemicals serotonin and norepinephrine, among others. The MAOIs are multiple-action medications, acting on monoamines, which include serotonin and norepinephrine. While the selectivity of the SSRIs results in an improved side effect profile over the earlier dual-action antidepressants, it may also reduce their antidepressant effect. SSRIs may have a slower onset of action, result in lower remission rates, and be less effective for the physical symptoms associated with depression than TCAs and MAOIs. Newer dual-action medications have been developed that inhibit the reuptake of both serotonin and norepinephrine. These medications, called serotonin-norepinephrine reuptake inhibitors, may have fewer side effects than the earlier dual-action medications and potentially reduce the symptoms of depression more effectively than the SSRIs. *(Prim Care Companion J Clin Psychiatry 2004;6[suppl 1]:7-11)*

Over the last decade, selective serotonin reuptake inhibitors (SSRIs) have become the most widely used class of antidepressants. Because the SSRIs act mainly on a single neurochemical, serotonin, they are single-action antidepressants. SSRIs have enjoyed acceptance among clinicians and patients mainly because of a better side effect profile than the medications that were popular previously, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). While a few of the TCAs are single action, many are dual action, acting mainly on the neurochemicals serotonin and norepinephrine, among others (Table 1). The MAOIs are multiple-action medications, acting on the monoamines, which include serotonin and norepinephrine. While the TCAs and MAOIs are still very useful medications, the side effect profiles of these medications limit clinical usefulness in many patients. The SSRIs were developed in an attempt to produce medications that caused fewer intolerable side effects by refining the mechanism of action while maintaining antidepressant efficacy.

Recently, some concerns have been raised that the single-action SSRIs may be less effective than the dual-action TCAs and MAOIs. The SSRIs may have a slower onset of action, lower remission rates, and less efficacy in controlling the physical symptoms of depression than

dual-action antidepressants. During the past few years, there has been a strong interest in the development of dual-action antidepressants with a better side effect profile. These research efforts have produced several new, well-tolerated dual-action antidepressants. Currently, the list of second-generation dual-action antidepressants includes the dual-action serotonergic and dopaminergic antidepressant bupropion and the dual-action serotonergic and noradrenergic antidepressants mirtazapine and venlafaxine, with duloxetine expected to be fully approved by the U.S. Food and Drug Administration (FDA) soon.

## EVIDENCE FOR THE ADVANTAGE OF DUAL-ACTION OVER SINGLE-ACTION MEDICATIONS

Delgado et al. performed serotonin and norepinephrine depletion studies<sup>1,2</sup> that support the theory that the antidepressant effects exerted by serotonergic and noradrenergic antidepressants are not entirely overlapping. When patients who had responded to primarily serotonergic medications were given a diet that depleted their serotonin levels, their symptoms returned, and when patients who responded to primarily noradrenergic medications were given a diet that depleted their norepinephrine levels, their symptoms returned. However, when the patients who responded to primarily serotonergic medications were depleted of norepinephrine, their symptoms did not significantly increase, and when the patients who responded to primarily noradrenergic medications were depleted of serotonin, their symptoms did not significantly increase. The theoretical conclusion one might derive from these depletion studies is that addressing both the serotonergic and noradrenergic aspects of depression might lead to broader antidepressant effects in an individual patient.

---

*From the Department of Psychiatry, University of Texas Medical School, Houston, and R/D Clinical Research, Inc., Lake Jackson, Tex.*

*This article is derived from the teleconference "New Treatments for Depression Characterized by Physical Symptoms," which was held May 15, 2003, and supported by an unrestricted educational grant from Eli Lilly and Company.*

*Corresponding author and reprints: Rakesh Jain, M.D., 135 Oyster Creek Dr., Suite G, Lake Jackson, TX 77566.*

**Table 1. Classes of Antidepressant Medications**

Tricyclic antidepressants
Amitriptyline
Clomipramine
Desipramine
Imipramine
Maprotiline
Monoamine oxidase inhibitors
Isocarboxazid
Phenelzine
Tranlylcypromine
Selective serotonin reuptake inhibitors
Citalopram
Escitalopram
Fluoxetine
Paroxetine
Sertraline
Norepinephrine and dopamine reuptake inhibitor
Bupropion
Noradrenergic and specific serotonergic antidepressant
Mirtazapine
Serotonin and norepinephrine reuptake inhibitors
Duloxetine <sup>a</sup>
Venlafaxine

<sup>a</sup>Still in U.S. Food and Drug Administration approval process.

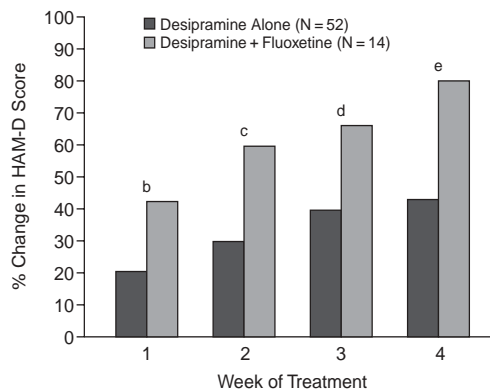
Research by Blier<sup>3</sup> also appears to indicate that noradrenergic interventions can enhance not only noradrenergic firing but also promote serotonergic firing, thereby creating synergism.

**COMBINING MEDICATIONS TO RECEIVE THE BENEFITS OF NOREPINEPHRINE AND SEROTONIN**

Evidence derived from clinical practice provides another window into the understanding of single-action antidepressants versus dual-action antidepressants. Antidepressant prescribing trends over the last few years reveal that clinicians frequently choose to augment partial responders to SSRIs with bupropion,<sup>4</sup> a norepinephrine and dopamine reuptake inhibitor that, in effect, creates a dual-action antidepressant treatment.

Nelson et al.<sup>5</sup> performed an open, 4-week trial comparing the antidepressant effects of the single-action TCA desipramine versus treatment with the combination of desipramine and the SSRI fluoxetine. Seventeen of 19 consecutive patients admitted to a general hospital for nonpsychotic major depression were given 20 mg/day of fluoxetine and 40 to 225 mg/day of desipramine in combination; 14 of the patients enrolled completed the study. Their results were then compared retrospectively with those of 52 patients in the same hospital who received 50 to 500 mg/day of desipramine alone. Not only did desipramine and fluoxetine in combination have a faster onset of action than desipramine alone, but the combination of the serotonergic (fluoxetine) and noradrenergic (desipramine) medications together was superior to desipramine alone in overall antidepressant effect. After the first week of treatment, the mean decrease in scores on the Hamilton Rating

**Figure 1. Percent Change in Hamilton Rating Scale for Depression (HAM-D) Scores in Patients Receiving Desipramine Plus Fluoxetine and Desipramine Alone<sup>a</sup>**



<sup>a</sup>Reprinted with permission from Nelson et al.<sup>5</sup>

<sup>b</sup>p = .007.

<sup>c</sup>p = .001.

<sup>d</sup>p = .004.

<sup>e</sup>p = .0001.

Scale for Depression (HAM-D) in the group given both medications was 42%, while the mean decrease in scores in the group given desipramine alone was 20% (Figure 1). The combination of desipramine and fluoxetine was superior in antidepressant effect throughout all 4 weeks of the study.

**SSRIs VS. OLDER DUAL- AND SINGLE-ACTION ANTIDEPRESSANTS**

Anderson<sup>6</sup> published a meta-analysis of 25 separate studies comparing SSRIs with TCAs. The results showed that the dual-action TCAs clomipramine and amitriptyline were superior to SSRIs in reducing the symptoms of depression, but the single-action TCAs desipramine, imipramine, and maprotiline were no more efficacious than SSRIs. The TCAs appeared to be less well tolerated than the SSRIs, with a 4.9% greater chance of discontinuation due to adverse events.

Two studies published by the Danish University Antidepressant Group comparing the TCA clomipramine with the SSRIs citalopram<sup>7</sup> and paroxetine<sup>8</sup> demonstrated superior antidepressant effects of the dual-mechanism medication clomipramine over the single-action medications citalopram and paroxetine. In the first study,<sup>7</sup> patients were given either 150 mg/day of clomipramine (N = 52) or 40 mg/day of citalopram (N = 50). Of the patients taking clomipramine, 60% remitted, with a score equal to or less than 7 on the HAM-D, while 28% of patients taking citalopram remitted. In the second study,<sup>8</sup> patients were given either 150 mg/day of clomipramine (N = 46) or 30 mg/day of paroxetine (N = 56). Of the patients taking clomipramine, 57% were in remission, whereas 22% of patients

Table 2. Mechanism of Action and Tolerability of Antidepressant Drug Classes<sup>a</sup>

Effect	Dual-Action Drugs			Selective Serotonin Reuptake Inhibitors		Tricyclic Antidepressants	
	Duloxetine	Mirtazapine	Venlafaxine	Fluoxetine	Paroxetine	Clomipramine	Imipramine
Mechanism of action							
5-HT enhancement	✓	✓	✓	✓	✓	✓	✓
NE enhancement	✓	✓	✓	...	...	✓	✓
α-2 antagonism	...	✓	...	...	...	...	...
α-1 antagonism	...	✓	...	...	...	✓	✓
Histamine <sub>1</sub> antagonism	...	✓	...	...	...	✓	✓
Muscarinic antagonism	...	✓	...	...	...	✓	✓
Tolerability							
Discontinuations due to adverse events	14.6%	16%	11%–19%	12%	20%	21%	33%
Weight gain	0.3%	12%	N/A	< 1%	N/A	9%	N/A
Abnormal ejaculation	0.7%	< 1%	12%–17%	< 1%	7%–13%	< 1%	N/A
Impotence	0.4%	< 1%	6%	2%	2%–6%	4%	N/A
Sustained hypertension	...	...	✓	...	...	✓	...
Orthostatic intolerance	...	✓	✓	...	...	✓	✓
QT prolongation	...	...	✓	...	...	✓	✓
Overdose threat	✓	✓	✓	✓	✓	...	...

<sup>a</sup>Adapted with permission from Tran et al.<sup>10</sup> All percentages are approximations. Abbreviations: 5-HT = serotonin, N/A = not applicable, NE = norepinephrine. Symbols: ✓ = present, ... = absent.

taking paroxetine were in remission. However, although the patients treated with clomipramine had better remission rates than those treated with paroxetine and citalopram, the TCA also had an inferior side effect profile.

#### SINGLE-ACTION SSRI VS. NEWER DUAL-ACTION ANTIDEPRESSANTS

In recent years, newer and better-tolerated dual-action antidepressants have been developed that are of significant clinical interest to practicing physicians. These include mirtazapine, venlafaxine, and the investigational medication duloxetine. Venlafaxine and duloxetine are serotonin-norepinephrine reuptake inhibitors (SNRIs), while mirtazapine acts on both serotonin and norepinephrine, but not through reuptake inhibition. The new dual-action antidepressants may provide a faster speed of onset and higher rates of remission than the older TCAs and MAOIs while avoiding their intolerable side effects.

Mirtazapine, a dual-action antidepressant, has demonstrated an earlier onset of action compared with SSRIs. Quitkin et al.<sup>9</sup> recently reviewed several double-blind studies comparing mirtazapine with SSRIs and found that mirtazapine produced a higher proportion of patients showing improvement in the first week. Of patients taking mirtazapine (N = 298), 13% had an onset of persistent improvement in the first week compared with 6% of the patients taking SSRIs (N = 285). Despite having good efficacy, mirtazapine has not become a first-line treatment for depression in most clinical situations because of 2 limiting side effects in a number of patients: weight gain and sedation.

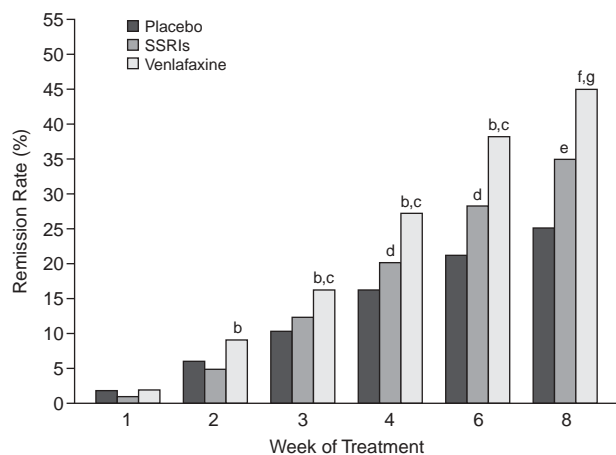
The SNRIs appear to have fewer side effects than the older dual-action medications, TCAs and MAOIs. Venla-

faxine and duloxetine inhibit both norepinephrine and serotonin reuptake but do not bind appreciably to the muscarinic, histaminergic, and α-adrenergic receptors that are believed to be responsible for many of the significant side effects of the TCAs.<sup>10</sup> (Table 2). However, the SNRIs are not side-effect free; venlafaxine is associated with an increased risk of sustained hypertension, especially at high doses.

Thase et al.<sup>11</sup> published a pooled analysis of 8 studies comparing venlafaxine and various SSRIs, including fluoxetine and paroxetine. The authors found that the SSRIs needed 4 weeks to separate from placebo in rates of remission (a score of ≤ 7 on the HAM-D) but venlafaxine needed only 2 weeks to do the same (Figure 2). Also, venlafaxine was superior to the SSRIs in the final remission rate achieved. In this pooled analysis, the remission rate for patients taking placebo was 25%, the remission rate for patients taking an SSRI was 35%, and the remission rate for patients taking venlafaxine was 45%. A follow-up study by Entsuah et al.<sup>12</sup> examined the studies included in the analysis by Thase et al. and found no significant age-by-treatment, gender-by-treatment, or age-by-gender-by-treatment interactions. The remission rates of the patients taking venlafaxine were significantly higher than those of the patients taking SSRIs, regardless of age or gender. These reviews<sup>11,12</sup> support the superior remission abilities of venlafaxine.

Smith et al.<sup>13</sup> analyzed 32 studies in which venlafaxine was compared with various antidepressants and found this SNRI to be significantly more effective in reducing the symptoms of depression than the SSRIs studied, which included fluoxetine, paroxetine, and sertraline. However, venlafaxine had no significant advantage over the TCAs studied, which included amitriptyline, clomip-

Figure 2. Remission Rates for 8 Pooled Studies Comparing Venlafaxine, SSRI, and Placebo Treatment<sup>a</sup>



<sup>a</sup>Reprinted with permission from Thase et al.<sup>11</sup>

<sup>b</sup> $p \leq .05$  for venlafaxine vs. SSRI.

<sup>c</sup> $p \leq .05$  for venlafaxine vs. placebo.

<sup>d</sup> $p \leq .05$  for SSRI vs. placebo.

<sup>e</sup> $p < .001$  for SSRI vs. placebo.

<sup>f</sup> $p < .001$  for venlafaxine vs. SSRI.

<sup>g</sup> $p < .001$  for venlafaxine vs. placebo.

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

ramine, and desipramine. This analysis strongly supports the case that dual-action antidepressants produce more robust remission effects in depression than SSRIs.

Duloxetine, currently pending FDA approval, is an SNRI but is significantly more potent than venlafaxine.<sup>14</sup> Bymaster et al.<sup>15</sup> published in vitro data showing that duloxetine is the most potent nontricyclic dual reuptake inhibitor, with inhibition constants ( $K_i$ ) of 0.8 nM for the serotonin transporter and 7.5 nM for the noradrenergic transporter (Table 3). While there are no published head-to-head clinical studies comparing duloxetine with venlafaxine for the treatment of major depression, the comparison of the  $K_i$  values of duloxetine and venlafaxine shows duloxetine to be substantially more potent at both the serotonin and norepinephrine reuptake inhibitor sites.

A number of placebo-controlled, randomized clinical trials<sup>16-18</sup> on duloxetine for the treatment of major depression have been conducted across the dose range of 40 to 120 mg/day, with a recent emphasis on 60 mg once-a-day dosing, and have had positive results. An 8-week, double-blind study by Goldstein et al.<sup>16</sup> compared duloxetine with fluoxetine for the treatment of major depressive disorder. Patients were randomly assigned to treatment with a dose of duloxetine titrated from 40 to 120 mg/day ( $N = 70$ ), 20 mg/day of fluoxetine ( $N = 33$ ), or placebo ( $N = 70$ ). Duloxetine was superior to the SSRI in producing remission, with rates of 30% for fluoxetine and 45% for duloxetine by last-observation-carried-forward analysis and 30% for fluoxetine and 56% for duloxetine by estimated probability of remission.

Table 3.  $K_i$  Values of Various Antidepressants<sup>a</sup>

Medication	Serotonin Reuptake Transporter (nM)	Norepinephrine Reuptake Transporter (nM)
Duloxetine <sup>b</sup>	0.8	7.5
Imipramine <sup>c</sup>	19	98
Venlafaxine <sup>b</sup>	82	2483
Fluoxetine <sup>c</sup>	7	1022

<sup>a</sup>Lower  $K_i$  values represent stronger affinity.

<sup>b</sup>Data from Bymaster et al.<sup>14</sup>

<sup>c</sup>Data from Bymaster et al.<sup>15</sup>

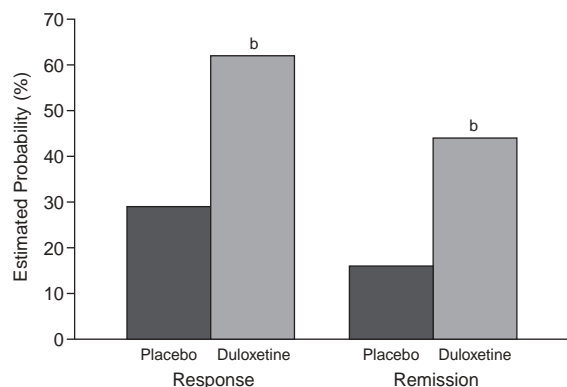
## ANTIDEPRESSANTS AND PAIN

Dual-action antidepressants may be especially more effective than single-action antidepressants in treating the somatic symptoms that frequently occur in depression. The dual-action TCAs and MAOIs are more effective for the painful physical symptoms associated with depression than the SSRIs, but their side effects make them less tolerable.<sup>19,20</sup> It is worth noting that an older dual-action antidepressant, the tricyclic amitriptyline, has enjoyed wide clinical use for the treatment of chronic pain conditions, in either the presence or absence of depression. The doses typically used are low, mostly because of side effects such as sedation, weight gain, dizziness, cardiac conduction effects, dry mouth, urinary hesitation, and others.

Studies have demonstrated the effectiveness of duloxetine in reducing the somatic symptoms associated with depression. Coexisting somatic symptoms were assessed prospectively in 2 paired major depression trials comparing duloxetine with placebo.<sup>17,18</sup> In these two 9-week trials, a total of 512 patients were randomly assigned to treatment with either 60 mg/day of duloxetine or placebo. A visual analog scale was used to assess pain symptoms. In the first study,<sup>17</sup> the estimated probability of remission for patients taking duloxetine was 44%, almost 3 times that of the probability of remission for patients taking the placebo (16%) (Figure 3). In the second study,<sup>18</sup> duloxetine was also significantly superior to placebo, with remission rates of 43% for patients taking duloxetine and 28% for patients taking placebo. Both studies also concluded that duloxetine significantly reduced the painful physical symptoms associated with depression compared with placebo. Patients in both studies improved in overall pain, back pain, shoulder pain, and time in pain while awake.

Venlafaxine has also been studied in patients with chronic pain conditions. Kunz et al.<sup>21</sup> reported results of a study of the effects of venlafaxine in diabetic neuropathic pain. A dose of 75 mg/day of venlafaxine, a low level thought to have only the efficacy of SSRIs, did not separate from the placebo in reduction of pain intensity. However, doses of 150 to 225 mg/day of venlafaxine did produce a significant reduction in pain intensity. This study supports the widely held clinical belief that medications that offer both serotonergic and noradrenergic interven-

**Figure 3. Estimated Probability of Response and Remission of Placebo (N = 115) and Duloxetine (N = 121) Treatment Groups<sup>a</sup>**



<sup>a</sup>Reprinted with permission from Detke et al.<sup>17</sup>

<sup>b</sup> $p < .001$  for duloxetine vs. placebo.

tions can be helpful in treating somatic symptoms, whether in the presence or absence of depression.

### CONCLUSION

Although the single-action SSRIs are still the most commonly prescribed antidepressants, dual-action antidepressants are experiencing a surge in scientific and clinical interest, particularly because the newer dual-action antidepressants mirtazapine, venlafaxine, and duloxetine enjoy a more benign side effect profile than the earlier dual-action antidepressants, the TCAs and MAOIs. While the TCAs and MAOIs are effective in treating depression, they have an inferior side effect profile that makes them less tolerable. While the SSRIs have fewer side effects than the TCAs and MAOIs, and have been extremely useful overall as a class of antidepressants, there are many indications in clinical practice and in research trials that dual-action serotonin and norepinephrine inhibitors are more effective than SSRIs in treating depression. SNRIs such as venlafaxine and duloxetine may have an earlier onset of action, superior remission abilities, and better efficacy in treating the physical symptoms of depression than the SSRIs. This makes further research and clinical exploration of this class of antidepressants very exciting.

**Drug names:** amitriptyline (Elavil and others), bupropion (Wellbutrin and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), escitalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), isocarboxazid (Marplan), maprotiline (Ludiomil and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor).

**Disclosure of off-label usage:** The author has determined that, to the best of his knowledge, amitriptyline and venlafaxine are not approved

by the U.S. Food and Drug Administration for the treatment of chronic pain conditions; and duloxetine is not approved for the treatment of depression.

### REFERENCES

- Delgado PL, Charney DS, Price LH, et al. Serotonin function and the mechanism of antidepressant action: reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. *Arch Gen Psychiatry* 1990;47:411–418
- Miller HL, Delgado PL, Salomon RM, et al. Clinical and biochemical effects of catecholamine depletion on antidepressant-induced remission of depression. *Arch Gen Psychiatry* 1996;53:117–128
- Blier P. Possible neurobiological mechanisms underlying faster onset of antidepressant action. *J Clin Psychiatry* 2001;62(suppl 4):7–11
- Mischoulon D, Nierenberg AA, Kizilbash L, et al. Strategies for managing depression refractory to selective serotonin reuptake inhibitor treatment: a survey of clinicians. *Can J Psychiatry* 2000;45:476–481
- Nelson JC, Mazure CM, Bowers MB Jr, et al. A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. *Arch Gen Psychiatry* 1991;48:303–307
- Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 1998;7(suppl 1):11–17
- Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. *Psychopharmacology* 1986;90:131–138
- 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
- Quitkin FM, Taylor BP, Kremer C. Does mirtazapine have a more rapid onset than SSRIs? *J Clin Psychiatry* 2001;62:358–361
- Tran P, Bymaster FP, McNamara RK, et al. Dual monoamine modulation for improved treatment of major depressive disorder. *J Clin Psychopharmacol* 2003;23:78–86
- Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 2001;178:234–241
- Entsuah AR, Huang H, Thase ME. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. *J Clin Psychiatry* 2001;62:869–877
- Smith D, Dempster C, Glanville J, et al. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. *Br J Psychiatry* 2002;180:396–404
- 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
- Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 2002;27:699–711
- Goldstein DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: a double-blind, placebo-controlled trial. *J Clin Psychiatry* 2002;63:225–231
- 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
- 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
- Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999;88:389–400
- Barkin RL, Fawcett J. The management challenges of chronic pain: the role of antidepressants. *Am J Ther* 2000;7:31–47
- Kunz NR, Goli V, Entsuah R, et al. Diabetic neuropathic pain management with venlafaxine extended release. *Eur Neuropsychopharmacol* 2000;10(suppl 3):S389