Major Depressive Disorder

Venlafaxine Randomized Controlled Trials

Phillip W. Long M.D. (July 25, 2006)

Summary:

- Venlafaxine has been shown to be effective in the treatment of Major Depressive Disorder in adults, but not in children or adolescents:
  - Four studies (1, 3, 4, 5) have shown venlafaxine to produce a better remission rate than placebo or a comparison medication.
  - Two studies (2, 11) have shown venlafaxine to better prevent relapse than placebo.
  - Five studies (6, 7, 8, 9) have shown venlafaxine to produce a better response rate than placebo or a comparison medication.
  - One study (10) showed that venlafaxine was ineffective for Major Depressive Disorder in childhood and adolescence.
    - The “placebo” in these studies was actually an “active placebo”. That is, the patient would regularly see a psychiatrist for counseling AND receive an inert substance that both the psychiatrist and the patient believed was an antidepressant medication. Thus, part of the improvement due to the “placebo” could be caused by the counseling.
- Venlafaxine’s remission rate is usually twice that of placebo (3, 4) and ranges from 37% to 59%.
- Venlafaxine has been shown to have a high discontinuation rate:
  - Three studies (3, 6, 11) reported discontinuation rates of 30% or higher.
  - Discontinuation rates for venlafaxine ranged from 9% to 62%.
- Venlafaxine hasn’t been conclusively shown to be superior to other modern antidepressant medications:
  - Venlafaxine has only been compared twice to paroxetine (1, 3), and in the second study venlafaxine had a 39% discontinuation rate.
  - Venlafaxine has only been compared three times to fluoxetine (1, 4, 5). Only two out of the three studies showed that venlafaxine was superior to fluoxetine.
  - Apart from paroxetine, fluoxetine, and imipramine; venlafaxine hasn’t been compared “head-to-head” with other antidepressant medications in the treatment of Major Depressive Disorder.
- None of these studies published the “Effect Size” of venlafaxine vs. the comparison treatment. Without knowing the “Effect Size”, it is very difficult to estimate the clinical significance of these research findings (despite the millions of dollars invested in this research).
- The majority of the venlafaxine studies only measured response rates (6, 7, 8, 9, 10, 12, 13) instead of more clinically useful information (like remission rates, relapse rates and discontinuation rates).
  - Only four studies measured remission rates (1, 3, 4, 5).
  - Only two studies (2, 11) measured relapse rates.
  - Less than half of the studies published their discontinuation rates (3, 4, 5, 6, 11, 13).
  - I question why so many of these studies only published their response rates (and failed to publish their remission rates and discontinuation rates). Since remission rates for all antidepressant medications are embarrassingly low (e.g., 37% to 59% for venlafaxine [3, 4]) and discontinuation rates are embarrassingly high (e.g., up to 39% at 12 weeks for venlafaxine [3]), do pharmaceutical companies have a bias against publishing remission rates and discontinuation rates for their antidepressants?

- Notwithstanding all of the above, I commonly use venlafaxine in my psychiatric practice since it is one of the most effective antidepressant medications currently available. However, sudden withdrawal from long-term use of venlafaxine can trigger a very uncomfortable (but not medically dangerous) withdrawal syndrome. I avoid triggering this withdrawal syndrome by taking at least 2 months to slowly wean my patients off venlafaxine.

Table summarizing all randomized controlled trials listed in PubMed using venlafaxine for the treatment of Major Depressive Disorder (as of July 25, 2006).

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<th>Randomized Controlled Trial</th>
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Venlafaxine Randomized Controlled Trials For Major Depressive Disorder


Venlafaxine XR demonstrates higher rates of sustained remission compared to fluoxetine, paroxetine or placebo.

**Shelton C, Entsuah R, Padmanabhan SK, Vinall PE.**

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The combined serotonin-norepinephrine reuptake inhibitor, venlafaxine XR, has demonstrated significant response and remission in patients diagnosed with depression when measured with the Hamilton Depression Rating Scale (HAM-D). This pooled analysis of data from five studies compared the sustained remission of depressive symptoms in patients treated with venlafaxine XR, the selective serotonin reuptake inhibitors (SSRIs) fluoxetine or paroxetine, or placebo. Data from 1391 subjects enrolled in five active and placebo-controlled studies who met the DSM-III-R or DSM-IV criteria for major depressive disorder were analysed. Three treatment groups were compared: venlafaxine XR (n = 560), fluoxetine/paroxetine (n = 298) and placebo (n = 496). Mean treatment duration was 8 weeks. Responders were defined as those patients whose HAM-D-21 score decreased by > or = 50% from baseline. Remission was defined as a HAM-D-17 score < or = 7. Sustained remission was defined as maintenance of remission through week 8 or the end of treatment (if before week 8) and for > or = 2 weeks. Between-group rate comparisons in outcome measures were carried out using Fisher's exact and log-rank tests. Venlafaxine XR produced significantly higher rates of sustained remission in depressed patients compared to fluoxetine/paroxetine or placebo over this 8-week treatment period.
period. As early as week 2, a significantly greater proportion of patients treated with venlafaxine achieved improved depression scores (remission and response). A significantly greater rate of remission and sustained remission occurred with venlafaxine compared to placebo. Remission was achieved earlier with venlafaxine and lasted throughout the remainder of the study. These results demonstrate that venlafaxine XR is more effective than fluoxetine/paroxetine for sustaining remission of depressive symptoms.

PMID: 15933485


Extended-release venlafaxine in relapse prevention for patients with major depressive disorder.

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Many studies have demonstrated that venlafaxine is an efficacious and safe treatment for major depressive disorder (MDD). This double-blind, placebo-controlled study was performed to evaluate the efficacy of venlafaxine extended-release (XR) (75-225 mg/day) in the prevention of relapse of depression. Patients with MDD who responded to an 8-week course of venlafaxine XR treatment, i.e., had a score ≤ 3 on the Clinical Global Impressions scale-Seriousness of Illness item (CGI-S) and a 21-item Hamilton Rating Scale for Depression (HAM-D(21)) score ≤ 10, were randomly assigned to receive continuation treatment (up to 6 months) with venlafaxine XR (n=161) or placebo (n=157). The main efficacy outcome measure was the number of patients who experienced a relapse of depression. Relapse was defined by either a combination of a patient meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for MDD and a CGI-S score > or = 4, two consecutive CGI-S scores > or = 4, or a final CGI-S score > or = 4 for a patient who withdrew from the study. The cumulative probability of relapse was calculated using the Kaplan-Meier method of survival analysis. During the 6-month evaluation period, significantly more patients in the placebo group had a relapse of MDD than did patients who continued treatment with venlafaxine XR. Cumulative relapse rates at 3 and 6 months were 19 and 28%, respectively, for venlafaxine XR, and 44 and 52%, respectively, for placebo. This study demonstrates that venlafaxine XR is an effective and safe continuation therapy.

PMID: 15003430


The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder or dysthymia.

Ballus C, Quiros G, De Flores T, de la Torre J, Palao D, Rojo L, Gutierrez M, Casais L, Riesgo Y.

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A 24-week, double-blind, randomized trial was performed to compare the efficacy and tolerability of venlafaxine and paroxetine in patients with major depression or dysthymia. Outpatients aged 18-70 years with a baseline score of 17 on the 21-item Hamilton Depression Rating Scale (HAM-D) were eligible. Patients were randomly assigned to venlafaxine, 37.5 mg, in the morning and evening or paroxetine, 20 mg, in the morning and placebo in the evening, which could be increased to venlafaxine, 75 mg twice daily, or paroxetine, 20 mg twice daily, after 4 weeks. Efficacy was assessed with the 21-item HAM-D, the Montgomery-Asberg Rating Scale, the Hamilton Anxiety Rating Scale, and the Clinical Global Impressions Scale. Forty-one patients were randomized to venlafaxine and 43 to paroxetine. At week 6, a response was observed in 55% of patients on venlafaxine and 29% on paroxetine (P = 0.031). At week 12, significantly (P = 0.011) more patients in the venlafaxine group had a HAM-D remission score of 8 or less (59% versus 31%). Discontinuation for any reason occurred in 16 (39%) patients on venlafaxine and 11 (26%) on paroxetine. The most common adverse events were nausea (28%), headache (18%) and dry mouth (15%) with venlafaxine and headache (40%) and constipation (16%) with paroxetine. Venlafaxine was effective and well tolerated for the treatment of patients with mild to moderate depression or dysthymia. A consistently higher proportion of patients had a response or remission on venlafaxine than on paroxetine.
A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression.

Rudolph RL, Feiger AD.

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BACKGROUND: We compared the efficacy and tolerability of venlafaxine XR with that of fluoxetine in a multicenter, randomized, double-blind, placebo-controlled study in depressed outpatients. METHODS: Outpatients, 18 years and older, who met DSM-IV criteria for major depressive disorder were included (n = 301 randomized; 232 completed). Patients were randomly assigned to eight weeks of treatment with either venlafaxine XR 75-225 mg/day (n = 100), fluoxetine 20-60 mg/day (n = 103), or placebo (n = 98). The primary efficacy outcome measures were the final ratings on the Hamilton Rating Scale for Depression (HAM-D21) total score, HAM-D21 depressed mood item, Montgomery-Asberg Depression Rating Scale total score, and Clinical Global Impressions Scale. RESULTS: Withdrawal from the study due to adverse events occurred in 6% of the patients in the venlafaxine XR group and 9% of the patients in the fluoxetine group. Patients treated with venlafaxine XR, but only rarely those treated with fluoxetine, had statistically significant improvements in their depression ratings compared with placebo at the end of the study. The percentages of patients who achieved full remission of their depression (HAM-D21 total score < or = 7) at the end of treatment were 37%, 22%, and 18% for the venlafaxine XR, fluoxetine, and placebo groups, respectively. The differences in remission rates between venlafaxine XR and the other groups were statistically significant (p < 0.05). LIMITATIONS: The superior remission outcome observed with venlafaxine XR treatment needs to be replicated in additional studies. CONCLUSION: Venlafaxine XR is a well-tolerated and efficacious treatment for depression. The results of this study suggest that venlafaxine XR is as well-tolerated as fluoxetine but may have some efficacy advantages over fluoxetine.

PMID: 10701474

Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group.

Silverstone PH, Ravindran A.

Department of Psychiatry, University of Alberta, Edmonton, Canada.

BACKGROUND: We conducted a randomized, double-blind, placebo-controlled study of the efficacy and safety of once-daily venlafaxine extended release (XR) and fluoxetine in outpatients with major depression and concomitant anxiety. METHOD: Patients who met DSM-IV criteria for major depressive disorder and satisfied eligibility criteria were randomly assigned to once-daily venlafaxine XR, fluoxetine, or placebo for 12 weeks. Efficacy was assessed with the Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), and Clinical Global Impressions scale. RESULTS: Among 359 outpatients, venlafaxine XR and fluoxetine were significantly superior (p < .05) to placebo on the HAM-D total score beginning at week 2 and continuing to the end of the study. Venlafaxine XR but not fluoxetine was significantly better than placebo at week 2 on the HAM-D depressed mood item. At week 12, the HAM-D response rate was 43% on placebo, 67% on venlafaxine XR, and 62% on fluoxetine (p < .05). The HAM-D remission rate was significantly higher (p < .05) at weeks 3, 4, 6, 8, 12, and final evaluation with venlafaxine XR and at weeks 8, 12, and final evaluation with fluoxetine than with placebo. The HAM-A response rate was significantly higher (p < .05) with venlafaxine XR than with fluoxetine at week 12. The incidence of discontinuation for adverse events was 5% with placebo, 10% with venlafaxine XR, and 7% with fluoxetine. CONCLUSION: Once-daily venlafaxine XR is effective and well tolerated for the treatment of major depression and concomitant anxiety and provides evidence for superiority over fluoxetine.

PMID: 10074873
A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression.

Rudolph RL, Fabre LF, Feighner JP, Rickels K, Entsuah R, Derivan AT.

Clinical Research and Development, Wyeth-Ayerst Research, Radnor, PA, USA.

BACKGROUND: We examined the efficacy and safety of three different dosages of venlafaxine hydrochloride (75, 225, and 375 mg/day) in a multicenter, randomized, double-blind, placebo-controlled, four-group study. METHOD: Outpatients, 18 to 65 years old, who met DSM-III criteria for major depression were included (N = 358 randomized; 194 completed). Of the total patients completing the trial, 59%, 56%, 51%, and 51% were in the placebo, 75-mg, 225-mg, and 375-mg groups, respectively. The primary outcome measures were the Hamilton Rating Scale for Depression (HAM-D21) total, HAM-D21 depression item, Montgomery-Asberg Depression Rating Scale total, and Clinical Global Impressions scale. RESULTS: Each dosage of venlafaxine was associated with statistically significant improvement as compared with placebo, based on the intent-to-treat sample. The two higher dosages were associated with a modestly greater antidepressant response than was the 75-mg dosage. Nausea, dizziness, somnolence, and anorexia were the most common adverse events attributable to venlafaxine. Since headache occurred at a similar frequency in both the drug and placebo groups, we did not consider it to be attributable to venlafaxine use. Withdrawal from the study due to adverse events occurred in 38%, 17%, 24%, and 30% of the patients in the placebo, 75-mg, 225-mg, and 375-mg groups, respectively. CONCLUSION: Venlafaxine, at dosages of 75-375 mg/day, is an effective and well-tolerated antidepressant. With increasing dosage, greater efficacy and possibly more adverse effects will occur.

PMID: 9541154


Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. The Venlafaxine XR 209 Study Group.

Thase ME.

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BACKGROUND: This was a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of once-daily venlafaxine extended release (XR) in out-patients with DSM-IV major depression. METHOD: Patients were randomly assigned to venlafaxine XR (75-225 mg) once daily or placebo for up to 8 weeks. The primary efficacy variables were the 21-item Hamilton Rating Scale for Depression (HAM-D) total score and HAM-D depressed mood item, the Montgomery-Asberg Depression Rating Scale (MADRS) total scores, and the Clinical Global Impressions (CGI) Severity scale. Data were analyzed on a modified intent-to-treat basis using the last-observation-carried-forward method. RESULTS: Venlafaxine XR (N = 91) was significantly more effective than placebo (N = 100) beginning at Week 2 on the CGI Severity scale, at Week 3 on the HAM-D depressed mood item, and at Week 4 on the HAM-D and MADRS; this superiority was maintained through Week 8. The most common treatment-emergent adverse events associated with venlafaxine XR were nausea, insomnia, and somnolence. The incidence of nausea was highest during the first week, decreased by 50% during the second week, and was comparable to that of placebo from Week 3 onward. CONCLUSION: These results demonstrate that venlafaxine XR is an effective and well-tolerated treatment of major depression.

PMID: 9378690


Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. Venlafaxine XR 208 Study Group.

Cunningham LA.

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This was a randomized, double-blind, placebo-controlled comparison of the efficacy and safety of once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR). Outpatients with DSM-III-R major depression were randomly assigned to venlafaxine XR, 75 mg once daily, venlafaxine IR, 37.5 mg twice daily, or placebo for a maximum of 12 weeks. If the response was inadequate after 2 weeks of treatment, the dosage of venlafaxine XR or IR could be increased to 150 mg daily. The primary efficacy variables were the 21-item Hamilton Depression (HAM-D) Rating Scale total score and depressed mood item, the Montgomery-Asberg Rating Scale (MADRS) total scores, and the Clinical Global Impressions (CGI) severity scale. Two hundred seventy-eight patients were evaluated for efficacy. Venlafaxine XR was significantly superior (p < 0.05) to placebo beginning at week 2 for the HAM-D, week 3 for the MADRS, and week 4 for the CGI severity. Similarly, venlafaxine IR was significantly superior (p < 0.05) to placebo beginning at week 2 on the HAM-D total and depressed mood item, week 3 on the MADRS total, and week 6 on the CGI severity scales. Venlafaxine XR exhibited superiority (p < 0.05) over venlafaxine IR at week 12 for all efficacy variables. The most common treatment-emergent adverse event with venlafaxine XR was nausea. The incidence of nausea was highest during the first 2 weeks with a low likelihood of developing nausea thereafter. The results of this study indicate that venlafaxine XR is safe, effective, and well tolerated for the treatment of major depression at once-daily doses ranging from 75 to 150 mg.

PMID: 9339881


Efficacy of venlafaxine in depressive illness in general practice.


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A double-blind, placebo-controlled study of 229 patients with a Research Diagnostic Criteria diagnosis of major, minor or intermittent depression was used to compare the clinical profiles of venlafaxine and imipramine in general practice. Venlafaxine produced a significant improvement compared to placebo in symptoms of depression and anxiety as rated by the total MADRS and percentage of responders, the CGI improvement, the CGI severity of illness, the BSA psychic anxiety item and the HSCL. On a number of these measures, venlafaxine was also significantly more effective than imipramine. Venlafaxine was significantly superior to both imipramine and placebo for the SARS total score and the items 'social/leisure' and 'extended family.' A similar proportion of patients discontinued treatment in each group, but fewer patients on venlafaxine discontinued treatment because of an unsatisfactory response.

PMID: 9242843


Venlafaxine in the treatment of children and adolescents with major depression.

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Major depression is commonly found in the child and adolescent population. Venlafaxine, a new antidepressant, has been used successfully in adults; however, its use in children and adolescents has been very limited. This study evaluated the efficacy and side effect profile of venlafaxine in the treatment of depression in children and adolescents. In a double-blind, placebo-controlled, 6-week study, 33 subjects between the ages of 8 and 17, who met DSM-IV criteria for major depression, were treated with either venlafaxine and therapy or placebo and therapy. Patient progress data were obtained by weekly rating assessments. Data on side effects were also obtained weekly. The statistical analysis indicated a significant improvement over time, but it could not be attributed to venlafaxine drug therapy. These findings are consistent with other studies where the efficacy of antidepressants in the treatment of major depression in this age population remains unproved. Low dosage and short length of treatment may account for the lack of efficacy. The findings did, however, suggest a low side-effect profile. Further studies are recommended to assess efficacy and to corroborate its safety in children and adolescents.

PMID: 9133767

Efficacy of venlafaxine and placebo during long-term treatment of depression: a pooled analysis of relapse rates.

Entsuah AR, Rudolph RL, Hackett D, Miska S.


The objective of this analysis was to determine the efficacy of venlafaxine in comparison with that of placebo during long-term treatment. A pooled analysis of relapse rates in outpatients with major depression continuing long-term treatment (up to 12 months) after responding to short-term treatment (6 weeks) was performed combining the data from four randomized, double-blind, placebo-controlled clinical trials. Relapses were defined as two consecutive Clinical Global Impression (CGI) severity scores greater than 3 (mildly ill), as a CGI severity score greater than 3 at withdrawal regardless of the reason for withdrawal, or as withdrawal due to lack of efficacy. Data from 304 patients (185 venlafaxine, 119 placebo) well balanced for baseline characteristics were included in the pooled analysis. Percentages of patients completing the long-term phase were 38% venlafaxine and 26% placebo (p = 0.034). Cumulative relapse rates by 6 months of long-term treatment were 11% venlafaxine and 23% placebo (p = 0.019). Cumulative relapse curves for the venlafaxine and placebo groups over the 1-year long-term treatment differed significantly (p = 0.022). The results from this analysis indicate that long-term treatment with venlafaxine in patients with major depressive disorder is effective in maintaining the initial response compared with placebo and suggest that venlafaxine will be effective in the prevention of relapse.

PMID: 8803651


Long-term safety and clinical acceptability of venlafaxine and imipramine in outpatients with major depression.

Shrivastava RK, Cohn C, Crowder J, Davidson J, Dunner D, Feighner J, Kiev A, Patrick R.

Eastside Comprehensive Medical Center, New York, New York.

The antidepressant efficacy and safety of venlafaxine was shown previously in 6-week, placebo-controlled trials. We evaluated the long-term safety and clinical acceptability of venlafaxine and imipramine in a double-blind, parallel-group, comparative study. Two hundred ninety depressed outpatients were treated with venlafaxine, and an additional 91 received imipramine for as long as clinically necessary, up to 1 year. The total daily dose of each drug could vary from 75 to 225 mg. The Clinical Global Impressions Scale and a therapeutic response rate that was based on Clinical Global Impressions Scale-Improvement and incorporated discontinuation information were used to evaluate efficacy. Safety determinations and patient subjective ratings were used to evaluate safety and clinical acceptability. During the study, the adverse events were generally mild to moderate and most subsided with continued treatment; the most frequent were nausea for venlafaxine and dry mouth for imipramine. The anticholinergic side effect burden was significantly higher in the imipramine group than in the venlafaxine group. Venlafaxine was judged significantly more acceptable than imipramine, on the basis of the subjective ratings by patients. Fewer venlafaxine-treated patients than imipramine-treated patients withdrew because of adverse events and unsatisfactory response. There was a consistent trend in the therapeutic response rates in favor of venlafaxine that reached statistical significance at months 2, 6, and 12. In this long-term study, patient acceptability was greater for venlafaxine than for imipramine, suggesting therapeutic advantages for venlafaxine in the long-term treatment of depression. Additional studies with other active comparators are underway to confirm and extend these encouraging results.

PMID: 7806687


Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients.

Schweizer E, Feighner J, Mandos LA, Rickels K.
BACKGROUND: Venlafaxine is a new phenylethylamine antidepressant that exhibits monoamine reuptake inhibition. The current study evaluates the efficacy of venlafaxine compared to that of imipramine in outpatients suffering from major depression of moderate-to-marked severity. METHOD: We conducted a double-blind, placebo-controlled, 6-week treatment study of 224 outpatients who met DSM-III-R criteria for major depression, and who had a score of at least 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D). Dosage was flexible and administered on a three-times-a-day schedule, with a mean maximum daily dose of 182 mg for venlafaxine and 176 mg for imipramine. RESULTS: For patients completing 6 weeks of treatment with venlafaxine, the HAM-D total score improved by 16.6 +/- 4.9 points. Improvement at 6 weeks was 13.6 +/- 6.3 points for patients treated with imipramine and 10.6 +/- 7.8 points for patients treated with placebo (p < .05 for active drug vs. placebo). Ninety percent of venlafaxine completers were rated as "much" or "very much" improved on the Clinical Global Impression-Improvement scale, compared to 79% treated with imipramine and 53% treated with placebo (p < .05). An endpoint analysis, where the last scores of patients who dropped out were carried forward to subsequent visits, showed significant efficacy only for venlafaxine and not imipramine, probably because of the higher attrition for the latter drug. Overall, both venlafaxine and imipramine were well-tolerated, with venlafaxine having a somewhat lower attrition rate due to adverse effects than imipramine (16% vs. 25%). CONCLUSION: These results, together with those of previously reported studies, suggest that venlafaxine has antidepressant efficacy comparable to that provided by available antidepressants.

PMID: 8071246