Plotting the Course to Remission: The Search for Better Outcomes in the Treatment of Depression

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Depression includes a wide range of symptoms that can impair a person's psychosocial and physical functioning. This impairment can lead to decreased productivity, increased health care utilization, alcohol and substance abuse, and an increased risk of suicide. While the treatment of depression has significantly advanced over the past 30 years, there is still room for improvement. Full remission of depressive symptoms is often elusive, and many patients never achieve full relief from their depression despite being regarded as responders to antidepressant treatment. Current treatments for depression tend to focus on emotional symptoms, not the physical and anxious symptoms also associated with depression. However, the physical and anxious symptoms of depression can be serious and sometimes more prominent than the emotional symptoms of depression, especially among special populations such as women. New treatment strategies, such as dual-acting agents and the combination of pharmacotherapy and psychotherapy, target the emotional and anxious symptoms of depression as well as symptoms associated with pain. In order to increase response and remission, depression should be seen as an illness comprising not only emotional symptoms but physical and anxious symptoms as well. *(J Clin Psychiatry 2004;65[suppl 12]:20–25)*

Response to an antidepressant medication is frequently the main goal in treating depression; however, treatment response does not guarantee a remission of depressive symptoms. Many patients treated with antidepressants who achieve a response never achieve a full remission of their depressive symptoms. A lack of full remission can be detrimental to a patient's well-being, placing him or her at a 50% to 80% risk for relapse of depressive symptoms.[1] With potentially more than 50% of patients treated for depression at risk for relapse, the aim of depression treatment has begun to shift from a goal of achieving a response to one of achieving a full remission of depressive symptoms.

In order to achieve a full remission of symptoms among patients with depression, clinicians need to focus on the entire spectrum of depression symptomatology. Besides the emotional symptoms of depression such as sad mood and hopelessness, other factors such as physical symptoms and anxiety affect remission. Although weight loss and gain, insomnia, and fatigue are included in the classification criteria of depression,[2] as many as 76% of patients with depression suffer from other, more painful physical complaints such as backache and chest pain.[3] Chronic and painful physical symptoms occur 4 times more often in people with major depressive disorder than in people without major depressive disorder.[4] These symptoms can significantly impair patients' daily functioning and delay the onset of remission. The majority of patients with major depressive disorder suffer from anxiety disorders as well.[5,6] Women tend to suffer from depression with pain and anxiety at higher rates than men. Analyses of data from the National Comorbidity Survey[7] and Epidemiologic Catchment Area Survey[8] revealed that while the rates of pure depression (Figure 1) are similar between women and men, women are twice as likely to suffer from anxious somatic depression (Figure 2) as men.[9,10] Achieving a full remission of depression requires a renewed awareness of the spectrum of depressive symptoms as well as knowledge of treatments that target all the symptoms of depression.

SYNERGISTIC EFFECTS OF NOREPINEPHRINE AND SEROTONIN

Currently, many antidepressant treatments focus on alleviating the emotional symptoms of depression and overlook painful and anxious symptoms that are also associated with depression. Traditionally, antidepressants have

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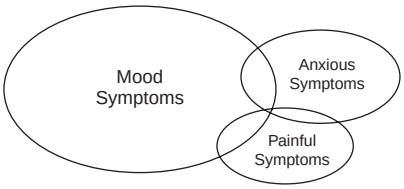
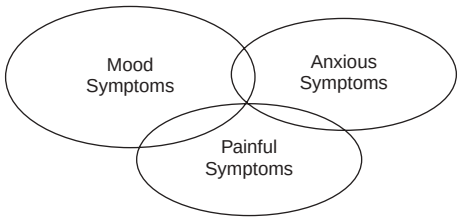
Figure 1. Pure Depression: Equally Common in Women and Men[a]



[a]Based on Silverstein.[9,10]

Figure 2. Anxious Somatic Depression: More Common in Women Than in Men[a]



[a]Based on Silverstein.[9,10]

been single-acting agents, functioning on either serotonin or norepinephrine neurotransmitters. However, serotonin and norepinephrine are considered to be shared biochemical mediators of depression, and the physical, anxious, and emotional symptoms of depression are affected by both neurologic pathways. Evidence[11–14] suggests that antidepressant treatments that modulate both pathways may be more effective in treating depression to full remission. For example, Nelson and colleagues[11] found that treatment with a combination of 2 single-action agents, fluoxetine (a serotonergic agent) and desipramine (a noradrenergic agent), was associated with a significantly higher rate of remission than either agent alone ($p = .001$).

The efficacy of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) was compared in a meta-analysis of 25 double-blind studies.[12] Dual-acting TCAs, such as clomipramine and amitriptyline, but not single-acting TCAs (e.g., desipramine), were significantly superior to SSRIs in terms of efficacy ($p = .017$).

That dual-acting TCAs are superior to single-acting SSRIs was also confirmed in 2 separate trials[13,14] by the Danish University Antidepressant Group. Both trials were double-blind multicenter studies that included patients with Hamilton Rating Scale for Depression (HAM-D) scores of ≥ 18 and/or a HAM-D subscale score of ≥ 9, and a DSM-III diagnosis of major depression. In one study,[13] 120 participants were randomly assigned to either clomipramine (150 mg/day) or paroxetine (30 mg/day) for 6 weeks. Participants ($N = 102$) in the second study[14] were randomly assigned to clomipramine (150 mg/day) or citalopram (40 mg/day) for 5 weeks. In both trials, a significantly larger percentage of clomipramine-treated patients (50% to 60% in study 1, 60% in study 2) were classified as responders when compared with paroxetine-treated patients (20% to 25%) and citalopram-treated patients (30%) ($p < .005$, each).

Although evidence[12–14] suggests that dual-acting TCAs are more efficacious than single-acting SSRIs in achieving a full remission of depressive symptoms, TCAs are not commonly the treatment of choice among psychiatrists due to their problematic side effect profile. Other dual-acting agents, such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and noradrenergic and specific serotonergic antidepressants (NaSSAs), are also associated with the increased efficacy found in dual-acting TCAs. Studies[15,16] comparing SNRIs and NaSSAs with single-acting SSRIs indicate that these dual-acting agents have similar tolerability to SSRIs and may be more effective than SSRIs in regards to relief, response, and remission.

Dual-Action Agents: Tolerability and Efficacy Against Depression

Venlafaxine and duloxetine (SNRIs) and mirtazapine (an NaSSA) are similar to TCAs in that they function via both the serotonin and norepinephrine pathways; however, unlike TCAs, the SNRIs and NaSSAs have somewhat different side effect profiles and are not lethal in overdose.[17,18] TCAs can have anticholinergic, histaminic, and adrenergic effects. Venlafaxine at higher doses can exert adverse cardiovascular effects, particularly hypertension. Mirtazapine may be associated with increased appetite, weight gain, and somnolence. The most common side effect of duloxetine is nausea.[19]

In an analysis of 8 double-blind studies, Thase and colleagues[15] found that venlafaxine and SSRI treatments had similar tolerability in patients treated for depression. The rate of discontinuation was slightly higher among venlafaxine-treated patients (9%) than SSRI-treated patients (7%). However, as early as week 2 a statistically significant improvement ($p \leq .05$) was seen with venlafaxine when compared with SSRIs. Final remission rates were also higher with venlafaxine treatment than SSRI treatment, with 45% of venlafaxine-treated patients and 35% of SSRI-treated patients achieving remission ($p < .001$).

Mirtazapine has also been found to have similar discontinuation rates when compared with SSRIs and is significantly more efficacious in reducing the symptoms of depression. In one study,[16] 133 patients with a DSM-III-R diagnosis of major depression and a total score of ≥ 21 on the HAM-D and ≥ 2 on the HAM-D item 1 (depressed mood) were randomly assigned to receive mirtazapine (mean daily dose 39.8 mg) or fluoxetine (mean daily dose 23.8 mg) for 6 weeks. Although not statistically significant, the percentage of patients who

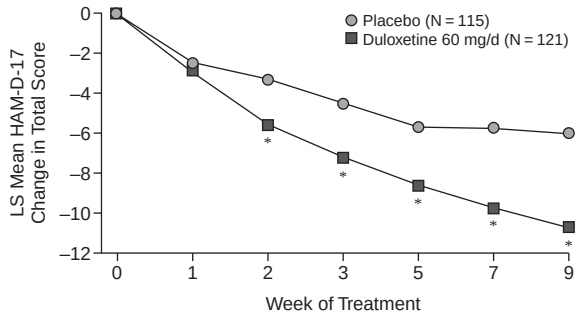
discontinued treatment due to adverse effects was higher among fluoxetine-treated patients (13.4%) than among mirtazapine-treated patients (10.6%). In terms of efficacy, the reduction from baseline in group mean 17-item HAM-D (HAM-D-17) scores was found to be significantly larger among mirtazapine-treated patients than among fluoxetine-treated patients at week 3 ($p = .016$) and week 4 ($p = .009$). By week 4, the mirtazapine group also had a significantly larger decrease from baseline on depressed mood item scores than the fluoxetine group ($p = .04$).

Several studies[15,16] have demonstrated the superior efficacy and similar tolerability of venlafaxine and mirtazapine compared with SSRIs. Guelfi and colleagues[20] conducted a double-blind study comparing the efficacy and tolerability of venlafaxine with mirtazapine. Participants ($N = 157$) with a DSM-IV diagnosis of chronic depression with melancholic features were randomly assigned to treatments with mirtazapine (mean daily dose 49.5 ± 8.3 mg) or venlafaxine (mean daily dose 255 ± 59.8 mg) for 8 weeks. Both medications were found to be equally effective in reducing the overall symptoms of depression, with substantial reductions in the group mean Montgomery-Asberg Depression Rating Scale and HAM-D-17 scores. In terms of tolerability, significantly more patients (15.3%) treated with venlafaxine dropped out due to adverse effects than patients treated with mirtazapine (5.1%) ($p = .037$).

Duloxetine has also been found to have higher rates of response and remission when compared with placebo and SSRIs.[21,22] In a double-blind randomized trial, Detke and colleagues[21] found that duloxetine (60 mg/day) had significantly greater estimated probabilities of response and remission by week 9 when compared with placebo ($p < .001$). Response was noted in 45% of duloxetine-treated patients and 23% of placebo-treated patients ($p < .001$), and remission was achieved by 31% of duloxetine-treated patients and 15% of placebo-treated patients ($p = .003$). Of the 123 patients receiving active treatment, only 17 discontinued the trial, suggesting good tolerability. Clinicians rated most adverse effects as mild or moderate, and nausea was the most common adverse effect.

In an analysis[22] of the remission rates of duloxetine versus SSRIs, data were pooled from 6 randomized, double-blind, placebo-controlled clinical trials. Remission was defined as a score of ≤ 7 on the HAM-D-17. Both SSRI and duloxetine treatment had significantly higher rates of remission than placebo ($p < .001$). Although a higher rate of remission was seen with duloxetine treatment (43%) than SSRI treatment (38.3%), this rate was not statistically significant.

Figure 3. SNRI Versus Placebo in Major Depressive Disorder: HAM-D-17 Total Score[a]



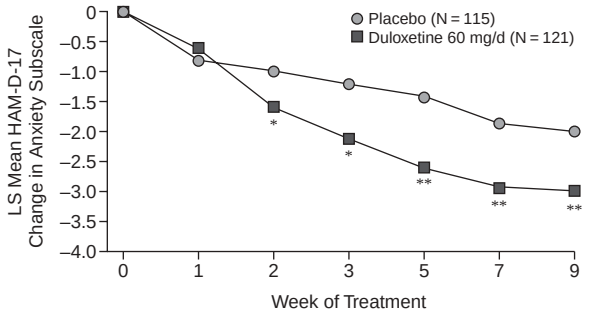
[a]Reprinted with permission from Detke et al.[21]
*$p < .001$.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LS = least squares, SNRI = serotonin-norepinephrine reuptake inhibitor.

Pain, Anxiety, and SNRIs

In order to achieve better remission rates, it is also important for antidepressant treatment to address both the painful physical symptoms and the anxious symptoms that are part of the depressive picture. Dual-acting agents such as venlafaxine at higher doses and duloxetine may have particular utility in achieving relief from the physical, anxious, and negative mood symptoms of depression. While both venlafaxine and duloxetine are effective and tolerable antidepressants, duloxetine has been shown to have a higher affinity for serotonin and norepinephrine transporters.[23] Thus, in addition to being efficacious in the treatment of negative mood, anxiety, and physical discomfort associated with major depressive disorder, in placebo-controlled trials[20,23,24] duloxetine appears to have greater potential for rapidly alleviating both the painful physical and anxious symptoms of depression.

In a double-blind, placebo-controlled trial,[21] the efficacy of duloxetine in alleviating painful physical symptoms was observed over a 9-week period. Participants ($N = 245$) diagnosed with major depressive disorder were randomly assigned to placebo or duloxetine (60 mg/day) treatment. As early as week 2, duloxetine was significantly superior to placebo in reducing HAM-D-17 total scores ($p < .001$) (Figure 3). When compared with placebo, duloxetine also significantly reduced scores on item 12 (somatic symptoms) of the HAM-D-17 ($p = .013$). Compared with placebo-treated patients, depressed patients treated with duloxetine experienced significantly greater improvement in overall pain, back pain, shoulder pain, and amount of time spent in pain while awake and found that there was less interference of daily activities due to pain ($p < .001$). Significantly greater improvement was seen with duloxetine than placebo in 5 of the 6 Visual Analog Scale (VAS) measures (overall pain, back pain, shoulder pain, amount of time in pain while awake, and interference with daily activities due to pain) at least once during the treatment period ($p < .001$, on each of these measures).

Figure 4. SNRI Versus Placebo in Major Depressive Disorder: Improvement in HAM-D-17 Anxiety Subscale[a]



[a]Reprinted with permission from Dunner et al.[25]
*p < .05.
**p < .005.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LS = least squares, SNRI = serotonin-norepinephrine reuptake inhibitor.

Dunner and colleagues[25] analyzed the effects of duloxetine on anxiety symptoms associated with depression. Data from 4 randomized, double-blind, placebo-controlled studies of patients who were depressed based on the Mini-International Neuropsychiatric Interview and DSM-IV diagnosis of major depressive disorder were assessed. By week 2, duloxetine proved to be more effective against anxiety than placebo ($p < .05$), and significant improvement continued to week 9 ($p < .005$) (Figure 4).

THE ROLE OF PSYCHOTHERAPY

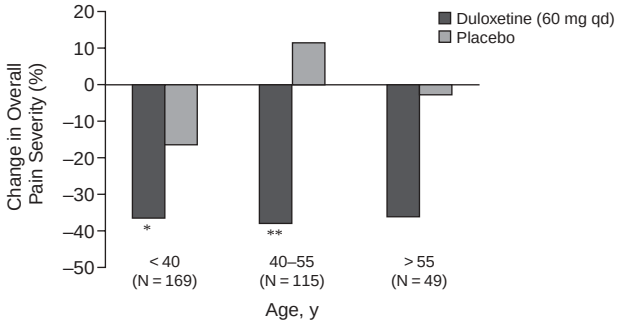
When treating patients with depression, psychiatrists should consider the potential benefits of psychotherapy. Psychotherapies such as interpersonal therapy (IPT) and cognitive-behavioral therapy (CBT), which focus on altering distorted or negative cognition and address interpersonal issues, may be beneficial as monotherapy or may be useful as adjunctive treatments in patients taking psychotropic agents. Despite the widespread use of psychotherapy to treat depression, a review[26] of psychotherapy studies revealed that only 9 studies published before 1998 addressed the efficacy of psychotherapy for recurrent depression and that only 2 of the 9 studies used proper randomization. More studies are clearly needed to assess the role of psychotherapy in the treatment of chronic and single-episode depression.

Recently, in a study by Keller and collegues,[27] the combination of pharmacotherapy and short-term psychotherapy was found to be significantly more efficacious than either pharmacotherapy or psychotherapy alone. Patients between the ages of 18 and 75 years with a DSM-IV diagnosis of chronic depression were randomly assigned to nefazodone treatment (N = 226), psychotherapy treatment (N = 228), or a combination of both nefazodone and psychotherapy treatment (N = 227) for 12 weeks. Participants in the psychotherapy treatment group and the combination treatment group received the Cognitive Behavioral-Analysis System of Psychotherapy (CBASP), a specialized cognitive-behavioral treatment that addresses interpersonal issues, twice a week for 4 weeks and then weekly for the remainder of treatment. Nefazodone dosing began at 200 mg/day in both the nefazodone-treated and combination-treated groups, with the mean final daily dose being 466 ± 144 mg for the nefazodone-treated group and 460 ± 139 mg for the combination-treated group. At endpoint, the combination treatment was found to be significantly more effective than nefazodone or CBASP treatment alone. The rate of response was significantly higher in the combination treatment group (85%) than in the CBASP (52%) or the nefazodone (55%) treatment groups ($p < .001$). Combination-treated patients also had higher rates of remission (42%) than nefazodone-treated (24%) or CBASP-treated (22%) patients by week 12 ($p < .001$).

In another study,[28] the efficacy of 2 different methods of coadministering pharmacotherapy and psychotherapy was observed in women with recurrent unipolar major depression. This study was composed of 339 patients who were randomly assigned to either a combination treatment of psychotherapy and pharmacotherapy or a sequential treatment in which psychotherapy was first administered alone and then nonresponders were prescribed pharmacotherapy in addition to psychotherapy. The combination treatment group received IPT treatment (weekly for 12 weeks, every 2 weeks for 8 weeks, and then monthly) as well as imipramine (at a target dose range of 150–300 mg/day). Sequential treatment involved weekly IPT treatment, and then, if a determination of nonresponse was made, an SSRI was prescribed and adjusted according to patients' needs. Remission was defined as a HAM-D score of ≤ 7 and a Raskin Severity of Depression Scale score of ≤ 5 for 3 weeks. Sequential treatment was found to have a significantly higher rate of remission, 79%, than combination treatment, 66% ($p = .02$). Although sequential treatment is necessarily a slower approach, and therefore may be frustrating for some patients, in special populations, such as pregnant women with depression, sequential treatment may be preferable since this would allow some women to be effectively treated for depression without the use of psychotropic agents.

Although these studies[27,28] found that CBASP and IPT are effective when combined with antidepressants to treat depression, more randomized, placebo-controlled, long-term studies are needed to examine the role of psychotherapy in enhancing response and improving remission. Current data suggest that psychotherapy is a viable option as an adjunctive treatment for depression.

Figure 5. Comparison of Efficacy in Younger and Older Women: VAS Overall Pain[a]



[a]Data from Burt et al.[33]
*p = .043 vs placebo.
**p < .001 vs placebo.
Abbreviation: VAS = Visual Analog Scale.

REMISSION OF DEPRESSION IN WOMEN

In 1990, the leading cause of disease and disability in women of childbearing age (15–44 years) was unipolar major depression.[29] Women are twice as likely as men to have anxious somatic depression.[9] The increased prevalence of depression in women as compared with men is thought to be due to a combination of psychosocial, genetic, and biological factors that include age-related altered roles and relationships, exposure to traumatic experiences, previous depressive history, and differences in temperament.[30,31] In some cases, depression in women appears to be precipitated by reproductive-related transitions, such as the premenstrual, postpartum, postmiscarriage, and perimenopause periods.[32]

A recent analysis[33] of data pooled from 2 identical, double-blind, placebo-controlled, randomized 9-week studies revealed that the SNRI antidepressant duloxetine was an effective treatment for both the emotional and physical symptoms of major depression in a cohort of women aged 40 to 55, an interval that approximates the perimenopausal years. In comparison with placebo-treated subjects, as early as week 1, duloxetine-treated women experienced statistically significant improvement in overall pain scores ($p < .005$) and displayed significant improvement in HAM-D-17 scores by week 2 ($p < .05$). Although the magnitude of improvement for women with major depression in both emotional and painful physical symptoms was similar across all age groups, responses in the placebo-treatment groups differed by age. Thus, the smallest placebo response was observed in the 40- to 55-year-old age group, whereas the greatest placebo response was noted in the group less than 40 years old. With regard to overall pain as measured on the VAS, although all duloxetine-treated groups displayed higher rates of improvement than placebo, women aged < 40 years and 40 to 55 years had statistically significantly better scores compared with those receiving placebo, with the most significant improvement in overall pain experienced by the 40- to 55-year-old age group (< 40 years, $p = .043$; 40–55 years, $p < .001$) (Figure 5).

Dual-acting antidepressants that modulate serotonin and norepinephrine may be effective for the acute treatment of both emotional and physical symptoms of depression in women and may be particularly effective for women of perimenopausal age. Additional studies are required to address the utility of SNRI antidepressants in treating somatic depression in endocrinologically confirmed perimenopausal women.

CONCLUSION

Since serotonin and norepinephrine are shared biochemical mediators in the modulation of depression, newer, balanced, and potent dual-acting agents, such as SNRIs and NaSSAs, may be more effective and tolerable than TCAs and SSRIs in the treatment of depression. Psychotherapy shows promise in enhancing remission rates. Clinicians should aim for full remission of symptoms when treating patients with depression. Achieving remission of depression includes targeting the emotional, physical, and anxious symptoms of depression.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin), duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nefazodone (Serzone and others), paroxetine (Paxil and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, clomipramine is not approved by the U.S. Food and Drug Administration for the treatment of depression; venlafaxine is not approved for the treatment of physical symptoms and pain; and duloxetine is not approved for the treatment of physical symptoms, pain, and anxiety.

REFERENCES

1. Cornwall P, Scott J. Partial remission in depressive disorders. Acta Psychiatr Scand 1997;95:265–271
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
3. Corruble E, Guelfi J. Pain complaints in depressed patients. Psychophathology 2000;33:307–309
4. Ohayon MM, Schatzberg AF. Using pain to predict depressive morbidity in the general population. Arch Gen Psychiatry 2003;60:39–47
5. Fawcett J. Targeting treatment in patients with mixed symptoms of anxiety and depression. J Clin Psychiatry 1990;51(11, suppl):40–43
6. Stein MB, Kirk P, Prabhu V, et al. Mixed anxiety-depression in a primary-care clinic. J Affect Disord 1995;34:79–84
7. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
8. Weissman MM, Livingston BM, Leaf PJ, et al. Affective disorders. In: Robins LN, Regier DA, eds. Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. New York, NY: Free Press; 1991:53–80
9. Silverstein B. Gender difference in the prevalence of somatic versus pure depression: a replication. Am J Psychiatry 2002;159:1051–1052

10. Silverstein B. Gender difference in the prevalence of clinical depression: the role played by depression associated with somatic symptoms. Am J Psychiatry 1999;156:480–482
11. Nelson J, Mazure C, Jatlow P, et al. Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biol Psychiatry 2004;55:296–300
12. Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. Depress Anxiety 1998;7(suppl 1):11–17
13. 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
14. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine: a controlled multicenter study. Psychopharmacology (Berl) 1986;90:131–138
15. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234–241
16. Wheatley D, van Moffaert M, Timmerman L, et al. Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. J Clin Psychiatry 1998;59:306–312
17. Effexor (venlafaxine). Physicians' Desk Reference. 57th ed. Montvale, NJ: Medical Economics; 2003:3413–3418
18. Remeron (mirtazapine). Physicians' Desk Reference. 57th ed. Montvale, NJ: Medical Economics; 2003:2389–2392
19. Schatzberg A. Efficacy and tolerability of duloxetine, a novel dual reuptake inhibitor, in the treatment of major depressive disorder. J Clin Psychiatry 2003;64(suppl 13):30–37
20. Guelfi JD, Anssear M, Timmerman L, et al. Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. J Clin Psychopharmacol 2001;21:425–431
21. 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
22. Thase M, Lu Y, Joliat M, et al. Remission in placebo-controlled trials of duloxetine with an SSRI comparator. In: New Research Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 22, 2003; San Francisco, Calif. Abstract NR840:313–314
23. 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
24. Fava M, Mallinckrodt C, Detke M, et al. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher rates of remission? J Clin Psychiatry 2004;65:521–530
25. Dunner D, Goldstein D, Mallinckrodt C, et al. Duloxetine in the treatment of anxiety symptoms associated with depression. Depress Anxiety 2003;18:53–61
26. Scott J. Where there's a will: cognitive therapy for people with chronic depressive disorders. In: Tarrier N, Wells A, Haddock G, eds. Treating Complex Cases: The Cognitive Behavioral Therapy Approach. Chichester, England: John Wiley; 1998:81–104
27. Keller MB, McCullough JP, Klein DN, et al. Comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342:1462–1470
28. Frank E, Grochocinski V, Spanier C, et al. Interpersonal psychotherapy and antidepressant medication: evaluation of a sequential treatment strategy in women with recurrent major depression. J Clin Psychiatry 2000;61:51–57
29. Murray CJL, Lopez AD, eds. 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
30. Stewart DE. The selling of women's health. J Nerv Ment Dis 2003; 191:561–562
31. Kendler KS, Kessler RC, Neale MC, et al. The prediction of major depression in women: toward an integrated etiologic model. Am J Psychiatry 1993;150:1139–1148
32. Burt VK, Stein K. Epidemiology of depression throughout the female life cycle. J Clin Psychiatry 2002;63(suppl 7):9–15
33. Burt VK, Stewart DE, Mallinckrodt CH, et al. Duloxetine in the treatment of major depressive disorder in women aged 40 to 55 years. Presented at the 2nd World Conference on Women's Mental Health; March 17–20, 2004; Washington, DC