New Developments in the Treatment of Depression

Stuart A. Montgomery, M.D.

Depression is a widespread, recurrent disease that sometimes remains inadequately managed by current drug therapy. There is a need to develop better antidepressants that ideally would have a more rapid onset of action, a higher response rate, and improved long-term efficacy. The latest generation of antidepressants have novel dual modes of action, and the results of recent clinical trials indicate that they may have superior efficacy to established drug therapies such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Dual acting drugs, such as venlafaxine, a serotonin-norepinephrine reuptake inhibitor, and mirtazapine, a noradrenergic and specific serotonergic antidepressant, have been shown to have a rapid onset of action. The long-term efficacy of mirtazapine and of venlafaxine was also found to be superior to that of TCAs. Pindolol was found to accelerate response to SSRI therapy. However, these results were dependent on the patient population. These studies clearly suggest that the latest generation of antidepressants offer a more rapid response to treatment, an improved response rate, and superior long-term efficacy than conventional therapy. The clinical importance of these results should not be overlooked. *(J Clin Psychiatry 1999;60[suppl 14]:10–15)*

Depression is a widespread, sometimes fatal disorder with far-reaching effects on social function and the patient's quality of life. Frequently, depression is undiagnosed and, once diagnosed, can remain difficult to treat. In Europe, among patients with major depression and substantial impairment who consult a doctor, only 10% received antidepressant therapy.[1] For those who do receive treatment, drug therapy is often associated with unpleasant side effects or can simply fail to adequately manage the condition. Thus, there is an ongoing need for improvements to the current treatments for depression. Any advances in drug therapy for the treatment of depression need to focus on the development of drugs that are potentially superior to the established treatments such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). There are a number of key characteristics that any new antidepressant agent should aim to have (Table 1). New antidepressant agents should have a faster onset of action than existing therapies, and, ideally, a higher proportion of patients should respond to treatment. The long-term efficacy of conventional treatments could also be improved. In addition, it would also be desirable to see benefits in the treatment of resistant depression or currently untreatable types of depression such as recurrent brief depression.

The results of some recent clinical studies suggest that recent advances in antidepressant therapy may lead to significant advantages over current conventional therapy. This article reviews some studies that provide data on the onset of action, the number of patients responding to treatment, and long-term efficacy for the newest classes of antidepressants.

EARLY ONSET OF ACTION

The development of an antidepressant with an early onset of action would offer a range of clinical advantages. Patients requiring hospitalization would potentially require a shorter stay in hospital. The debilitating symptoms of depression could be relieved more quickly, and the risk of suicide might be lessened. There might also be an accompanying reduction in the morbidity and mortality of comorbid illnesses.

Despite the potential benefits of developing an agent with an early onset of action, conventional clinical trials are not designed to assess the timing of onset of action. Traditional studies determine efficacy at the end of treatment and cannot differentiate between the earliest clinical effect and an early response to treatment. In general, these studies lack the sensitivity to detect early changes in depression and would require unfeasibly large numbers of patients to detect significant differences between antidepressants early in treatment.

Studies specifically designed to assess the early onset of action of antidepressant agents should have frequent early clinical assessments (i.e., twice a week in the first 2

From the Imperial College of Medicine, St. Mary's, London, United Kingdom.

Presented at the symposium "Issues in the Long-Term Management of Depression," which was held May 31, 1998, in Toronto, Canada, in conjunction with the 151st Annual Meeting of the American Psychiatric Association and supported by an unrestricted educational grant from NV Organon, Oss, The Netherlands.

Reprint requests to: Stuart A. Montgomery, M.D., P.O. Box 8751, London, UK, W13 8WH.

Table 1. Development Targets for New Antidepressants

Faster onset of action
Greater number of responders to treatment
Better long-term efficacy
Effective in resistant depression
Effective in currently untreatable conditions

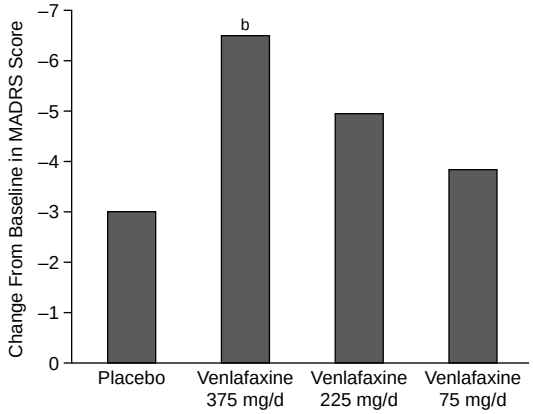
weeks of treatment). An aggressive dosage regimen should also be adopted to ensure that the patient receives sufficient drug dosage as early as possible. A survival analysis of the time taken to achieve a defined response is a suitably sensitive method to detect any early response to treatment. A study to assess early onset of action should include a placebo control to assess absolute efficacy and a reference comparator drug to determine relative efficacy. These studies would need to recruit an adequate sample size of patients to test relative efficacy early in treatment. Early differences between antidepressants may be easier to detect in patients with severe depression, and thus, these patients may constitute the most suitable population for such studies. A consensus meeting of the European College of Neuropsychopharmacology in 1994 considered that relative responses in the first 2 weeks should form the basis of a claim for a rapid-response antidepressant.

Several clinical studies have been conducted that suggest that some of the latest antidepressant agents may indeed have an earlier onset of action. One such agent, venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), was shown to have a significantly greater antidepressant effect than did placebo in 1 week.[2] This study demonstrated that in hospitalized patients with depression and melancholia, there was a statistically significant improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) score of patients receiving rapid dose titrations of venlafaxine after only 4 days of treatment compared with placebo.

Similar results were obtained in a double-blind, multicenter, randomized study involving 358 patients with major depression.[3] After only 1 week of venlafaxine treatment, significantly greater reductions in the MADRS score (Figure 1) and Hamilton Rating Scale for Depression (HAM-D) scores were observed compared with placebo for higher doses of venlafaxine (225 and 375 mg/day). Mean HAM-D, MADRS, and Clinical Global Impressions (CGI) severity scores improved in all treatment groups, but to a greater extent in the active treatment groups, and these differences were significant for HAM-D and MADRS for all dosage groups compared with placebo by 6 weeks.[3] In a separate clinical study, depressed patients were also shown to respond more quickly to venlafaxine than to TCA therapy with imipramine, particularly at high doses of venlafaxine.[4]

Mirtazapine had a significantly faster response rate than did SSRIs in 2 separate comparator studies. Benkert and coworkers[5] reported that in their study of 274 patients

Figure 1. Change in Mean Total MADRS Score After 1 Week of Treatment With Venlafaxine or Placebo[a]



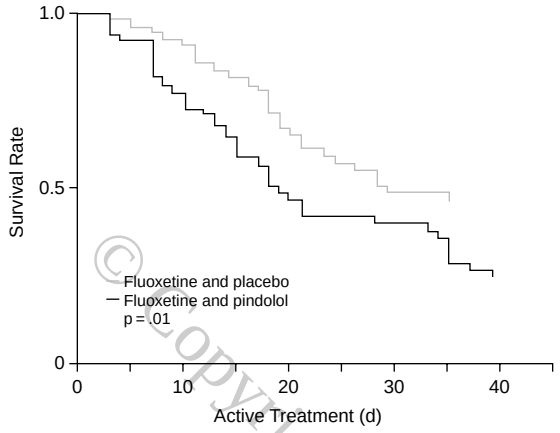
[a]Data from reference 3. Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.
[b]Significantly different from placebo ($p < .01$).

with major depression they found a significant advantage for mirtazapine with significantly more responders compared with paroxetine from as early as week 1 (24% for mirtazapine vs. 9% for paroxetine) that persisted to week 4 (58% vs. 45%, respectively). Similarly, mirtazapine was reported to be more effective than citalopram at week 2 in 270 patients.[6] Neither of these studies were designed especially to address early onset and therefore did not examine efficacy at day 4 or 10 as is recommended. The studies were relatively underpowered to test for early response, and the findings are therefore the more remarkable.

Pindolol is an adrenergic β-blocker with selective serotonin receptor antagonist activity and can be used to augment SSRI antidepressant therapy. Numerous clinical studies, both open label and placebo controlled, have shown that pindolol augmentation can accelerate the rate of response of depressed patients to SSRIs.[7] In one of these, a double-blind, placebo-controlled study conducted in depressed patients in primary care in Spain, 55 patients received fluoxetine (20 mg/day) plus pindolol (2.5 mg t.i.d.), and 56 received fluoxetine plus placebo.[8] The mean time to achieve a sustained response of at least a 50% reduction in the HAM-D score was significantly shorter in the pindolol-treated group (19 vs. 29 days, Figure 2). The proportion of responders was significantly higher in the pindolol-treated group (75% vs. 59%), and response was sustained in a significantly higher proportion of pindolol-treated patients (69% vs. 48%). Both HAM-D and MADRS mean scores were reduced by a significantly greater extent in the pindolol group ($p < .05$).[8]

However, a similar study conducted in 43 hospital-based outpatients with depression did not find that pindolol accelerated the response to SSRIs.[9] Patients who received fluoxetine (20 mg/day) plus pindolol (2.5 mg t.i.d.) took 4 weeks to achieve a 50% improvement in HAM-D

Figure 2. Kaplan-Meier Plot of the Time to a Sustained Response[a]



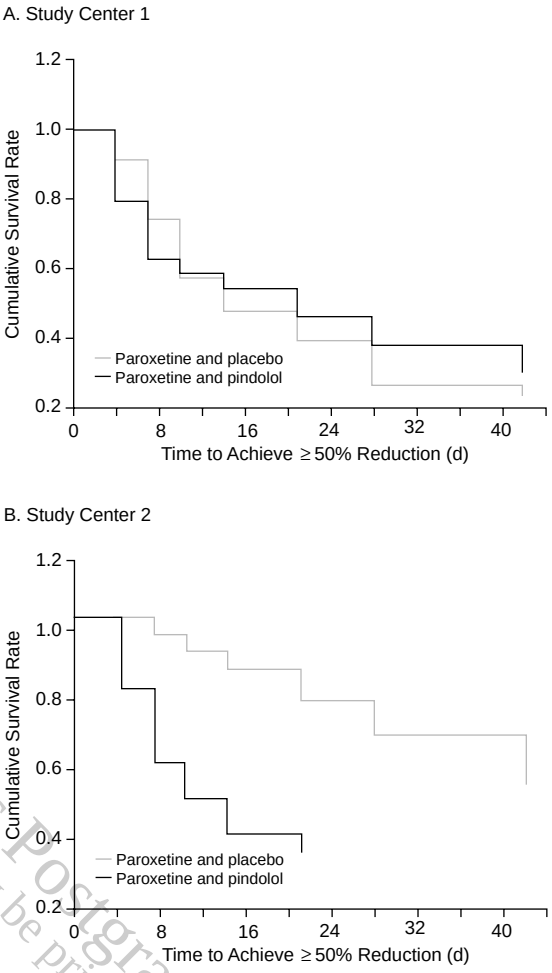
[a]Adapted from reference 8, with permission. Response defined as ≥ 50% reduction in Hamilton Rating Scale for Depression (HAM-D) score from baseline maintained at day 42.

score, the same time required in the fluoxetine-plus-placebo control group. It is thought that differences in the 2 study populations, hospital rather than primary care patients, could account for these contradictory results with pindolol augmentation. Indeed, a similar effect was observed in a double-blind, placebo-controlled study conducted in 80 outpatients.[10] Patients with major depression were recruited at 2 study centers and randomized to 2 treatment groups: paroxetine, 20 mg/day, with either pindolol, 2.5 mg t.i.d., or placebo. Pindolol significantly reduced the response time to treatment, an effect evident after 4 days of treatment. However, this effect was only apparent at one of the study centers, center 2, which mainly recruited patients who had less recurrent disease and were general practitioner referred rather than hospital based (Figure 3).[10] The finding that pindolol augmentation of SSRIs is apparently effective in first- and second-episode depression but not in more recurrent or chronic depression raises an intriguing question about the kind of changes that occur at serotonin-1A (5-HT_{1A}) autoreceptors with increasing recurrence of major depression. Investigating this phenomenon might well shed light on the evolution of resistant depression. What is it, one might well ask, about recurrence that changes 5-HT_{1A} receptor sensitivity?

BETTER OVERALL EFFICACY

Several studies conducted by the Danish University Antidepressant Group in the late 1980s questioned the relative efficacy of SSRIs such as citalopram[11] and paroxetine[12] in inpatients compared with clomipramine, which was significantly more effective. More recent studies have demonstrated that newer antidepressants may also have superior efficacy to the SSRIs and TCAs for the acute treatment of depression. In addition to an earlier response

Figure 3. Kaplan-Meier Plots of the Time to Response in Patients Treated With Paroxetine and Either Pindolol or Placebo[a]



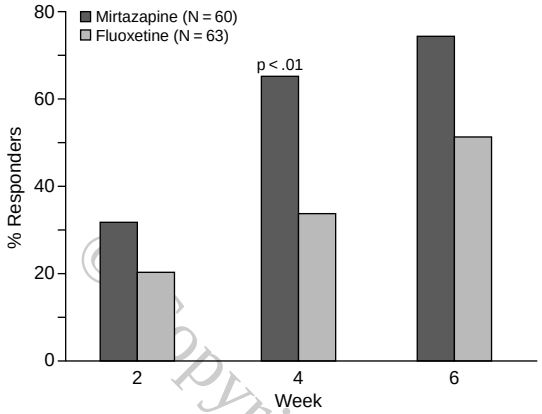
[a]Adapted from reference 10, with permission. Response defined as ≥ 50% reduction in MADRS score from baseline.

to treatment, the latest antidepressants may offer advantages over conventional therapy in terms of an increased number of responders and improved long-term efficacy. For our purposes, response is defined as ≥ 50% improvement in depressive symptoms compared with baseline.

Improved Response Rate

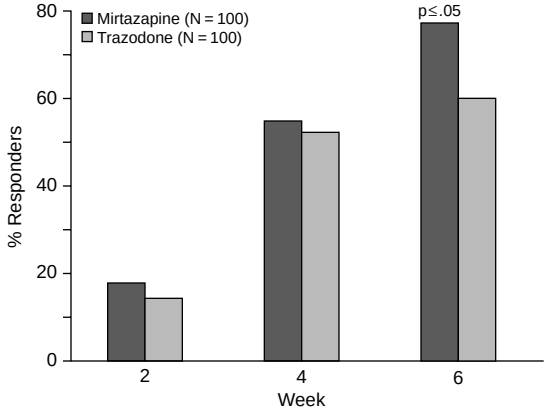
Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) that has a novel dual action. It has been shown to have superior efficacy to that of several established antidepressants in the proportion of patients responding to acute treatment.[13,14] In a double-blind, randomized, multicenter study, 133 patients with moderate-to-severe major depression received either mirtazapine (15–60 mg/day) or fluoxetine (20–40 mg/day).[14] At each assessment in this 6-week study, the proportion of responders was markedly higher in the mirtazapine group, and the difference between mirtazapine and fluoxetine reached

Figure 4. Percentage of Patients Responding to Treatment With Mirtazapine or Fluoxetine[a]



[a]Adapted from reference 14, with permission. Response defined as ≥ 50% reduction in 17-item HAM-D score from baseline.

Figure 5. Percentage of Patients Responding to Treatment With Mirtazapine or Trazodone[a]



[a]Adapted from reference 13, with permission. Response defined as ≥ 50% reduction in 17-item HAM-D score from baseline.

statistical significance at week 4 ($p < .01$, Figure 4). Furthermore, more patients were classed as "much" or "very much" improved on the CGI scale in the mirtazapine group (63%) than in the fluoxetine group (54%). The mean HAM-D scores were reduced to a significantly greater extent in the mirtazapine group from week 3 onward.[14]

Mirtazapine has also been found to have a superior response rate to trazodone, an agent with an established antidepressant efficacy. A randomized, double-blind, multicenter study was conducted in which 200 hospitalized patients with major depression received mirtazapine or trazodone for 6 weeks.[13] At each time point, the response rate was higher in the mirtazapine group, and by 6 weeks, the difference between the 2 treatments was statistically significant (78% vs. 61%, $p \leq .05$; Figure 5). Both HAM-D and MADRS mean scores were higher in the mirtazapine group at each time point, and the reduction in the HAM-D score was significantly higher in the mirtazapine group at 6 weeks.[13]

Significant advantages in response rates have been shown for the SNRI venlafaxine compared with SSRI therapy (fluoxetine). A double-blind, randomized study was conducted in 68 patients who were hospitalized with major depression and melancholia.[15] After 4 weeks, a significantly greater proportion of patients responded to treatment with venlafaxine compared with fluoxetine according to both the HAM-D (76% vs. 41%) and MADRS (70% vs. 50%) total scores. The mean total HAM-D and MADRS scores were both significantly lower in the venlafaxine group at 4 and 6 weeks. Venlafaxine has also been shown to have superior efficacy to TCAs in the number of responders. A double-blind, placebo-controlled, multicenter study was conducted in which 229 outpatients with mild-to-moderate depression received either venlafaxine, imipramine, or placebo.[16] Significantly more patients responded to venlafaxine than imipramine after 10 (82% vs. 62%) and 13 (83% vs. 66%) weeks of treatment.

Another SNRI, milnacipran, has been shown to be superior in terms of response to treatment to either fluoxetine or fluvoxamine.[17] Meta-analyses of 3 trials involving a total of 306 patients with severe major depression found that the SNRI had a markedly greater proportion of responders according to both HAM-D and MADRS scores than either fluoxetine or fluvoxamine. A greater proportion of responders was also found for milnacipran when data for the 2 SSRIs were pooled together (HAM-D, 64% vs. 50%; MADRS, 67% vs. 51%).[17]

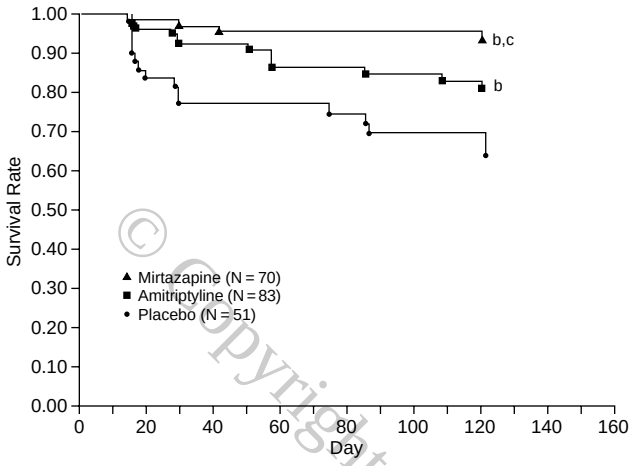
A further study was conducted recently in which milnacipran (100 mg/day and 200 mg/day) was compared with fluoxetine (20 mg/day) in inpatients with endogenous major depression.[18] While the results demonstrated that milnacipran consistently tended to have superior efficacy to fluoxetine on HAM-D, MADRS, and CGI scales, these advantages achieved statistical significance in only a few instances.

Improved Long-Term Efficacy

Depression is increasingly seen as a chronic disease, and, as such, long-term treatment of at least 6 months is recommended for all types of depression.[19] In particular, long-term treatment is especially important for the suppression of new episodes of disease in patients with recurrent depression. By controlling and preventing depression, effective long-term treatment can help to reduce the considerable health care costs associated with it. The results of long-term efficacy trials can also serve as a good indicator of a new antidepressant's overall efficacy. Thus, sustained efficacy is a key characteristic of any new antidepressant agent.

A number of clinical studies provide evidence that the latest advances in antidepressant therapy offer superior long-term efficacy compared with traditional TCAs. Recently, a double-blind, placebo-controlled, randomized

Figure 6. Survival Curves for Time to Relapse During 20 Weeks of Treatment With Mirtazapine, Amitriptyline, or Placebo[a]



[a]Adapted from reference 19, with permission.
[b]$p \leq .05$ vs. placebo.
[c]$p \leq .05$ vs. amitriptyline.

study over a 2-year period compared the long-term efficacy of a NaSSA, mirtazapine, with that of a conventional TCA, amitriptyline, in 217 patients with major depression who had responded to acute treatment.[19] A survival analysis of the time to relapse (17-item HAM-D score ≥ 16 or because of lack of efficacy) was carried out. The time to relapse was significantly longer in the mirtazapine group than in the amitriptyline group over a 20-week period ($p \leq .01$, Figure 6). The proportion of patients who sustained the response was higher with mirtazapine than amitriptyline after 20 weeks (71.6% vs. 61.6%), and this difference was statistically significant over the whole study (77.0% vs. 57.0%; $p = .008$). The proportion of patients relapsing was lower in the mirtazapine group than the amitriptyline group over 20 weeks (4.1% vs. 7%) and over the entire study (4.1% vs. 11.6%), but this difference did not reach statistical significance. Both active treatments had significantly longer times to relapse, and fewer patients on active treatment experienced relapse, than patients on placebo over 20 weeks and during the whole study ($p \leq .05$).[19]

The SNRI venlafaxine has been shown to have a long-term efficacy superior to that of the TCA imipramine.[20] In a double-blind, multicenter study, outpatients with major depression were treated for up to 1 year with venlafaxine (N = 290) or imipramine (N = 91). Both treatments demonstrated significant improvements in CGI severity scores throughout the study. These scores improved to a greater extent in the venlafaxine group than in the imipramine group throughout the study, but this difference was not statistically significant. The response to treatment ("much" or "very much" improved on the CGI) was greater in the venlafaxine group and was significantly better at months 2, 6, and 12.[20]

CONCLUSIONS

Depression remains poorly treated in a large number of patients, and there is still a need to develop antidepressants that offer distinct advantages over conventional treatments. To improve the overall management of depression, there is a call for antidepressants that have an earlier onset of action, a greater response rate, and improved long-term efficacy. The latest generation of antidepressants, which includes drugs such as mirtazapine, an NaSSA, and venlafaxine, an SNRI, has a dual mode of action that affects both noradrenergic and serotonergic neurotransmission. Direct clinical comparisons of these novel antidepressants with conventional antidepressants suggest that there are clear improvements in efficacy for these new classes of agents. Furthermore, this difference may be particularly apparent in patients with endogenous depression and in those who are hospitalized or who have severe depression. It is clear from the results reviewed here that novel antidepressants such as NaSSAs and SNRIs offer demonstrable advantages over SSRI and TCA treatments, with a more rapid response, higher acute response rates, and improved long-term efficacy. While these findings need to be confirmed by specifically designed, prospective studies, it is essential that the importance of these results is not overlooked.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), clomipramine (Anafranil), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), paroxetine (Paxil), pindolol (Visken), trazodone (Desyrel and others), venlafaxine (Effexor).

REFERENCES

1. Lepine J-P, Gastpar M, Mendlewicz J, et al. Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). Int Clin Psychopharmacol 1997;12:19–30
2. Guelfi JD, White C, Hackett D, et al. Effectiveness of venlafaxine in patients hospitalized for major depression and melancholia. J Clin Psychiatry 1995;56:450–458
3. Rudolph RL, Fabre LF, Feighner J, et al. Randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. J Clin Psychiatry 1998;59:116–122
4. Benkert O, Grunder G, Wetzel H, et al. A randomized, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. J Psychiatr Res 1996;30: 441–452
5. Benkert O, Szegedi A, Kohnen R. Rapid onset of therapeutic action in major depression: a comparative trial of mirtazapine and paroxetine. In: Scientific Abstracts of the 37th Annual Meeting of the American College of Neuropsychopharmacology; Dec 14–18, 1998; Las Croabas, Puerto Rico:311
6. Agren H, Leinonen E, Scarstein J, et al., and the Nordic Antidepressant Study Group. Efficacy and tolerability of mirtazapine vs citalopram: a double-blind, randomized study in patients with major depressive disorder. In: Scientific Abstracts of the 37th Annual Meeting of the American College of Neuropsychopharmacology; Dec 14–18, 1998; Las Croabas, Puerto Rico:320
7. Blier P, Bergeron R. Use of pindolol to potentiate antidepressant medication. J Clin Psychiatry 1998;59(suppl 5):16–23
8. Perez V, Gilaberte I, Faries D, et al. Randomised, double-blind placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. Lancet 1997;349:1594–1597
9. Berman RM, Darnell AM, Miller HL, et al. Effect of pindolol in hastening response to fluoxetine in the treatment of major depression: a double-blind,

placebo-controlled trial. Am J Psychiatry 1997;154:37–43
10. Tome de la Granja MB, Isaak MT, Harte R, et al. Paroxetine and pindolol: a randomised trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. Int Clin Psychopharmacol 1997;12:81–90
11. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine: a controlled multicenter study. Psychopharmacol 1986;90:131–138
12. 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
13. van Moffaert M, de Wilde J, Vereecken A, et al. Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression. Int Clin Psychopharmacol 1995;10:3–9
14. Wheatley DP, van Moffaert M, Timmerman L, et al. Mirtazapine efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe depressive disorder. J Clin Psychiatry 1998;59:306–312
15. Clerc GE, Ruimy P, Verdeau-Pailles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. Int Clin Psychopharmacol 1994;9:139–143
16. Lecrubier Y, Bourin M, Moon CAL, et al. Efficacy of venlafaxine in depressive illness in general practice. Acta Psychiatr Scand 1997;95:485–493
17. Lopez-Ibor J, Guelfi JD, Pletan Y, et al. Milnacipran and selective serotonin reuptake inhibitors in major depression. Int Clin Psychopharmacol 1996;11 (suppl 4):41–46
18. Guelfi JD, Ansseau M, Corruble E, et al. A double-blind comparison of the efficacy and safety of milnacipran and fluoxetine in depressed inpatients. Int Clin Psychopharmacol 1998;13:121–128
19. Montgomery SA, Reimitz P-E, Zivkov M. Mirtazapine versus amitriptyline in the long-term treatment of depression: a double-blind placebo-controlled study. Int Clin Psychopharmacol 1998;13:63–73
20. Shrivastava RK, Cohn C, Crowder J, et al. Long-term safety and clinical acceptability of venlafaxine and imipramine in outpatients with major depression. J Clin Psychopharmacol 1994;14:322–329