# Newer Antidepressants: Review of Efficacy and Safety of Escitalopram and Duloxetine

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*Background:* Two antidepressants with different mechanisms of action, escitalopram and duloxetine, have recently been developed for the treatment of major depressive disorder. This article reviews the available controlled data on these agents with regard to efficacy, safety, and tolerability. *Method:* We identified four 8-week, double-blind, placebo-controlled studies of escitalopram in the acute treatment of major depression. Three of the studies involved an active comparator, citalopram. We identified 6 placebo-controlled studies of duloxetine in major depressive disorder. Two of the studies included fluoxetine as an active comparator, and 2 included paroxetine as an active comparator. *Results:* A review of the data from the controlled studies supports the efficacy of both escitalopram and duloxetine in the treatment of patients with major depression. Three of the 4 escitalopram studies were positive, and 1 was a failed study. Four of the 6 duloxetine studies were positive. Both escitalopram and duloxetine performed better than at least 1 selective serotonin reuptake inhibitor comparator. The safety and tolerability profiles of both drugs are quite benign. The reported incidence of treatment-emergent adverse events was somewhat lower with escitalopram than with duloxetine, with the possible exception of sexual dysfunction. Discontinuations due to adverse events were lower for escitalopram than for duloxetine, although rates were comparable with higher doses of escitalopram (20 mg/day). *Conclusion:* Both escitalopram and duloxetine are useful in the treatment of major depressive disorder.

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The options to treat patients suffering from major depressive disorder are expanding. Within the past few years, several new medications with markedly different effects on the neurotransmitters serotonin and norepinephrine have been developed for the treatment of depression. In August 2002, the U.S. Food and Drug Administration (FDA) approved the use of escitalopram, a selective serotonin reuptake inhibitor (SSRI), for the treatment of major depressive disorder, and in September 2002, the U.S. FDA approved new labeling for escitalopram as maintenance treatment for patients with major depressive disorder. Escitalopram is the *S*-enantiomer of citalopram and has been demonstrated in animal studies to possess the serotonergic reuptake blocking properties of the racemate citalopram.[1] Another option that is expected to receive approval by the FDA for the treatment of major depression is duloxetine. Duloxetine is an inhibitor of both serotonin and norepinephrine reuptake (SNRI).[2]

These 2 medications have different mechanisms of action. Escitalopram is a highly specific inhibitor of serotonin reuptake. It has very little noradrenergic or dopaminergic activity. Duloxetine inhibits the reuptake of both serotonin and norepinephrine. Do these differences in mechanism of action translate into differences in terms of efficacy, safety, and tolerability? The only valid way to address this issue would be a head-to-head trial between these 2 agents in an appropriate sample of patients. To our knowledge, no such study has been conducted. In the absence of such data, we review existing controlled data on each of these medications to assess their utility in treating patients with a depressive illness.

## ESCITALOPRAM

There have been 4 placebo-controlled clinical trials of escitalopram for the acute treatment of depression. Of these studies, 3 were positive and 1 was a failed study.
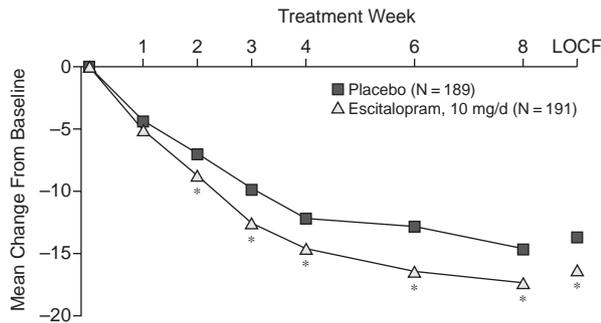
*Corresponding author and reprints: Robert M. A. Hirschfeld, M.D., Titus H. Harris Chair, Professor and Chair, Department of Psychiatry and Behavioral Sciences, The University of Texas-Medical Branch, 1.302 Rebecca Sealy, 301 University Blvd., Galveston, TX 77555–0188 (e-mail: rohirsch@utmb.edu).*

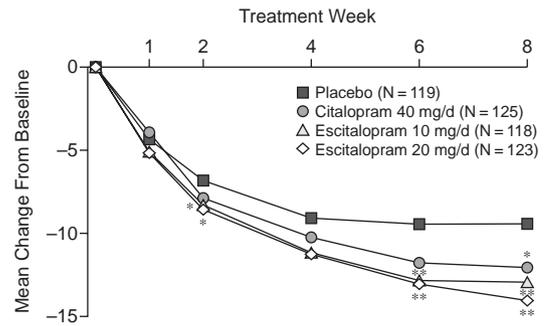Figure 1. Change in MADRS Score for Patients Taking Escitalopram or Placebo[a]



aReprinted with permission from Wade et al.[3]
*p < .01.
Abbreviations: LOCF = last observation carried forward,
 MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 2. Change in MADRS Score for Patients Taking Escitalopram, Citalopram, or Placebo[a]



aReprinted with permission from Burke et al.[4]
*p ≤ .05 vs. placebo.
**p < .01 vs. placebo.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating
 Scale.

Each of the 3 positive studies has been published independently[3–5]; data from the failed study have been included in 2 pooled analyses[6,7] and in a published report of a relapse prevention study.[8] In the failed study, neither active agent separated from placebo on the primary endpoint using the last-observation-carried-forward (LOCF) analysis. This "failed" study should be distinguished from a "negative" study, in which an active comparator does separate from placebo, while the experimental agent does not. A negative study suggests that the experimental drug is not effective, whereas a failed study suggests that the sample was not sufficiently representative of the population.

All of the trials were 8-week, double-blind, placebo-controlled studies. Of the positive studies, 2 used citalopram as an active comparator[4,5] and 1 involved only escitalopram and placebo.[3] Furthermore, 2 positive trials were fixed-dose studies[3,4] and the other was flexibly dosed.[5] The failed trial employed citalopram as an active comparator and flexible dosing.

Of the 3 positive studies, 1 was conducted at 40 primary care centers in Europe and Canada.[3] During the 8-week double-blind treatment period, patients were randomly assigned to receive either a fixed dose of 10 mg/day of escitalopram (N = 191) or placebo (N = 189). The primary measure of efficacy was the change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) score. Secondary measures included the Clinical Global Impressions Severity of Illness scale (CGI-S) and CGI-Improvement scale (CGI-I). On the MADRS total score, escitalopram produced statistically significant improvement compared with placebo (p = .002) as shown in Figure 1. Additionally, escitalopram demonstrated statistically significantly better efficacy compared with placebo from week 1 onward on the CGI-I, at week 2 onward in MADRS total score, and at week 3 onward on the CGI-S.

The proportion of responders (patients with ≥ 50% reduction of baseline MADRS score) was significantly higher for escitalopram (55%) than for placebo (42%). Moreover, significantly more escitalopram-treated patients (48%) achieved complete remission, defined in this study as a MADRS score ≤ 12, than did patients taking placebo (34%). Escitalopram was well tolerated. Nausea was the only adverse event that occurred significantly more often in the escitalopram group than in the placebo group, and there was no difference between placebo and escitalopram in the proportion of patients who discontinued treatment due to adverse events.

A second study compared escitalopram in 2 different doses (10 mg/day and 20 mg/day) with citalopram (40 mg/day) and placebo in outpatients with major depression (baseline MADRS score ≥ 22).[4] This 8-week trial involved a 1-week, single-blind, placebo lead in and upward titration after 1 week for the citalopram group (from a starting dose of 20 mg/day to the target dose of 40 mg/day) and the 20-mg escitalopram group (from a starting dose of 10 mg/day). A total of 491 patients entered the double-blind phase of the study, divided fairly equally among the 4 cells. There were no clinically significant differences among the groups. The average age of patients in each group was approximately 40 years, and groups were about two-thirds female. At endpoint, all 3 active agents produced significantly better improvement on the MADRS and the Hamilton Rating Scale for Depression (HAM-D) compared with placebo (Figure 2). The most frequent adverse event was nausea in the 3 treatment groups (Table 1). Other treatment-emergent adverse events occurred in fewer than 15% of patients. Discontinuations due to adverse events occurred in only 4.2% of the escitalopram 10-mg/day group compared with 2.5% of the placebo group. This difference was not statistically significant.

Table 1. Most Frequent Adverse Events Observed
in Patients Receiving Escitalopram, Citalopram,
or Placebo (% of patients)[a]

| Adverse Event | Placebo (N = 122) | Citalopram 40 mg/d (N = 125) | Escitalopram 10 mg/d (N = 119) | Escitalopram 20 mg/d (N = 125) |
|---|---|---|---|---|
| Nausea | 6 | 22 | 21 | 14 |
| Diarrhea | 7 | 11 | 10 | 14 |
| Insomnia | 3 | 11 | 10 | 14 |
| Dry mouth | 7 | 10 | 10 | 9 |
| Ejaculatory disorder[b] | 0 | 4 | 9 | 12 |

[a]Reprinted with permission from Burke et al.[4] Listed are those adverse events that occurred in at least 10% of patients in any active treatment group and were more prevalent than in the placebo treatment group.
[b]As a percentage of male patients; number of reports ranged from 2–5 per active treatment group.

Figure 3. Change in MADRS Score in Pooled Analysis of Patients Taking Escitalopram (10 or 20 mg/d), Citalopram (20–40 mg/d), or Placebo[a]



[a]Reprinted with permission from Gorman et al.[6]
*p < .05 vs. placebo.
**p < .001 vs. placebo.
†p < .05 vs. citalopram.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 4. Change in MADRS Inner Tension Item Score in Pooled Analysis of Patients Taking Escitalopram (10 or 20 mg/d), Citalopram (20–40 mg/d), or Placebo[a]
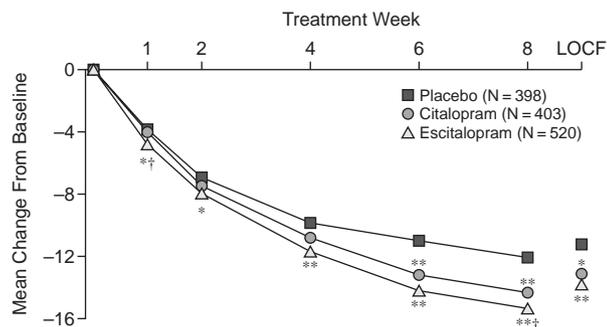


[a]Reprinted with permission from Gorman et al.[6]
*p < .05 vs. placebo.
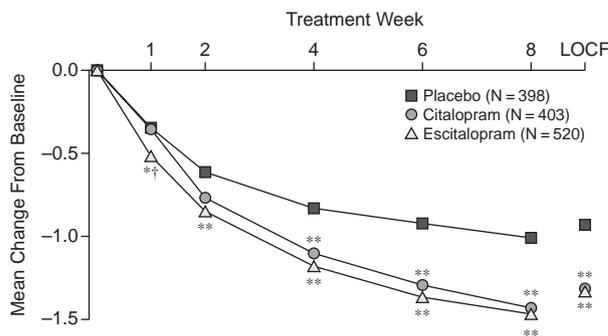**p < .001 vs. placebo.
†p < .05 vs. citalopram.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Similarly, there were no differences in discontinuation rates between the escitalopram 20-mg/day and citalopram 40-mg/day groups (10.4% for escitalopram and 8.8% for citalopram), although these rates were significantly higher than that for placebo in both groups (p ≤ .05).

The third study compared flexible doses of escitalopram (10–20 mg/day) and citalopram (20–40 mg/day) with placebo.[5] Results from the flexible-dose trial were consistent with findings from the fixed-dose studies: escitalopram demonstrated rapid antidepressant effect according to the MADRS, separating from placebo at every time point throughout the study in the observed-cases data set and from week 2 onward in the LOCF analysis. Few escitalopram- and citalopram-treated patients discontinued the study due to adverse events (3% and 4%, respectively). Nausea was the only adverse event that was reported to occur in > 10% of escitalopram-treated patients with an incidence greater than that of placebo.

Although none of the studies that included citalopram as an active comparator were powered sufficiently to detect differences between active treatments, the results of these 3 studies have been pooled,[6] yielding an intent-to-treat (ITT) population of 520 patients in the escitalopram 10- or 20-mg/day group, 403 patients in the citalopram 20- to 40-mg/day group, and 398 patients in the placebo group. Measures of efficacy included the MADRS and the CGI.

The results on the MADRS for the pooled analysis are shown in Figure 3. Both citalopram and escitalopram significantly differed from placebo at endpoint. Escitalopram separated from placebo at week 1 and continued to outperform placebo throughout the trial. Of interest, the separation of escitalopram from citalopram at week 1 and week 8 is both statistically and clinically significant.

The effects of escitalopram and citalopram on symptoms of anxiety were assessed using the MADRS inner tension item. As seen in Figure 4, escitalopram separated from placebo at week 1 and continued to separate both statistically and clinically for the duration of the trial. Citalopram separated from placebo for the first time at week 4, and this advantage was sustained throughout the trial. Similar to the findings with the MADRS total score, escitalopram separated statistically from citalopram at week 1 on the MADRS measure of anxiety.

An issue of considerable clinical importance is the efficacy of escitalopram in patients with more severe depressive symptoms. In this pooled analysis, a group of patients with baseline MADRS scores ≥ 30 were analyzed separately (Figure 5). These findings parallel those of the entire population. Escitalopram separated from placebo at week 1 in this group of more severely depressed patients

Figure 5. Change in MADRS Score in Pooled Analysis of Patients With Severe Depression (baseline MADRS score ≥ 30) Taking Escitalopram (10 or 20 mg/d), Citalopram (20–40 mg/d), or Placebo[a]
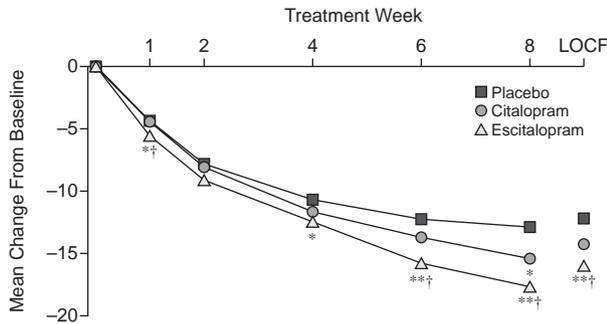


[a]Reprinted with permission from Gorman et al.[6]
*p < .05 vs. placebo.
**p < .001 vs. placebo.
†p < .05 vs. citalopram.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2. Most Common Adverse Events Associated With Escitalopram (occurring in ≥ 5% of treated patients and at a rate greater than placebo) in Placebo-Controlled Trials in Major Depression[a]

| Adverse Event | Placebo, % (N = 592) | Escitalopram, % (N = 715) |
|---|---|---|
| Nausea | 7 | 15 |
| Insomnia | 4 | 9 |
| Ejaculation disorder[b] | 0 | 9 |
| Diarrhea | 5 | 8 |
| Somnolence | 2 | 7 |
| Dry mouth | 5 | 6 |
| Dizziness | 4 | 6 |
| Influenza-like symptoms | 4 | 5 |

[a]Reprinted with permission from Burke.[9]
[b]Percentages are relative to the number of male patients (placebo, N = 188; escitalopram, N = 225).

and maintained superiority over placebo throughout the 8 weeks of treatment, although the difference was not statistically significant at week 2. Again, escitalopram separated from citalopram at week 1. Additionally, escitalopram separated from citalopram at weeks 6 and 8 (observed cases) and at endpoint (LOCF).

An analysis of response and remission data revealed that both escitalopram and citalopram had significantly higher response rates than placebo. Response was defined as ≥ 50% improvement from baseline MADRS score. The response rate was 59% for escitalopram and 53% for citalopram, with 41% of patients responding to placebo. Remission was defined as a MADRS score of ≤ 10. Both escitalopram and citalopram had statistically higher remission rates at week 6 and week 8. The remission rate for escitalopram was 37% at week 6 and 40% at week 8. The remission rate for citalopram was 34% at week 6 and 38% at week 8. Remission rates for placebo were 25% at week 6 and 31% at week 8.

The profile of treatment-emergent adverse events was remarkably benign. Table 2 shows that in the 4 placebo-controlled trials, adverse events that occurred in at least 5% of escitalopram-treated patients and at a rate at least twice that of placebo included only nausea, insomnia, somnolence, and ejaculation disorder. Other than nausea, no adverse event had an incidence > 10% in the escitalopram group. The rate of discontinuation due to adverse events in patients treated with escitalopram 10 to 20 mg/day and placebo were 5.9% vs. 2.2%, respectively.[9]

The results from these 4 trials demonstrate that escitalopram is efficacious in the treatment of patients with major depression, including those with more severe depression symptomatology. Clinically important improvements

in depression (as well as in symptoms of anxiety) may be seen in as rapidly as 1 week. The safety and tolerability profile of citalopram is quite benign.
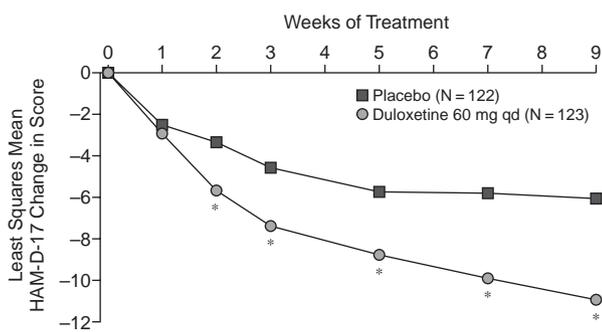
## DULOXETINE

There have been 6 placebo-controlled studies of the acute treatment of major depression with duloxetine.[2] The first study,[10] conducted at 18 centers in the U.S., was a double-blind, randomized, placebo-controlled trial of duloxetine 60 mg/day. It involved outpatients with major depressive disorder with a score of 15 or greater on the 17-item HAM-D (HAM-D-17) and 4 or greater on the CGI-S. The primary efficacy measure was the HAM-D-17 total score. Response was defined as a 50% or greater reduction in the HAM-D-17 total score from baseline, and remission was defined as a score of ≤ 7 on the HAM-D-17.

The study involved 123 patients in the duloxetine, 60-mg/day, cell and 122 patients in the placebo cell. The average age of patients was approximately 42 years, and approximately two thirds of the sample were female. Results from the study show that duloxetine at 60 mg/day was better than placebo in reducing depressive symptomatology as assessed by the HAM-D-17. The first separation from placebo was at 2 weeks and continued throughout the study (Figure 6). The respective estimated probabilities of response and remission were 62% and 44%, both significantly better than placebo, using a likelihood-based mixed-effects model repeated-measures (MMRM) analysis. Rates of response calculated using LOCF were 45% for duloxetine-treated patients and 23% for placebo-treated patients. The rates of remission using the LOCF approach were 31% for duloxetine and 15% for placebo. These differences were statistically significant.

Efficacy was evident in a variety of clinical areas including anxiety, the core factors of depression, retardation, and sleep. In addition, quality of life improved significantly. In this trial, nearly 14% of patients in the

Figure 6. Effect of Placebo and Duloxetine on HAM-D-17 Total Score[a]



[a]Reprinted with permission from Detke et al.[10]
*p < .001 vs. placebo.
Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Table 3. Duloxetine Clinical Trials for Acute Treatment of Major Depression[a]

| Study | Treatment Group | Dose, mg | Total N | Duration, wk |
|---|---|---|---|---|
| 1 and 2 | Duloxetine | 60 | 251 | 9 |
| | Placebo | | 261 | |
| 3 and 4 | Duloxetine | 40–120 | 152 | 8 |
| | Fluoxetine | 20 | 70 | |
| | Placebo | | 145 | |
| 5 and 6 | Duloxetine | 40 | 177 | 8 |
| | Duloxetine | 80 | 175 | |
| | Paroxetine | 20 | 176 | |
| | Placebo | | 179 | |

[a]Adapted with permission from Nemeroff et al.[2]

Table 4. Duloxetine Clinical Trials in Acute Treatment of Major Depression: Results Against Placebo[a]

| Outcome | Study 1 60 mg | Study 2 60 mg | Study 3 120 mg | Study 4 120 mg | Study 5 40 mg | Study 5 80 mg | Study 6 40 mg | Study 6 80 mg |
|---|---|---|---|---|---|---|---|---|
| HAM-D-17 total score[b] | * | * | * | NS | NS | NS | * | * |
| Response | * | * | NS | NS | NS | NS | NS | * |
| Remission | * | NS | * | NS | NS | NS | NS | * |

[a]Adapted with permission from Nemeroff et al.[2]
[b]Primary efficacy variable.
*p ≤ .05.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, NS = nonsignificant.

Figure 7. Estimated Probabilities of Remission (MMRM analysis) in Studies in Which Duloxetine Demonstrated Superiority Over Placebo on the Primary Efficacy Measure[a]



[a]Reprinted with permission from Nemeroff et al.[2]
*p < .05 vs. placebo.
†p < .005 vs. placebo.
‡p < .05 vs. paroxetine.
Abbreviation: MMRM = mixed-effects model repeated-measures.

duloxetine group discontinued treatment because of adverse events compared with 2.5% of those taking placebo.
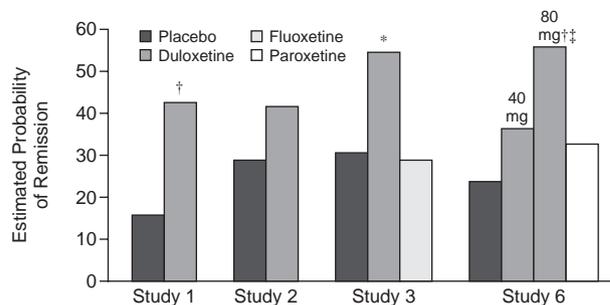
In another placebo-controlled trial of duloxetine,[11] fluoxetine was included as an active comparator. Patients with major depressive disorder were treated for 8 weeks with fluoxetine, 20 mg/day, duloxetine, titrated from 40 mg/day (20 mg b.i.d.) to 120 mg/day (60 mg b.i.d.) over the first 3 weeks, or placebo. At 8 weeks, duloxetine treatment reduced depressive symptomatology significantly more than did placebo. The reduction in depressive symptoms was numerically greater in the duloxetine group than in the fluoxetine group, but the difference was not statistically significant. Again, an MMRM analysis was used to calculate likelihood of response (50% reduction from baseline HAM-D-17 score) and remission (HAM-D-17 score ≤ 7). An estimated probability of response of 64% was found for duloxetine with an estimated remission rate of 56%. Using the LOCF approach, the response rate for duloxetine-treated patients was 49% compared with 36% for placebo (p = .167), and the remission rates were 43% for duloxetine compared with 27% for placebo (p = .072). The most frequently reported adverse events for duloxetine (reported by > 15% of duloxetine-treated patients

and at a rate greater than placebo) included dry mouth, insomnia, somnolence, sweating, asthenia, and dizziness. Changes in sexual functioning in patients treated with duloxetine were not different from placebo using the Arizona Sexual Experience scale (ASEX), a self-report measure of sexual functioning.

The design characteristics of these 2 studies and the 4 additional controlled studies are presented in Table 3.[2] Studies 1 and 2 were identical in design and involved a fixed-dose, 2-arm study against placebo. Studies 3 and 4 were identical in design and involved a flexible dosing of duloxetine, a placebo control, and fluoxetine. Studies 5 and 6 were identical in design and involved 2 doses of duloxetine, 40 mg/day and 80 mg/day, an active comparator of paroxetine (20 mg/day), and placebo.

The results of these studies are summarized in Table 4. In 4 of the studies, duloxetine was superior to placebo on the primary efficacy variable, the HAM-D-17 total score. With regard to response, in 3 of the studies, duloxetine was statistically superior to placebo. Similarly, with regard to remission, duloxetine was statistically superior to placebo in 3 of the 6 studies. Duloxetine demonstrated superiority over placebo at all studied doses (10–120

Figure 8. Treatment-Emergent Adverse Events in Patients Taking Duloxetine or Placebo: Pooled Placebo-Controlled Data[a]
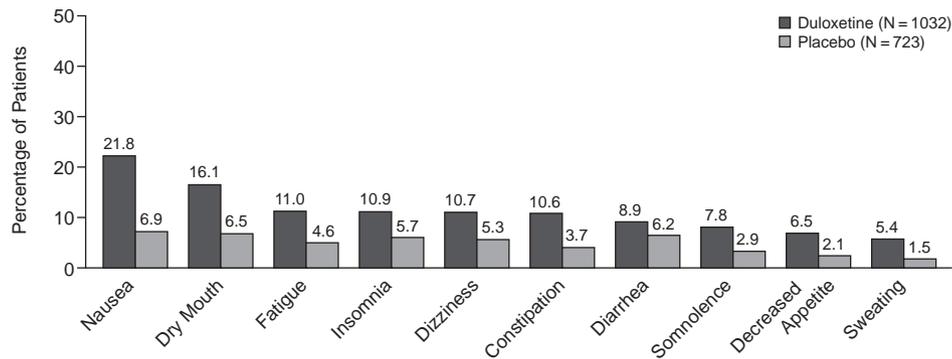


[a]Adapted with permission from Nemeroff et al.[2] Adverse events reported by 5% or more of the duloxetine-treated patients. All differences p < .001 vs. placebo, except for diarrhea (nonsignificant).

mg/day). Additionally, duloxetine at 80 mg/day demonstrated superiority over paroxetine 20 mg/day on the HAM-D-17 total score.[12]

Figure 7 shows the estimated probabilities of remission (MMRM analysis) in patients receiving duloxetine, fluoxetine, and paroxetine over placebo in studies in which duloxetine demonstrated superiority on the primary efficacy measure.[2] The probabilities of remission were significantly higher for duloxetine than for the placebo groups in Studies 1, 3, and 6. Moreover, the probability of remission for duloxetine-treated patients (80 mg/day) was significantly higher than that for paroxetine-treated patients (20 mg/day).

With regard to treatment-emergent adverse events in the pooled database from placebo-controlled trials, the results are shown in Figure 8. The most frequently reported adverse events were nausea (22%) and dry mouth (16%). Less frequent adverse events included fatigue, insomnia, dizziness, and constipation and were reported at a rate of approximately 11%. The rate of discontinuation due to adverse events was significantly higher for duloxetine than for placebo (14.6% vs. 5.0% for duloxetine and placebo, respectively, p < .001). However, a comparison against active comparators showed no significant differences in the rate of discontinuation between duloxetine (13.6%) and paroxetine (10.2%) (p = .33) and between duloxetine (9.9%) and fluoxetine (5.7%) (p = .44).[2]

A concern with a noradrenergic agent is its potential effect on blood pressure. In the reported studies, however, there was no significant treatment-emergent hypertension, and there were no differences in comparison with placebo. With regard to weight, there was a slight reduction in weight in duloxetine-treated patients in the short term placebo-controlled studies.[2]

No significant differences between placebo and duloxetine groups were observed in sexual functioning, as measured by the ASEX total score.[2] On individual items of the ASEX, the only significant difference was observed among men in response to the question "How easily can you reach an orgasm?" There were no significant differences observed in the responses of women.[2]

Overall, the efficacy of duloxetine was well established in 4 of the 6 placebo-controlled studies. Duloxetine appears to be generally well tolerated.

## CONCLUSION

This article has presented data on the efficacy and safety of 2 recently developed antidepressants, one of which is currently available in the United States. With regard to efficacy, both escitalopram and duloxetine were significantly better than placebo. Both performed better than at least 1 SSRI comparator. Safety profiles of both escitalopram and duloxetine were sufficiently benign. In general, the incidence of treatment-emergent adverse events was somewhat lower with escitalopram than with duloxetine, with the possible exception of sexual dysfunction. Discontinuations due to adverse events were lower for escitalopram than for duloxetine. However, the rates of discontinuations were comparable between the higher doses of escitalopram (20 mg/day) and duloxetine. In summary, both escitalopram and duloxetine present attractive additional options for the treatment of patients with depression.

*Drug names:* citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac and others), paroxetine (Paxil and others).

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