Influence of Sex and Menopausal Status on Response, Remission, and Recurrence in Patients With Recurrent Major Depressive Disorder Treated With Venlafaxine Extended Release or Fluoxetine: Analysis of Data From the PREVENT Study

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ABSTRACT

Objective: To evaluate the effects of sex and menopausal status on acute-, continuation-, and maintenance-phase treatment outcomes in patients with recurrent major depressive disorder (MDD).

Method: This was a secondary analysis of data from the Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years (PREVENT) trial, a multiphase, multicenter, double-blind study in which adult outpatients with recurrent MDD (by *DSM-IV* criteria) were randomly assigned to 10 weeks of acute-phase venlafaxine extended release (ER) (75–300 mg/d) or fluoxetine (20–60 mg/d). Patients achieving response or remission had 6 months of continuation-phase treatment. Responding or remitting patients in the venlafaxine ER group were randomly assigned to venlafaxine ER or placebo for 2 consecutive 12-month maintenance phases; fluoxetine-treated patients continued receiving fluoxetine. The outcome measures for this analysis were acute- and continuation-phase response and remission rates (as measured by the 17-item Hamilton Depression Rating Scale) and time to depression recurrence in the maintenance phases according to sex and menopausal status at baseline.

Results: The intent-to-treat population comprised 781 patients in the venlafaxine ER group (65% women) and 266 patients in the fluoxetine group (61% women); 64% of all women were premenopausal, and 25% were postmenopausal (5% perimenopausal; not analyzed). At acute-phase end, remission rates in the venlafaxine ER vs fluoxetine groups were 44% vs 47% in men, 51% vs 52% in women, 50% vs 52% in premenopausal women, and 52% vs 55% in postmenopausal women. At continuation-phase end, remission rates in the venlafaxine ER vs fluoxetine groups were 71% vs 74% in men, 72% vs 67% in women, 72% vs 69% in premenopausal women and 71% vs 63% in postmenopausal women. Response rates were consistent with these findings. Based on a Cox proportional hazards model, sex was not a significant predictor of recurrence during the first or second maintenance phase (hazard ratio [HR] = 1.233; $P = .3712$ and HR = 1.103; $P = .8075$, respectively), and neither was menopausal status at acute-phase baseline (HR = 0.941; $P = .8234$ and HR = 0.531; $P = .2065$, respectively).

Conclusions: In this study of patients with recurrent MDD, treatment outcomes with venlafaxine ER and fluoxetine did not differ on the basis of sex or menopausal status. Our confidence in these findings is limited by the lack of a placebo arm during the acute and continuation phases and by the small sample sizes for subgroup analyses in the maintenance phases.

Trial Registration: ClinicalTrials.gov identifier: NCT00046020

J Clin Psychiatry 2014;75(1):62–68

Submitted: *April 9, 2012; accepted May 9, 2013.*
Online ahead of print: *November 26, 2013 (doi:10.4088/JCP.12m07841).*
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Major depressive disorder (MDD) is a chronic, seriously impairing disorder and is ranked as the second leading cause of health-related disability among women.[1] Epidemiologic data on the prevalence of MDD indicate that it is approximately twice as common in women as in men,[2] and the risk for first onset in women is highest during the reproductive years.[3] In recent years, it has become evident that the menopausal transition is a period of increased risk for depression in women both with and without a previous history of MDD.[4–6]

Sex differences also have been reported in the pharmacologic treatment of MDD. Research suggests that the pharmacokinetics and pharmacodynamics of antidepressant medications can vary between male and female patients and that treatment response may differ by sex.[7–13] Furthermore, there is evidence that response to some antidepressants varies by menopausal status.[9,11,14–16] These findings suggest that the presence of estrogen may promote a greater response to antidepressants through enhancement of serotonergic activity.[9,11–13,15] However, this effect appears to be associated mainly with selective serotonin reuptake inhibitors (SSRIs), as other studies have found no significant sex difference in response to selective serotonin-norepinephrine reuptake inhibitors (SNRIs).[10,15] Additionally, previous studies have assessed these effects during acute treatment only; there are limited data evaluating the role of sex and menopausal status on long-term treatment outcomes in patients with depression. Given these potential differences in treatment outcomes, further research on the effects of sex and menopausal status on response to treatment is necessary in order to ensure that the most appropriate treatment is selected for each patient.

The Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years (PREVENT) trial was a multiphase, multicenter, randomized, double-blind study that evaluated acute and long-term treatment outcomes in patients with recurrent MDD who were treated with either the SNRI venlafaxine extended release (ER) or the SSRI fluoxetine.[17] There were no

Clinical Points

- Major depressive disorder (MDD) is about twice as common in women as in men, and the menopausal transition is a period of increased risk for depression in women.
- Evidence suggests that response to antidepressants may differ by sex and age, although data on response according to menopausal status are limited.
- This post hoc, secondary analysis found no differences in acute-, continuation- and maintenance-phase treatment outcomes with venlafaxine extended release or fluoxetine according to sex or menopausal status in patients with recurrent MDD.

statistically significant differences between treatments in response or remission rates at the end of a 10-week acute phase or at the end of a 6-month continuation phase.[17] In 2 consecutive 12-month maintenance phases, the probability of recurrence was significantly lower with venlafaxine ER vs placebo over 12 and 24 months,[18,19] and there was no significant difference between venlafaxine ER and fluoxetine over 24 months.[20]

This secondary analysis of data from the PREVENT study was designed to evaluate the effects of sex and menopausal status on acute and long-term treatment outcomes with venlafaxine ER or fluoxetine. Specifically, we assessed differences in treatment remission and response from the acute and continuation phases and examined time to depression recurrence in the maintenance phases according to sex and menopausal status. Based on the published literature, we expected to observe differences in the response to fluoxetine according to sex and menopausal status, but not with venlafaxine ER. To our knowledge, this is the first analysis of the effects of sex and menopausal status on long-term antidepressant treatment outcomes.

METHOD

This was a post hoc secondary analysis based on data from the acute, continuation, and maintenance phases of the PREVENT trial. The PREVENT trial enrolled patients from 29 sites in the United States and was conducted from August 2000 through October 2005 according to the US Food and Drug Administration Code of Federal Regulations and in accordance with the ethical principles of the Declaration of Helsinki.[17–19] The study is registered with ClinicalTrials.gov (identifier: NCT00046020).

PREVENT Trial

Details on the methods and results of the PREVENT trial have been reported elsewhere.[17–19] To summarize, eligible patients were randomly assigned in a 3:1 ratio to 10-week acute treatment with either flexible-dose venlafaxine ER (75–300 mg/d) or fluoxetine (20–60 mg/d). Patients who met criteria for response (17-item Hamilton Depression Rating Scale [$HDRS_{17}$][21] total score ≤ 12 and ≥ 50% reduction from baseline) at the end of the acute phase entered a 6-month continuation phase on the same treatment. Responders at the end of the continuation phase were enrolled into the first of 2 consecutive 12-month maintenance phases; at the start of each maintenance phase, responding patients in the venlafaxine ER group were randomly assigned to treatment with venlafaxine ER or placebo, and patients in the fluoxetine group continued on fluoxetine. All treatments were administered in a double-blind manner throughout all study phases.

Eligible participants were adult (aged ≥ 18 years) outpatients with at least a 1-month history of MDD (based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition[22]) and recurrent depression (≥ 3 major depressive episodes, with ≥ 2 episodes, including the current episode, occurring in the past 5 years, with ≥ 2 months between the end of the previous episode and the beginning of the current episode). Patients were required to have an $HDRS_{17}$ total score of ≥ 20 at screening and ≥ 18 at randomization. Exclusion criteria were chosen to select a patient population with a principal diagnosis of MDD (ie, nonbipolar/nonpsychotic) who were in good health.[17] Women who were pregnant, postpartum, or breastfeeding were excluded.

The primary efficacy assessment was the $HDRS_{17}$, which was administered by blinded, certified raters. The $HDRS_{17}$ was administered at screening baseline; weeks 1, 2, 3, 4, 6, 8, and 10 during the acute phase; and once monthly during the continuation and maintenance phases.

Analyses

The present analysis was performed on the intent-to-treat (ITT) population for the acute and continuation phases, which included all patients who had at least 1 dose of study medication and at least 1 postbaseline $HDRS_{17}$ evaluation.[17] The proportions of patients who achieved remission ($HDRS_{17}$ reduction ≤ 7) or a satisfactory therapeutic response ($HDRS_{17}$ reduction ≤ 12 or ≥ 50% decrease from baseline) were evaluated at acute-phase week 10 and continuation-phase month 6. Outcomes were assessed according to treatment assignment (ie, venlafaxine ER or fluoxetine) and evaluated separately by sex and menopausal status at acute-phase baseline (ie, premenopausal or postmenopausal). Logistic regression models were used to analyze the data. The numbers and percentages of remitters, responders, and nonresponders and *P* values from the models were summarized.

Analyses were performed on the efficacy evaluable population for the maintenance phases, which included all patients who had at least 1 dose of study medication and at least 1 postbaseline $HDRS_{17}$ evaluation. Time to depression recurrence at the end of the first maintenance phase (month 12) and the end of the second maintenance phase (month 24) was assessed according to treatment assignment (ie, venlafaxine ER, fluoxetine, or placebo) and evaluated separately by sex and menopausal status. Recurrence was defined as an $HDRS_{17}$ score > 12 and an $HDRS_{17}$ reduction from acute-phase baseline that was not more than 50% at

2 consecutive visits or at the last valid visit prior to patient discontinuation. Kaplan-Meier survival analyses were used to determine time to recurrence and Cox proportional hazards models were used to estimate the overall effect of sex and menopausal status, with age as a covariate, on depression recurrence. Differences between cohorts were compared using *P* values and hazard ratios (HRs) from the Cox proportional hazards model. All statistical tests in this analysis were 2-sided, with significance set at the .05 level.

Menopausal status was determined on the basis of documentation of each patient's status at the acute-phase baseline visit (according to patient-reported menstrual history). Menopause was defined on the basis of complete cessation of menses (≥ 1 year since last menstrual period). Two subgroups of patients were excluded from menopausal analyses. First, post-hysterectomy patients labeled as premenopausal were excluded because it could not be determined conclusively if post-hysterectomy patients with intact ovaries were still premenopausal. These patients made up < 10% of the total premenopausal group, and there was a sufficiently large sample size without these patients. Second, all perimenopausal patients were excluded because the sample size was insufficient for reliable analysis (n = 36). Perimenopause was defined on the basis of changes in cycle length and flow and the presence of intermittent menopausal symptoms (eg, occasional hot flashes, some vaginal dryness).

Table 1. Patients Included in the Current Analysis by Treatment Group, Sex, and Menopausal Status

	Venlafaxine ER, n	Fluoxetine, n	Placebo, n
Acute phase[a]	781	266	…
Men	276	105	…
Women	505	161	…
Premenopausal	315	113	…
Postmenopausal	135	33	…
Continuation phase[b]	496	176	…
Men	160	68	…
Women	336	108	…
Premenopausal	198	74	…
Postmenopausal	98	24	…
First 12-month maintenance phase[c]	129	79	129
Men	40	28	42
Women	89	51	87
Premenopausal	57	34	57
Postmenopausal	24	15	29
Second 12-month maintenance phase[d]	43	45	40
Men	17	20	12
Women	26	25	28
Premenopausal	13	15	16
Postmenopausal	9	8	9

[a]In PREVENT, 1,047 patients were randomly assigned to treatment in the acute phase.
[b]Overall, 715 patients were enrolled in the continuation phase; 672 were included in this analysis.
[c]Efficacy evaluable population = 337 patients.
[d]Efficacy evaluable population = 128 patients.
Abbreviation: ER = extended release.

RESULTS

Patients

The numbers of patients included in this analysis for each phase are shown in Table 1 by treatment group, sex, and menopausal status. In the acute-phase ITT population, 1,047 patients in total were randomly assigned to treatment. The proportions of men to women in the venlafaxine ER (35:65) and fluoxetine (39:61) groups were similar. Of the 715 patients enrolled in the continuation phase, 672 patients were included in the present analysis. In the first 12-month maintenance phase, the efficacy evaluable population consisted of 337 patients and in the second maintenance phase (24 months), the efficacy evaluable population consisted of 128 patients (Table 1).

Selected baseline demographics and clinical characteristics of the patient populations are presented in Tables 2 and 3. The number of women taking hormone replacement therapy or oral contraceptives at acute-phase baseline was 141 (31%) in the venlafaxine group and 44 (30%) in the fluoxetine group.

Acute- and Continuation-Phase Outcomes

At acute-phase week 10, there were no statistically significant differences between the venlafaxine ER and fluoxetine groups in remission rates among men (44% vs 47%, respectively) or women (51% vs 52%, respectively; Figure 1A). Similarly, there were no statistically significant differences between remission rates in the venlafaxine ER and fluoxetine treatment groups between premenopausal (50% vs 52%, respectively) and postmenopausal women (52% vs 55%) at acute-phase week 10, as well as at each time point throughout the acute phase. At the month 6 continuation-phase visit, remission rates in the venlafaxine ER and fluoxetine groups also were not significantly different among men (71% vs 74%, respectively) or women (72% vs 67%, respectively; Figure 1B) or among premenopausal (72% vs 69%, respectively) or postmenopausal (71% vs 63%, respectively) women.

Results of analyses of response rates were consistent with those of remission rates, with no significant differences observed among treatment groups. At acute-phase week 10, response rates for the venlafaxine ER and fluoxetine groups were 75% and 79%, respectively, among men and 80% and 79%, respectively, among women. Similarly, response rates in the venlafaxine ER and fluoxetine treatment groups were 80% and 77%, respectively, among premenopausal women and 79% and 88%, respectively, among postmenopausal women. At the month 6 continuation-phase visit, response rates in the venlafaxine ER and fluoxetine groups also were not significantly different among men (90% vs 96%, respectively) or women (90% vs 90%, respectively) or among premenopausal (89% vs 88%, respectively) or postmenopausal women (91% vs 92%, respectively). Based on logistic regression analyses, there were no significant treatment-by-sex or treatment-by–menopausal status interactions.

There was somewhat limited power to detect differences among postmenopausal women due to the small number of women in the fluoxetine group.

Table 2. Baseline Demographics and Clinical Characteristics of Acute- and Continuation-Phase Populations[a]

	Acute Phase (ITT population)			Continuation Phase (all patients enrolled)		
Characteristic	Venlafaxine ER (n = 781)	Fluoxetine (n = 266)	*P* Value	Venlafaxine ER (n = 530)	Fluoxetine (n = 185)	*P* Value
Age, mean (SD), y	39.6 (12.2)	40.0 (11.6)	.676[b]	40.4 (12.0)	40.9 (11.5)	.617[b]
Men/women, n (%)	276 (35)/505 (65)	105 (39)/161 (61)	.226[c]	174 (33)/356 (67)	72 (39)/113 (61)	.133[c]
Ethnicity, white, %	84	84	.560[c]	86	85	.352[c]
$HDRS_{17}$ total score, mean (SD)	22.6 (3.1)	23.0 (3.2)	.093[b]	22.4 (3.1)	22.7 (3.0)	.295[b]
Severity of depression, n (%)			.047[c]			.067[c]
Moderate ($HDRS_{17}$ score < 24)	525 (67)	161 (61)		371 (70)	116 (63)	
Severe ($HDRS_{17}$ score ≥ 24)	256 (33)	105 (39)		159 (30)	69 (37)	
CGI-S score, mean (SD)	4.3 (0.6)	4.3 (0.6)	.333[b]	4.3 (0.5)	4.3 (0.6)	.255[b]
Duration of current episode, mean (SD), mo	7.06 (6.81)	7.27 (6.44)	.662[b]	7.11 (7.09)	7.79 (6.94)	.257[b]

[a]All data are from acute-phase baseline.
[b]*F* test from 1-way analysis of variance.
[c]χ^2 test.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent to treat.

Table 3. Baseline Demographics and Clinical Characteristics of Maintenance-Phase Populations[a]

	First Maintenance Phase (efficacy evaluable population)			Second Maintenance Phase (ITT population)			
Characteristic	Placebo (n = 129)	Venlafaxine ER (n = 129)	Fluoxetine (n = 79)	Placebo B[b] (n = 40)	Venlafaxine ER (n = 43)	Placebo A[c] (n = 48)	Fluoxetine (n = 47)
Age, mean, y	42.6	42.0	43.0	42.8	44.8	45.2	46.7
Men/women, %	33/67	31/69	35/65	30/70	40/60	31/69	47/53
Ethnicity, white, %	88	81	89	80	81	90	85
$HDRS_{17}$ total score, mean (SD)							
Acute-phase baseline	22.5 (3.0)	22.3 (3.3)	22.3 (3.0)	21.5 (2.7)	22.2 (3.0)	22.3 (2.5)	22.6 (3.1)
Maintenance-phase baseline	4.9 (3.5)	4.3 (3.3)	4.4 (3.4)	4.1 (3.7)	4.8 (2.6)	4.4 (3.3)	3.9 (3.4)
Duration of current episode, mean, mo	7.10	6.32	7.85	5.62	7.03	8.29	7.26

[a]All data are from acute-phase baseline unless otherwise indicated.
[b]Patients on venlafaxine who were randomly assigned to placebo for second maintenance phase.
[c]Patients on venlafaxine who were randomly assigned to placebo for the first maintenance phase.
Abbreviations: ER = extended release, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent to treat.

Maintenance-Phase Outcomes

Kaplan-Meier analyses showed a significant effect of sex on time to recurrence in the first maintenance phase for the fluoxetine group (log-rank test, $P = .0467$), but not for the venlafaxine ER (log-rank test, $P = .4852$) or placebo (log-rank test, $P = .5651$) groups (Figure 2). For the fluoxetine treatment group, the probability of recurrence increased more slowly over time for male patients compared with female patients. In the second maintenance phase, sex had no significant effect on time to recurrence for the venlafaxine ER (log-rank test, $P = .8283$), fluoxetine (log-rank test, $P = .2224$), or placebo (log-rank test, $P = .3351$) groups (Figure 3). Overall, sex was not a significant predictor of recurrence in the first maintenance phase (HR = 1.233; $P = .3712$) or the second maintenance phase (HR = 1.103; $P = .8075$).

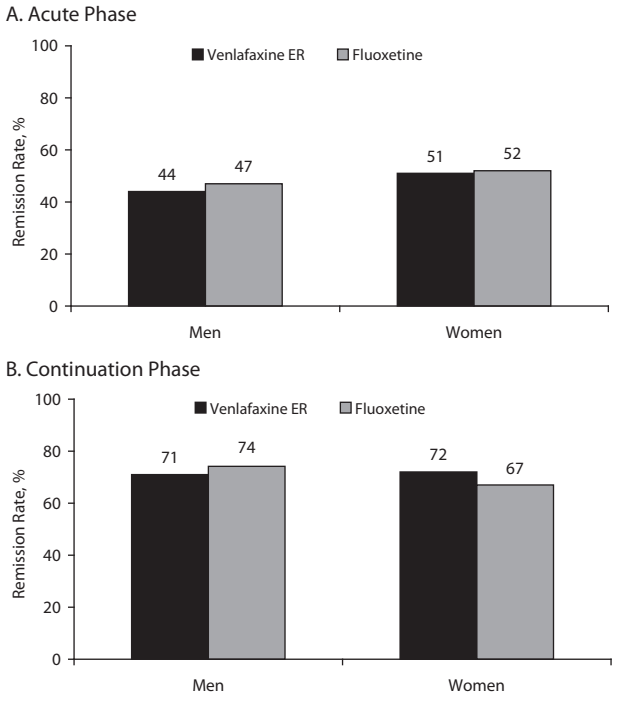
Analyses of menopausal status (at acute-phase baseline) showed no significant effect on time to recurrence in either the first or second maintenance phase for the venlafaxine ER (log-rank tests, $P = .9630$ and $P = .0863$, respectively), fluoxetine (log-rank tests, $P = .7379$ and $P = .2277$, respectively), and placebo (log-rank tests, $P = .9202$ and $P = .8396$, respectively) groups. Overall, menopausal status at acute-phase baseline was not a significant predictor of recurrence in the first maintenance phase (HR = 0.941; $P = .8234$) or the second maintenance phase (HR = 0.531; $P = .2065$).

DISCUSSION

This post hoc analysis of data from the PREVENT trial examined the effects of sex and menopausal status on acute-, continuation-, and maintenance-phase outcomes among patients with recurrent MDD who were treated with venlafaxine ER or fluoxetine. Overall, outcomes did not differ on the basis of sex or menopausal status at acute-phase baseline. Rates of remission and response in the venlafaxine ER and fluoxetine groups at both the acute- and continuation-phase endpoints were not significantly different between men or women or between premenopausal or postmenopausal women.

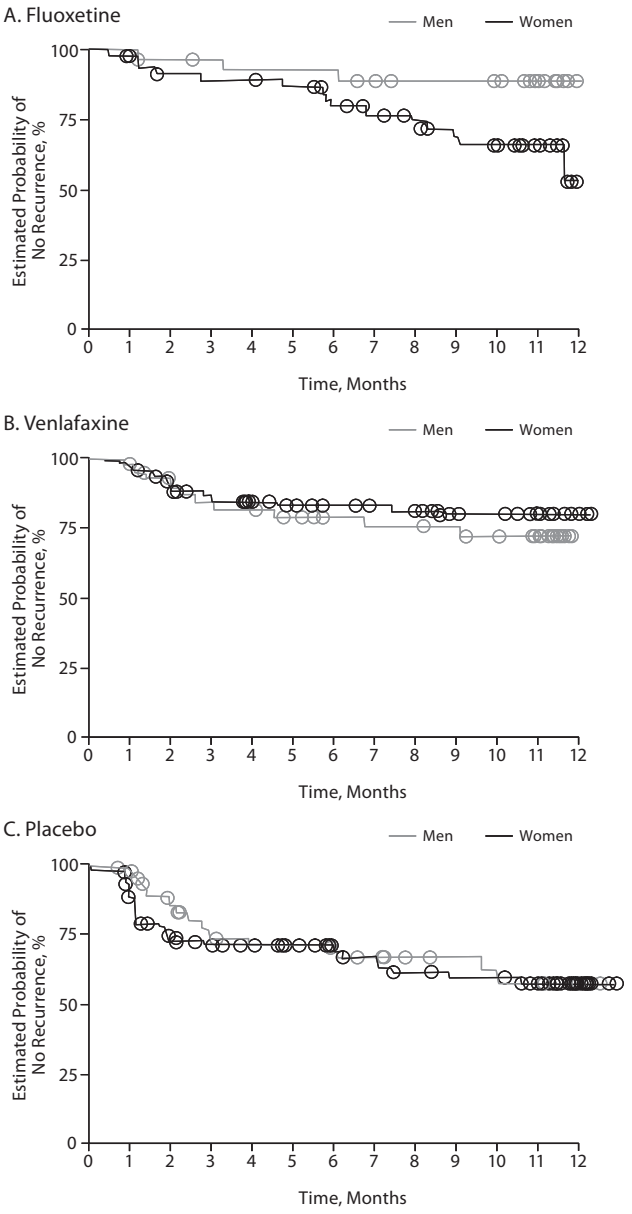
Similarly, in the maintenance phases, sex and menopausal status were not significant predictors of recurrence based on a proportional hazards regression analysis. However, logistic regression analysis of the first 12-month maintenance phase alone indicated that men were significantly less likely to have a recurrence than women in the fluoxetine group, with the probability of recurrence increasing more slowly over time for men compared with women. The reason for this

Figure 1. $HDRS_{17}$ Remission Rates by Treatment and Sex: (A) Acute Phase (week 10, ITT population, LOCF) and (B) Continuation Phase (month 6, ITT population, LOCF)



Abbreviations: ER = extended release, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent to treat, LOCF = last observation carried forward.

Figure 2. Kaplan-Meier Curves for Probability of No Recurrence, First Maintenance Phase (12 months, efficacy evaluable population)[a]



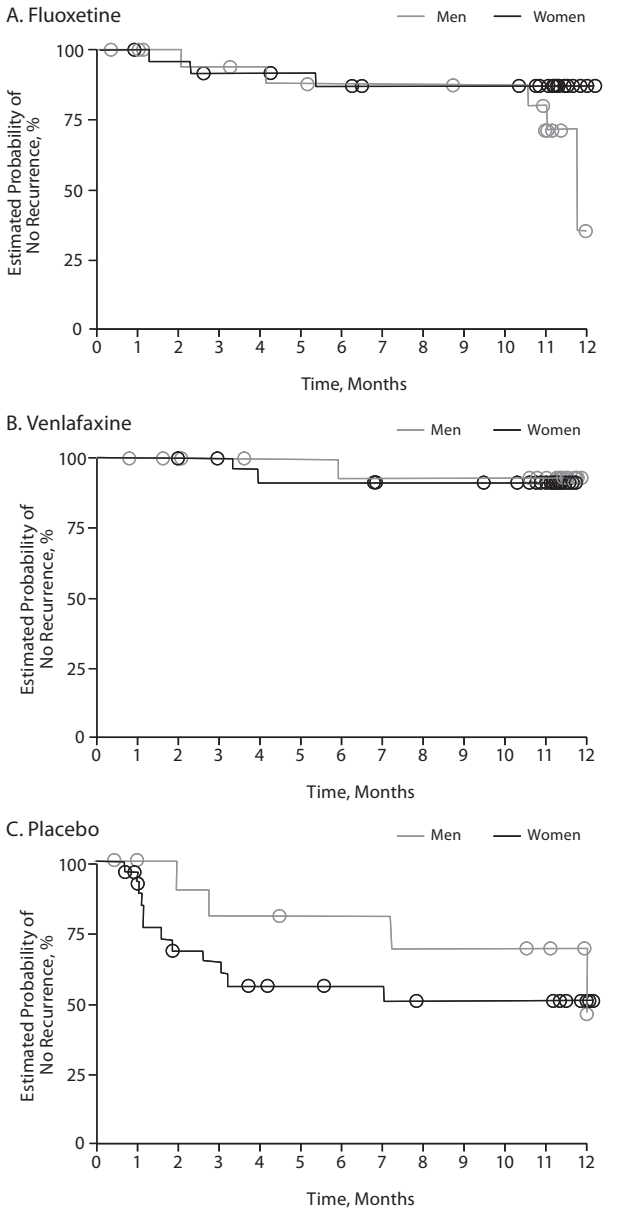
[a]Circles represent censored values.

difference is unclear and deserves further study. However, interpretation of these results should be made with caution owing to the small sample sizes for the subgroup analyses during maintenance treatment.

Contrary to some evidence suggesting sex differences in antidepressant treatment response,[7–13] we did not find overall sex differences (men vs women) in response to either venlafaxine ER or fluoxetine in our study. This finding for venlafaxine ER is consistent with other studies that have found no sex difference in response to SNRIs.[10,15] The result for fluoxetine was surprising, as several studies, including an analysis of the recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) data,[13] have indicated that women may respond better than men to SSRIs,[8,13] whereas other studies have found no such sex differences.[16,23–25] Additionally, although some studies have found that SSRIs may be more effective in premenopausal women compared with postmenopausal women,[9,14–16] our results are consistent with data from other studies that suggest menopausal status does not moderate response to SSRIs[24,26] or SNRIs.[15] With respect to maintenance antidepressant treatment, to our knowledge, our analysis is the first to examine the influence of sex and menopausal status on depression recurrence. Additional randomized, controlled trials of outpatients with MDD will be necessary to corroborate our findings on the nonsignificant differences between men and women and between premenopausal and postmenopausal women in time to depression recurrence during maintenance treatment.

The strengths of this analysis are the large sample size for the acute and continuation phases, the length of treatment, and that it is the first reported analysis of the effects of sex and menopausal status utilizing maintenance therapy data. Interpretation of the results of this analysis is limited by several factors. First, this was a post hoc analysis of data from a long-term clinical trial. Like most clinical trials, patients with serious or unstable secondary medical conditions were excluded, so patients in this analysis may not be representative of depressed outpatients in clinical practice. Moreover, the PREVENT trial enrolled patients with a history of highly recurrent depression (3 or more episodes, 2 in the past 5 years), and differences between groups may have been masked

Figure 3. Kaplan-Meier Curves for Probability of No Recurrence, Second Maintenance Phase (24 months total, ITT population)[a]



[a]Circles represent censored values.
Abbreviation: ITT = intent to treat.

by overall recurrence rates in this selected population. In addition, women taking hormone therapy were not excluded from the post hoc analysis. Evidence suggests that hormone therapy may enhance response to SSRIs in postmenopausal women,[27,28] and thus the inclusion of women taking hormone therapy or hormonal contraceptives may have confounded the results. However, a post hoc logistic regression analysis did not reveal any significant differences in acute-phase remission rates in women taking hormone therapy or hormonal contraceptives compared with women who were not taking these medications (data not shown). Interpretation of the results also is limited by the small sample sizes for the subgroup analyses: only those patients who responded during the acute phase and did not relapse during the continuation phase entered the maintenance phase. Due to the small sample size, there was somewhat limited power to detect differences among cohorts, particularly among patients in the fluoxetine group and among treatment groups at the end of the second maintenance phase. Furthermore, owing to the length of treatment, a small proportion of women may have transitioned from premenopausal to perimenopausal status over the course of the study. Menopausal status was assessed at acute-phase baseline but was not assessed again during the study. Finally, the design of the study did not allow valid statistical comparisons between the fluoxetine and placebo groups in the maintenance phases. The capacity to detect a differential signal in these analyses may have been compromised by the lack of a placebo arm during acute and continuation treatment and the goal of enhancing entry into the maintenance phases of the study.

CONCLUSION

Among this sample of patients with recurrent MDD with high rates of response and remission achieved during acute- and continuation-phase treatment with venlafaxine ER or fluoxetine, an analysis of sex and menopausal status did not find a difference in treatment outcomes. Our confidence in these findings is limited by the lack of a placebo arm during the acute and continuation phases and by the small sample sizes for subgroup analyses in the maintenance phases.

Drug names: fluoxetine (Prozac and others), venlafaxine (Effexor and others).
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Potential conflicts of interest: **Dr Kornstein** has been a consultant to or has participated in advisory boards for Pfizer, Eli Lilly, Takeda, Trovis, Forest, Lundbeck, Allergan, and Otsuka; has received grant/research support from Pfizer, Eli Lilly, Euthymics, Forest, Boehringer-Ingelheim, and Rexahn; and has received royalties from Guilford Press. **Mr Pedersen** is an employee of Pfizer (previously Wyeth) and holds Pfizer stock. **Dr Holland** has been a consultant to Pfizer and Novartis; has received grant/research support from Eli Lilly, Cyberonics, Forest, Genentech, Baxter, and Novartis; and has been a speaker or participated in advisory boards for Pfizer, Novartis, and Eli Lilly. **Dr Nemeroff** has received research grants from the National Institutes of Health and the Agency for Healthcare Research and Quality; has been a consultant for Xhale, Takeda, SK Pharma, Shire, Roche, and Eli Lilly; holds CeNeRx, PharmaNeuroBoost, Revaax Pharma, Xhale, and NovaDel Pharma stock; has other financial interests in CeNeRx and PharmaNeuroBoost; holds patents for a method and devices for transdermal delivery of lithium (US 6,375,990B1) and a method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2); has participated in scientific advisory boards for the American Foundation for Suicide Prevention, CeNeRx, the National Alliance for Research on Schizophrenia and Depression, Xhale, PharmaNeuroBoost, the Anxiety Disorders Association of America, Skyland Trail, and AstraZeneca (2009); and has been on the boards of directors for the American Foundation for Suicide Prevention, Mt Cook Pharma (2010), NovaDel (2011), Skyland Trail, and Gratitude America. **Dr Rothschild** has been a consultant for Allergan, GlaxoSmithKline, Eli Lilly, Noven, Pfizer, Shire, Sunovion, and Takeda; has received grant/research support from National Institute for

Mental Health, Cyberonics, Takeda, and St Jude Medical; and received honorarium from the American Psychiatric Press, Inc (books) and the University of Massachusetts Medical School for the Rothschild Scale for Antidepressant Tachyphylaxis. **Dr Thase** has no conflicts of interest pertaining to this article, although he reports the following relationships with companies that develop treatment for depression or provide education pertaining to those treatments. Dr Thase has been an advisor/consultant to Alkermes, AstraZeneca, Bristol-Myers Squibb, Dey, Eli Lilly, Forest, Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, Lundbeck, MedAvante, Merck, Neuronetics, Novartis, Otsuka, Ortho-McNeil, Pamlab, Pfizer (formally Wyeth Ayerst), Schering-Plough (formerly Organon), Shire, Sunovion, Takeda (Lundbeck), and Transcept; has received grant support from the Agency for Healthcare Research and Quality, Eli Lilly, GlaxoSmithKline (ended 2010), National Institute of Mental Health, Otsuka, and Sepracor; has equity holdings in MedAvante; and receives royalty income from American Psychiatric Foundation, Guilford Publications, Herald House, Oxford University Press, and WW Norton & Company. His spouse is employed by Embryon (formerly Advogent), which does business with Bristol-Myers Squibb and Pfizer/Wyeth. **Dr Trivedi** has been a consultant to or participated in advisory boards for Abbott, Abdi Ibrahim, Akzo (Organon), Alkermes, AstraZeneca, Axon Advisors, Bristol-Myers Squibb, Cephalon, Eli Lilly, Evotek, Fabre-Kramer, Forest, GlaxoSmithKline, Janssen, Johnson & Johnson, Libby, Lundbeck, Mead-Johnson, MedAvante, Medtronic, Neuronetics, Otsuka, Pamlab, Parke-Davis, Pfizer, PGxHealth, Rexahn, Sepracor, Shire, Sierra, Takeda, Tal Medical/Puretech Venture, Transcept, Vantage Point, and Wyeth-Ayerst; and has received research support from the Agency for Healthcare Research and Quality, Corcept Therapeutics, Cyberonics, Merck, National Alliance for Research on Schizophrenia and Depression, National Institute of Mental Health, National Institute on Drug Abuse, Naurex, Novartis, Pharmacia & Upjohn, Predix (EPIX), Solvay, Targacept, and Valeant. **Dr Ninan** is an employee of Pfizer and holds Pfizer stock. **Dr Keller** received funding from Wyeth as a paid consultant in the design and conduct of the PREVENT study, was a paid consultant to Medtronic and CeNeRx, received a grant/research support from Pfizer, and participated in an advisory board for CeNeRx.

Funding/support: Sponsored by Wyeth Research, Collegeville, Pennsylvania, which was acquired by Pfizer Inc in October 2009.

Previous presentation: The data in this manuscript have been previously presented at the North American Society for Psychosocial Obstetrics and Gynecology Annual Meeting, February 8–10, 2007, Portland, Oregon; and the American Psychiatric Association Annual Meeting, May 19–24, 2007, San Diego, California.

Acknowledgments: Medical writing support was provided by Kathleen Dorries, PhD, and medical editing support was provided by Jennifer Karpinski, BA, both of Embryon, LLC, a Division of Advanced Health Media, LLC (formerly Medesta Publications Group, a Business of Advogent). This assistance was funded by Wyeth, which was acquired by Pfizer Inc in October 2009. Further medical editing support was provided by Helen Varley, PhD, UBC-Envision Group, Horsham, UK, and funded by Pfizer Inc.

Additional information: The PREVENT database is owned by Pfizer and is not publicly available. The primary datasets for the acute, continuation, and maintenance phases are reported fully in references 17–19.

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