Response and Remission Rates in Different Subpopulations With Major Depressive Disorder Administered Venlafaxine, Selective Serotonin Reuptake Inhibitors, or Placebo

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Background: Most examinations of the clinical efficacy of drugs used to treat depression pool subjects across gender and age groups. This investigation compared these patient subpopulations on the basis of remission and response rates associated with venlafaxine and selective serotonin reuptake inhibitor (SSRI) treatment.

Method: A meta-analysis of original data from 8 comparable double-blind, active-controlled, randomized clinical trials (4 also placebo-controlled) was conducted. Antidepressant efficacy was assessed for patients (N = 2045) aged 18 to 83 years (subgroups: ≤ 40, 41–54, 55–64, and ≥ 65 years) who met DSM-III-R criteria for major depression or DSM-IV criteria for major depressive disorder and were randomly assigned to receive venlafaxine (immediate release, N = 474; extended release, N = 377), one of several SSRIs (N = 748), or placebo (N = 446) for up to 8 weeks. Symptoms of depression were assessed using the Hamilton Rating Scale for Depression (HAM-D). Remission was defined as a HAM-D-17 score ≤ 7, response was defined as ≥ 50% decrease in HAM-D-21 score, and absence of depressed mood was defined as a HAM-D depressed mood item score of 0.

Results: We detected no significant age-by-treatment, gender-by-treatment, or age-by-gender-by-treatment interactions; men and women of different ages within a given antidepressant treatment group exhibited similar rates of remission, response, and absence of depressed mood. Regardless of age or gender, remission rates during venlafaxine therapy were significantly higher than during SSRI therapy (remission rates at week 8: venlafaxine, 40%–55% vs. SSRI, 31%–37%; $p < .05$). Regardless of patient age or gender, onset of remission was more rapid with venlafaxine than with SSRI treatment. By contrast, rates of absence of depressed mood with venlafaxine (34%–42%) and SSRIs (31%–37%) did not differ significantly and tended to be similar for all patient subgroups.

Conclusion: These data suggest that men and women have comparable responses to SSRIs and venlafaxine across various age groups. Moreover, patients exhibited a more rapid onset and a greater likelihood of remission with venlafaxine therapy than with SSRI therapy regardless of age or gender.

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Major depression is a common, potentially disabling, and often chronic condition.[1–8] Investigations consistently show that major depression occurs approximately twice as often in women as in men and that this difference exists across most cultures.[2,9] The gender disparity in rate of first onset of major depression emerges around 13 to 15 years of age and continues for the remainder of life.[9] Age at first onset in women also tends to be earlier; incidence peaks around 30 years of age, remains high throughout the childbearing years, and then decreases after the age of 45 years.[10,11] In contrast, age at first onset tends to be later in men, and incidence peaks in the middle adult years of life.[11] Patterns of comorbidity and symptoms among women and men differ. Depression in women tends to occur in tandem with symptoms of anxiety, while depression in men is often accompanied by substance abuse. Moreover, before menopause, women are also somewhat more likely to overeat, gain weight, or oversleep than comparably aged men.[12] Younger depressed women also may manifest fewer abnormalities of hypothalamic-pituitary-adrenocortical axis regulation and sleep neurophysiology when compared with depressed men of similar age or depressed perimenopausal or postmenopausal women.[13]

The reasons for these gender differences in age at onset, rate of incidence, patterns of comorbidity, and neurobiology are not well understood. The consistency with

which the difference in prevalence emerges across cultural boundaries suggests the importance of genetic factors in the expression of neuroendocrinologic-clinical manifestations. The apparently pivotal nature of both menarche and menopause in the expression of clinical and neurobiological correlates of depression certainly suggests that circulating sex hormone levels influence the vulnerability to, and manifestations of, major depression in women.[14] It is also conceivable that there may be universal social and/or environmental risk factors that may account for the age-related variation in clinical manifestations of major depression among both women and men.

Disparities in the incidence of depression have also been observed between different age groups and further suggest that the diagnosis of major depression may encompass different subtypes of depression that arise from separate etiologic factors. Incidence of major depression among individuals aged 18 to 65 years displays 2 distinctly separate peaks; the first occurs around the age of 30 years, and the second occurs around the age of 50 years.[11] In the population aged 65 years or older and living in the community, the prevalence of depressive symptoms is approximately 15%, and major depression tends to occur in 1% to 3%.[15] Rates of incidence of both depressive symptoms and major depression increase dramatically among the elderly in conjunction with increasing levels of formal medical care received, with the highest rates observed among those elderly receiving long-term care in nursing homes.[16,17] The etiology of early-onset versus late-onset major depression is very likely to be different. For instance, evidence suggests that early-onset major depression is associated with a family history of depression (e.g., genetic risk factors), while late-onset major depression may be associated with cerebrovascular and/or neurodegenerative changes.[18,19]

These epidemiologic findings clearly suggest that the vulnerability to major depression may differ substantially between women and men and that age may play an important moderating role. However, whether these factors have a meaningful impact on response to antidepressant drug therapy has not been conclusively determined. Many investigations indicate important differences between women and men and younger versus older adults in drug absorption, volume of distribution, hepatic metabolism, percentage of body fat, renal clearance, and other variables that affect drug bioavailability.[20] Despite such evidence, in most clinical trials of antidepressant drugs, responses to drug treatments are considered without respect to subject age or gender. However, some studies suggest that younger women are less responsive to tricyclic antidepressant drug therapy as compared with therapy with monoamine oxidase inhibitors or selective serotonin reuptake inhibitors (SSRIs).[21,22] Other studies report that more severely depressed older adults may be less responsive to SSRIs than to tricyclics, especially when patients have a cardiovascular or cerebrovascular comorbidity.[23–25] Because these studies used nortriptyline as the tricyclic comparator, it is possible that noradrenergic effects are relatively more important for treatment of older depressed patients than for younger depressed patients, although this has not been demonstrated among depressed patients in general.[23–26]

The goal of the present investigation was to determine whether age and gender importantly influence response to antidepressant therapy with either SSRIs or venlafaxine, which inhibits reuptake of norepinephrine as well as serotonin. Previously, we observed that patients treated with venlafaxine or venlafaxine extended release (XR) had a significantly greater chance of remission than patients treated with various SSRIs in a meta-analysis of 2045 patients treated in double-blind clinical trials.[27] In the current article, we examine whether this advantage is apparent across age and gender groupings or is localized to a patient subgroup, such as men or older women. Portions of these data, derived from phase 2 or 3 clinical trials, have been presented previously.[27–32]

METHOD

Eight phase 2 or 3 trials conducted in the United States, Canada, and Europe were included in our pooled analysis, and principal results from 6 of these studies[33–38] have been published as research articles or abstracts accompanied by posters. Data from the other 2 trials are unpublished (Study 347, data on file, Wyeth-Ayerst Laboratories, Collegeville, Pa., Dec. 1992; Study 349, data on file, Wyeth-Ayerst Laboratories, Collegeville, Pa., July 1994). Patient populations and study designs were comparable (Table 1). Each study used a randomized, double-blind, parallel-group procedure with up to 8 weeks of active treatment to evaluate venlafaxine or venlafaxine XR, fluoxetine, paroxetine, or fluvoxamine. Four of the 8 studies also included placebo controls.[35–38] Seven of the studies were outpatient trials; the eighth enrolled only inpatients.[33] All studies were approved by the appropriate human ethics committees at the participating sites and were conducted according to the guidelines of the Declaration of Helsinki and its amendments. Table 1 summarizes the characteristics of each study.

Patient Populations

The pooled analysis included inpatients (N = 68) and outpatients (N = 1977). Enrolled patients were at least 18 years old and had met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM-III-R)[39] or DSM-IV[40] for major depression or major depressive disorder, respectively. Moreover, each patient had a minimum score of either 20 on the 21-item Hamilton Rating Scale for Depression (HAM-D-21)[41] or 25 on the Montgomery-Asberg Depression Rating Scale

(MADRS)[42] (depending on the study) both prestudy and at baseline (study day 1), with no greater than a 20% decrease in severity between prestudy and baseline evaluations.

Women who were pregnant, lactating, or had a positive β-human chorionic gonadotropin pregnancy test were not eligible to participate. Also excluded were patients who had a significant history of cardiovascular, renal, hepatic, and/or seizure disorders, as well as those patients who had abnormal baseline physical examination laboratory and/or electrocardiogram (ECG) findings. Other reasons for exclusion were a history of alcohol or drug abuse or use of any investigational or antipsychotic drugs within 30 days; monoamine oxidase inhibitors within 14 days; or antidepressants, anxiolytics, or sedative-hypnotic drugs within 7 days of study day 1.

Table 1. Summary of the 8 Studies Included in the Pooled Analysis[a]

Study	Treatment	Dose Range (mg/d)	All Patients (N = 2117)[b]/ITT Population (N = 2045)	Treatment Duration (wk)
Rudolph and Feiger (Study #211)[35]	Venlafaxine XR	75–225	100/95	8
	Fluoxetine	20–60	103/103	
	Placebo	...	98/97	
Clerc et al (Study #340)[33]	Venlafaxine	100–200	34/33	6
	Fluoxetine	20–40	34/34	
Study #347[c]	Venlafaxine	75–150	77/77	6
	Fluvoxamine	100–200	34/34	
Dierick et al (Study #348)[34]	Venlafaxine	75–100	153/145	8
	Fluoxetine	20	161/157	
Study #349[d]	Venlafaxine	75–150	82/75	8
	Paroxetine	20–40	85/80	
Silverstone et al (Study #360)[36]	Venlafaxine XR	75–225	128/121	12
	Fluoxetine	20–60	121/114	
	Placebo	…	118/118	
Salinas et al (Study #367)[38]	Venlafaxine XR	75–150	165/161	8
	Paroxetine	20	81/80	
	Placebo	…	83/82	
Rudolph et al (Study #372)[37]	Venlafaxine	75–375	156/144	6
	Fluoxetine	20–80	152/146	
	Placebo	…	152/149	

[a]Adapted with permission from Thase et al.[27] Abbreviations: ITT = intent-to-treat, XR = extended-release formulation.
[b]Number of patients enrolled.
[c]Data on file, Wyeth-Ayerst Laboratories, Collegeville, Pa., Dec. 1992.
[d]Data on file, Wyeth-Ayerst Laboratories, Collegeville, Pa., July 1994.

Study Procedure

Eligible outpatients underwent a prestudy evaluation within 7 to 10 days of entering the double-blind treatment period. Prestudy assessments included a complete medical and psychiatric history, administration of the HAM-D-21, a complete physical examination, assessment of vital signs, standard clinical laboratory testing, a serum pregnancy test for women, and a 12-lead ECG. Further measurements, taken during the prestudy period and on study day 1, included the MADRS and the Clinical Global Impressions-Severity of Illness scale (CGI-S).[43] At some study centers, patients underwent a 7-day, single-blind, placebo lead-in period before the double-blind drug treatment phase began.

Patients who satisfied the study criteria were randomly assigned to receive venlafaxine XR or venlafaxine immediate-release (IR) formulations, an SSRI (fluoxetine, paroxetine, or fluvoxamine), or placebo (see Table 1 for summary of doses). All study medications, including placebo, were supplied in identical capsules and administered with food in the morning.

Efficacy and Safety Assessments

The HAM-D, from which HAM-D-21 scores as well as 17-item HAM-D (HAM-D-17) scores were generated, was administered on study days 7, 14, 21, 28, 42, and, in some studies, 56 to assess treatment efficacy. Patients were examined and were questioned regarding any adverse events. Adverse events, including any signs or symptoms emergent on treatment and any clinically significant changes on physical examination in vital signs, 12-lead ECG, and clinical laboratory findings during treatment, were recorded.

Statistical Analysis

Analysis of variance was used to test for comparability of treatment groups for continuous variables, such as age, clinical characteristics, and baseline scores for the HAM-D-21, MADRS, and CGI-S. The Fisher exact test was used to compare nominal variables at baseline, such as gender and race. Remission was defined as a HAM-D-17 score ≤ 7 and was interpreted as freedom from symptoms or signs of illness activity.[44] Responders were patients whose HAM-D-21 score decreased ≥ 50% from baseline. Absence of depressed mood was defined as a score of 0 on the depressed mood item of the HAM-D-21. Rates of remission, response, and absence of depressed mood were calculated using endpoint scores, such that the final observation for patients who withdrew prematurely from the study was used. For each data collection timepoint, remission, response, and absence of depressed mood rate differences between venlafaxine, SSRI, and placebo for the pooled age subpopulations (≤ 40, 41–54, 55–64, and ≥ 65 years) and gender subpopulations were determined using the Fisher exact test. Tests for main effects and interactions were conducted using a generalized linear model (GenMod; SAS Institute Inc., Cary, N.C.), in which age was defined as a continuous variable. In these models, outcome measures were week-8 values for remission, response, and absence of depressed mood; independent variables were treatment, gender, age, age-by-treatment, gender-by-treatment, and age-by-gender-by-treatment as interaction terms. For these models, tests of hypotheses were 2-sided and were considered significant when the

Table 2. Patient Demographic and Baseline Characteristics[a]

Characteristic	Venlafaxine (N = 865)	SSRI (N = 757)	Placebo (N = 450)
Age			
Mean, y	42	42	41
Range, y	18–79	18–83	18–80
Weight, lb, mean	161	162	172
Women/men, %	65/35	64/36	62/38
Psychic anxiety item score, mean	2	2	2
HAM-D-21 score, mean	26	26	26
MADRS score, mean	31	31	30

[a]Adapted with permission from Thase et al.[27]
Abbreviations: HAM-D-21 = 21-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.

p value was ≤ .05. To identify possible differences between the patient subgroups with respect to reports of adverse events, multiple pairwise comparisons were conducted using the Fisher exact test; to avoid type I errors due to the number of comparisons conducted, a Bonferroni adjustment was made, and the p value was considered significant at ≤ .004.

RESULTS

Patient Demographics

Two thousand seventy-two patients were randomly assigned to treatment groups. Baseline demographics and clinical characteristics were comparable between treatment groups (Table 2). Two thousand forty-five patients were included in the intent-to-treat analyses of venlafaxine (IR formulation, N = 474; XR formulation, N = 377), the SSRIs (N = 748), and placebo (N = 446). Patients included in these intent-to-treat analyses were further categorized according to age (≤ 40, N = 946; 41–54, N = 788; 55–64, N = 232; ≥ 65 years, N = 79) and gender (men, N = 734; women, N = 1311). Patients participating in the study ranged in age from 18 to 83 years. Women comprised 64% of the patients. All data from 1 investigational site (27 patients total) were excluded prior to the analysis because their validity could not be verified during the field monitoring review. There were no differences in baseline HAM-D-21 total, MADRS, and CGI-S scores between patients randomly assigned to the different drug treatment groups, nor were such differences observed within patient subpopulations subsequently defined according to age and gender.

Safety and Adverse Events

The frequency of the most commonly reported adverse events among patient subgroups receiving venlafaxine, SSRIs, or placebo is presented in Table 3. The most commonly reported adverse events were nausea, headache, insomnia, and dizziness. Fewer than 3% of patients in each of the treatment groups experienced changes in blood pressure during the 8-week treatment period. Among men, there were fewer reports of headache with venlafaxine than with SSRIs or placebo. In contrast, frequency of headache reported by women was comparable with venlafaxine, SSRIs, and placebo, while nausea was more frequently reported with venlafaxine. For both men and women, reported rates of insomnia and dizziness were comparable to those with placebo, regardless of treatment received. Among patients in the group aged ≤ 40 years, nausea, dizziness, and insomnia were more frequently reported with venlafaxine than with placebo. Among patients in the other 3 age categories, with only 2 exceptions, frequency of reporting these adverse events tended to be similar between the treatment groups (see Table 3). For all patient subgroups examined, differences in frequency of headache, nausea, insomnia, and dizziness reported with SSRIs versus with placebo did not reach statistical significance at the p value of ≤ .004.

Patient Age and Antidepressant Efficacy

For the cohort as a whole, on the basis of remission and response, both active medications were significantly more effective than placebo.[27] None of the efficacy measures were influenced by patient age (p > .05). Further, no significant age-by-treatment interaction terms were noted for remission, response, or absence of depressed mood, based on the planned GenMod analyses (all p values > .10); these findings indicate that by study week 8, patients of different ages showed similar rates of remission, response, and absence of depressed mood as a result of treatment with venlafaxine or an SSRI. Patients in the groups aged ≤ 40 and 41–54 years receiving venlafaxine exhibited significantly higher rates of remission (46% and 44%, respectively) than did those receiving an SSRI (37% and 33%, respectively) (venlafaxine vs. placebo, all p values ≤ .001; vs. SSRIs, all p values ≤ .01) (Figure 1). By contrast, patients in 3 of the 4 age groups (≤ 40, 55–64, and ≥ 65 years) receiving venlafaxine exhibited a response rate (61%–79%) that was statistically comparable to that of patients receiving SSRIs (51%–62%); for patients aged 41–54 years, rate of response was higher with venlafaxine (63%) than with SSRIs (53%) (vs. SSRIs, p ≤ .01). Similarly, for patients in 3 of the 4 age groups (41–54, 55–64, and ≥ 65 years), rates of absence of depressed mood for patients receiving venlafaxine (34%–42%) or an SSRI (31%–37%) were not statistically different; patients in the group aged ≤ 40 years given venlafaxine showed rates of absence of depressed mood (39%) significantly higher than those given an SSRI (31%) or placebo (23%) (vs. SSRIs, p ≤ .03; vs. placebo, p ≤ .001) (Figure 2).

In 3 of the 4 age groups examined (≤ 40, 41–54, and 55–64 years), onset of remission (relative to placebo) occurred sooner with venlafaxine (week 4, venlafaxine vs. placebo, p < .02) than with SSRIs (week 8, SSRIs vs.

Table 3. Frequency of the Most Commonly Reported Adverse Events, by Gender and Age

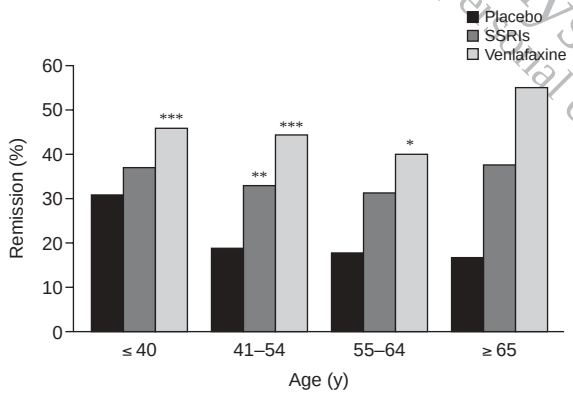
Gender	Men (N = 734)						Women (N = 1311)					
	Venlafaxine (N = 296)		SSRIs (N = 267)		Placebo (N = 171)		Venlafaxine (N = 555)		SSRIs (N = 481)		Placebo (N = 275)	
Adverse Event	N	%	N	%	N	%	N	%	N	%	N	%
Headache	44*	15	69	26	48	28	117	21	111	23	77	28
Nausea	59	20	43	16	17	10	155†	28	101	21	44	16
Insomnia	47	16	35	13	19	11	78	14	63	13	28	10
Dizziness	38	13	19	7	10	6	72	13	43	9	28	10

Age	≤ 40 Years (N = 946)						41–54 Years (N = 788)					
	Venlafaxine (N = 382)		SSRIs (N = 357)		Placebo (N = 207)		Venlafaxine (N = 334)		SSRIs (N = 260)		Placebo (N = 194)	
Adverse Event	N	%	N	%	N	%	N	%	N	%	N	%
Headache	84	22	96	27	48	23	57†	17	57	22	62	32
Nausea	111†	29	82	23	31	15	73	22	47	18	29	15
Insomnia	65†	17	46	13	17	8	43	13	34	13	25	13
Dizziness	69‡	18	29	8	14	7	37	11	23	9	17	9

Age	55–64 Years (N = 232)						≥ 65 Years (N = 79)					
	Venlafaxine (N = 97)		SSRIs (N = 96)		Placebo (N = 39)		Venlafaxine (N = 38)		SSRIs (N = 35)		Placebo (N = 6)	
Adverse Event	N	%	N	%	N	%	N	%	N	%	N	%
Headache	15	15	23	24	13	34	4	10	5	14	1	17
Nausea	23§	24	12	13	1	3	6	17	1	3	0	0
Insomnia	14	14	12	13	3	8	1	2	0	0	0	0
Dizziness	8	8	8	8	5	13	1	2	0	0	1	17

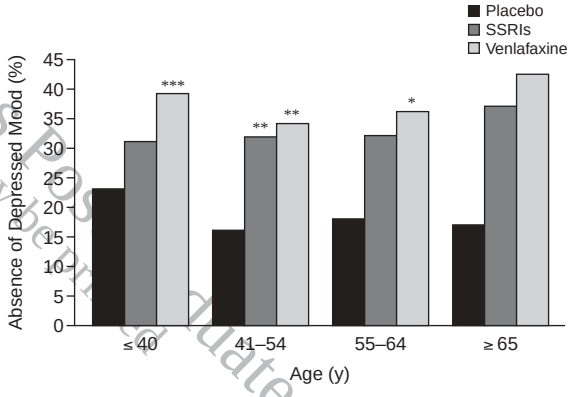
*Venlafaxine vs. placebo, $p < .002$; vs. SSRIs, $p \leq .001$.
†Venlafaxine vs. placebo, $p \leq .001$.
‡Venlafaxine vs. placebo and vs. SSRIs, $p < .001$.
§Venlafaxine vs. placebo, $p \leq .003$.

Figure 1. Remission After 8 Weeks of Treatment, by Age[a]



[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.
Remission across all age groups for venlafaxine vs. SSRIs, $p < .05$.
*$p \leq .01$ vs. placebo.
**$p \leq .001$ vs. placebo.
***Venlafaxine vs. placebo, $p \leq .001$; vs. SSRIs, $p \leq .01$.

Figure 2. Absence of Depressed Mood After 8 Weeks of Treatment, by Age[a]



[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.
*$p \leq .04$ vs. placebo.
**$p \leq .001$ vs. placebo.
***Venlafaxine vs. placebo, $p \leq .001$; vs. SSRIs, $p \leq .03$.

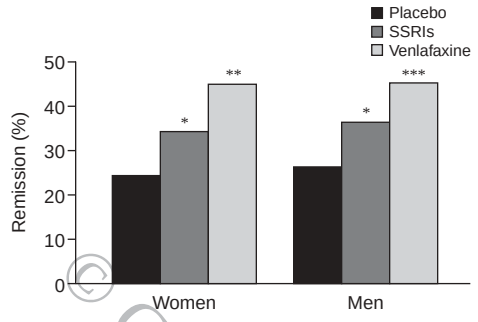
placebo, $p \leq .001$). A similar, although less robust, pattern was seen with response; patients aged ≤ 40 and 41–54 years exhibited response with only 2 weeks of venlafaxine treatment (vs. placebo, $p \leq .02$), but with 4 weeks of SSRI treatment (vs. placebo, $p \leq .03$). Onset of absence of depressed mood tended to be similar regardless of patient age and was not related to the class of antidepressant received. Perhaps because of the small number of patients in the 55–64 and ≥ 65 years age categories, differences between the active treatment groups that were similar in timing and magnitude to those seen in the other age groups failed to reach statistical significance (see Figures 1 and 2).

Patient Gender and Antidepressant Efficacy

No significant gender-by-treatment or age-by-gender-by-treatment interaction terms for remission, response, or absence of depressed mood were revealed, based on the planned GenMod analyses as well as further analyses using multiple linear regression models (all p values > .10). Male and female patients of different ages exhibited similar outcomes by study week 8; for both genders, venlafaxine and SSRI treatments led to significantly higher percentages of patients exhibiting remission and response than was seen among placebo-treated control patients.

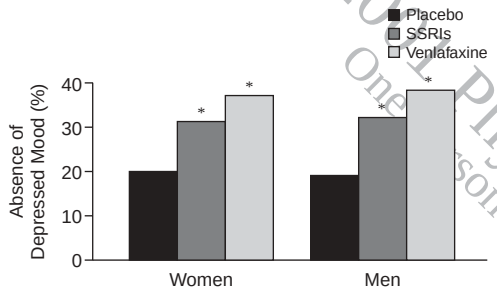
At the end of the 8-week study period, men and women receiving venlafaxine exhibited comparable rates of re-

Figure 3. Remission After 8 Weeks of Treatment, by Gender[a]



[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.
*p < .05 vs. placebo.
**Venlafaxine vs. placebo, p ≤ .001; vs. SSRIs, p ≤ .001.
***Venlafaxine vs. placebo, p ≤ .001; vs. SSRIs, p ≤ .04.

Figure 4. Absence of Depressed Mood After 8 Weeks of Treatment, by Gender[a]

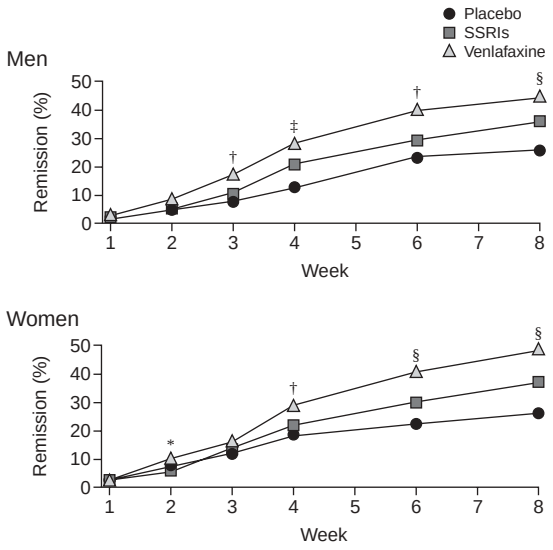


[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.
*p ≤ .003 vs. placebo.

mission (men, 45%; women, 45%) that were significantly higher than for patients receiving either placebo (men, 26%; women, 24%) or an SSRI (men, 36%; women, 34%) (venlafaxine vs. placebo, all p values ≤ .001; venlafaxine vs. SSRIs, all p values ≤ .04) (Figure 3). As observed in our analysis of separate age subpopulations, by week 8 of the study, men and women receiving venlafaxine exhibited comparable rates of response (men, 63%; women, 65%) that were higher than those seen with placebo (men, 41%; women, 43%) (all p values ≤ .001) (not shown). For women, rates of response with venlafaxine at week 8 (65%) were greater than those for women receiving SSRIs (57%) (p ≤ .01). For both men and women, rates of absence of depressed mood for patients receiving venlafaxine (men, 38%; women, 37%) or an SSRI (men, 32%; women, 31%) were similar and significantly higher compared with placebo (men, 19%; women, 20%) (all p values ≤ .003; Figure 4).

The percentage of men exhibiting remission after 3 weeks of treatment with venlafaxine (17%) was significantly higher than with either placebo (8%) or with SSRIs (10%) (venlafaxine vs. placebo, p ≤ .01; vs. SSRIs,

Figure 5. Onset of Remission During Treatment, by Gender[a]



[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.
*p ≤ .02 vs. SSRIs.
†Venlafaxine vs. placebo, p ≤ .01; vs. SSRIs, p ≤ .028.
‡Venlafaxine vs. placebo, p ≤ .001; SSRIs vs. placebo, p ≤ .03.
§Venlafaxine vs. placebo, p ≤ .001; vs. SSRIs, p ≤ .039; SSRIs vs. placebo, p ≤ .046.

p ≤ .028), and a similar pattern was seen among women given venlafaxine after 4 weeks of treatment (Figure 5). Regardless of gender, onset of response (relative to placebo) tended to occur sooner with venlafaxine than with SSRIs. For instance, the percentage of women exhibiting response after 2 weeks of treatment with venlafaxine (25%) was higher than with placebo (15%) and SSRIs (20%) (vs. placebo, p ≤ .001; vs. SSRIs, p < .05), and a similar, although nonsignificant, trend was seen among men. In women, onset of absence of depressed mood occurred earlier with venlafaxine (week 2) than with SSRIs (week 4); onset of absence of depressed mood in men was similar when either venlafaxine (week 3) or an SSRI (week 3) was given (not shown).

DISCUSSION

We found that rates of remission, response, and absence of depressed mood associated with antidepressant drug therapy did not differ between men and women of different ages. Moreover, we observed that the efficacy advantage favoring venlafaxine over SSRIs was not limited to a particular subgroup of depressed patients, at least as defined by the presently used age subgroupings or gender.

Technical Considerations

The use of meta-analytic techniques, in which results from a number of studies are combined, is a valuable strategy to study the relative efficacy of various treat-

ments. This approach allows investigators to gather more conclusive evidence and form stronger conclusions, because a much larger number of patients are evaluated than in any single study.[24] Inherent limitations, such as differences in study designs and methods or systematic differences in patient populations, can affect the validity of the meta-analysis. The present investigation overcomes some of these limitations because protocol designs and implementation were all under direct supervision of the same sponsoring organization and were similar for the various studies. As a result, the patient selection and evaluations were consistent across studies, resulting in greater sensitivity to detect modest differences.

One of the major problems with datasets derived from randomized clinical trials is the limited generalizability to less highly selected clinical populations. In the present analysis, patients with significant complicating substance abuse, anxiety disorders, and general medical disorders were excluded. Inclusion of more complicated patients may have resulted in lower overall response and remission rates. However, there is no reason to suspect that such exclusions differentially affected outcomes with one medication group relative to another.

Our measures of response and remission for each group, based on HAM-D-21 and HAM-D-17 scores, were calculated using endpoint scores. This method includes all intent-to-treat patients and may underestimate the benefits of a treatment because the ultimate outcomes of patients who discontinue treatment are not known.[25] However, patients who withdraw early from studies tend to do so because of a lack of efficacy or because of adverse events. In a clinical setting, these problems can be dealt with in a number of ways (e.g., adjust drug dose, change drugs, or prescribe a combination of drugs) to yield a satisfactory outcome for the patient.

The conclusiveness of our analysis of adverse event frequency is somewhat limited, given that none of the studies included in the present meta-analysis were sufficiently powered to compare adverse event frequency between treatment groups. The 4 adverse events examined were arbitrarily chosen on the basis of frequency of patient reporting, rather than clinical relevance, and were compared using a Bonferroni adjustment. It should be noted that with unadjusted p values we detected differences in adverse event frequency between SSRI and placebo treatment groups in some patient subgroups.

Another limitation of this meta-analysis is the number of SSRIs studied and, in particular, the disproportionately large number of patients treated with fluoxetine. None of the studies included in the analysis examined sertraline or citalopram. Although there is little evidence of meaningful within-class differences in the efficacy of the 5 SSRIs, more confidence could be placed in the findings if our dataset included more patients treated with SSRIs other than fluoxetine.

Antidepressant Drug Therapies Are Effective for a Broad Range of Patient Subpopulations

The present investigation provides important empirical evidence suggesting that 2 types of newer antidepressant drugs exert similar benefits across a wide range of patient subgroups. The current results are in line with those of a recent report in which similar rates of therapeutic response were seen in a comparison of men and women with major affective disorders treated with lithium.[45]

However, our results differ from those of a recent report by Kornstein and colleagues[22] in which men and women with chronic depression were found to differ in their response to treatment with either imipramine or an SSRI. We were also unable to replicate Kornstein and colleagues'[22] observation that response varied among female patients according to menopausal status, with a decrement in responding to SSRI treatment but not tricyclics among postmenopausal women. The difference in outcomes between the present study and the Kornstein et al. study may be attributed to differences in antidepressant agents employed and patients included. Kornstein and colleagues[22] studied patients with chronic depression; such patients may have a relatively low placebo response rate, and, consequently, this may result in an apparently greater advantage for the active antidepressant medications studied. Furthermore, Kornstein and colleagues[22] compared the therapeutic effects of imipramine and sertraline, agents not included in the present analysis, and observed a significant tolerability advantage for sertraline relative to imipramine among younger women. Previous work has determined that, for the studies examined in the present analysis, there was no difference in attrition due to side effects between the venlafaxine and SSRI groups,[27] which would lessen potential differences in endpoint efficacy measures. Finally, Kornstein et al.[22] collected detailed data on menopausal status and hormonal replacement therapy, whereas these variables were uncontrolled in the present analysis. Therefore, we cannot rule out subtle differences between men and women and among women of different ages that may have been obscured in the present investigation.

Therapeutic Advantages of Treatment With Venlafaxine

The present data recapitulate our recent finding that the serotonin-norepinephrine reuptake inhibitor venlafaxine is more effective than the SSRIs studied in these randomized clinical trials. Moreover, our findings expand those of the earlier Thase et al.[27] report by determining that this advantage is not limited to a particular patient subgroup, as defined by gender and age. The difference between venlafaxine and SSRIs was observed on endpoint remission and response rates, as well as estimates of speed of remission and response. However, there was no consistent significant difference between the active treatments on

the third outcome measure, absence of depressed mood, perhaps because absence of depressed mood is a less sensitive indicator of therapeutic improvement (it is based on a single HAM-D item), or it could reflect that the advantage of venlafaxine is attributable to improvement in other aspects of the depressive syndrome.

CONCLUSION

Although it is widely stated that the various classes of medications are equally effective in treating men and women with major depression,[46,47] until now there was little empirical and convincing evidence to support this proposition. Randomized clinical trials are relatively insensitive to differences in antidepressant efficacy, given small treatment group sizes, the variability inherent in multicenter trials, and the absence of any examinations of the possible influence of patient variables on therapeutic outcomes.[48] The present investigation addresses several of these limitations. Of greatest importance, the large number of patients in each treatment group in this pooled analysis generated enough statistical power to detect modest, although clinically important, treatment-related differences in therapeutic outcomes. Our findings clearly suggest that class of antidepressant agent importantly influences therapeutic outcome. This finding was robust, including a wide age range and both men and women.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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