Probing the Safety of Medications in the Frail Elderly: Evidence From a Randomized Clinical Trial of Sertraline and Venlafaxine in Depressed Nursing Home Residents

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Background: In nursing home residents and other frail elderly patients, old age and potential drug-drug and drug-disease interactions may affect the relative safety and efficacy of medications. The purpose of this study was to examine the efficacy and tolerability of venlafaxine and sertraline for the treatment of depression among nursing home residents.

Method: The study was a 10-week randomized, double-blind, controlled trial of venlafaxine (doses up to 150 mg/day) versus sertraline (doses up to 100 mg/day) among 52 elderly nursing home residents with a DSM-IV depressive disorder and, at most, moderate dementia. The primary measure of outcome was the Hamilton Rating Scale for Depression (HAM-D). Adverse events were monitored and recorded systematically during the trial.

Results: Twelve subjects were discontinued due to serious adverse events (SAE), 5 were discontinued due to other significant side effects, and 2 withdrew consent. Tolerability estimated by the time to termination was lower for venlafaxine than sertraline for serious adverse events (log rank statistic = 5.28, p = .022), for serious adverse events or side effects (log rank statistic = 8.08, p = .005), or for serious adverse events, side effects, or withdrawal of consent (log rank statistic = 10.04, p = .002). Mean (SD) HAM-D scores at baseline were 20.2 (3.4) for sertraline and 20.3 (3.7) for venlafaxine; intent-to-treat endpoint HAM-D scores were 12.2 (5.1) and 15.7 (6.2) (F = 3.45; p = .069). There were no differences in categorical responses for the intent-to-treat sample or completers.

Conclusion: In this frail elderly population, venlafaxine was less well tolerated and, possibly, less safe than sertraline without evidence for an increase in efficacy. This unexpected finding demonstrates the need for systematic research on the safety of drugs in the frail elderly.

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Evaluating the benefits versus the risks of medications may be most difficult in elderly patients who require treatment for multiple chronic illnesses. Nowhere are these issues more salient than in nursing home residents and other frail elderly patients, where the physiologic and metabolic effects of aging as well as drug-disease and drug-drug interactions all complicate pharmacotherapy.[1–5] Nevertheless, there has been little research in this area. Instead, estimates of the benefits and risks of medications in frail elderly patients are derived from extrapolations from clinical trials in younger and healthier populations, from knowledge of the basic pharmacology of relevant agents, and from expert opinion. Within nursing homes, recommendations have been codified in federal regulations, guidelines for surveyors, resident assessment protocols, and quality indicators. However, the evidence available to guide treatment remains limited. Moreover, in contrast to the case with children, federal U.S. Food and Drug Administration (FDA) regulations for the labeling of pharmacologic agents require only limited research on geriatric populations, and provide few incentives that might stimulate such studies.

In this context, it is useful to view antidepressant medications as representing both specific issues in geriatric pharmacotherapy and examples of the general problem. The use of antidepressants has increased markedly since the passage of nursing home reform legislation in the late 1980s. Before that time, approximately 10% of nursing

home residents with a clinical diagnosis of depression were being treated.[6] At present, 36% of all residents are receiving these agents.[7] This dramatic change can be traced to a number of factors including regulatory changes, the development and acceptance of new antidepressants, and scientific advances. While there have been significant increases in recent years in the number of controlled clinical trials that focus on the elderly or include older patients, most enroll only relatively healthy "young-old" individuals.

In nursing homes, as in other settings, the most widely prescribed class of antidepressants is the selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram, fluoxetine, paroxetine, and sertraline).[8,9] Although their use in older patients in community settings has been supported in clinical trials, there have been questions about their efficacy in nursing home residents.[10–14] There are also questions about what constitutes the most appropriate next step in treatment for those who do not respond to initial treatment with these agents. A recent expert consensus panel[15] on the pharmacologic treatment of late-life depression recommended venlafaxine, a dual-action serotonin-norepinephrine reuptake inhibitor, as an alternative first-line treatment for severe major depression in older patients and a preferred agent for those who do not respond to SSRIs. Moreover, previous research in younger adults has suggested that patients may respond more rapidly or more completely to venlafaxine than to SSRIs.[16–19] However, evidence of its efficacy and safety in the treatment of older patients is limited.[20] We, therefore, designed a double-blind, randomized clinical trial to compare the outcomes of treatment with venlafaxine versus sertraline in nursing home residents to test the hypothesis that venlafaxine would be more efficacious than sertraline while being equal to it in safety and tolerability. Because the study was designed specifically to test for differences in outcomes between the 2 agents, it compared the 2 agents directly, without a placebo comparator. Contrary to the hypothesis, our results demonstrated that venlafaxine was less well tolerated and, probably, less safe than sertraline without any evidence for a counterbalancing improvement in therapeutic outcomes. These findings raise questions about the treatment of depression in nursing home residents. More generally, they raise concerns that current approaches to the development, testing, and monitoring of drugs do not adequately evaluate the benefits versus risks in nursing home residents and other frail elderly patients.

METHOD

Subject Recruitment

As described previously, subjects were recruited from 13 nursing facilities that included public Veterans Administration (VA), for-profit, and nonprofit homes.[21] Subjects were targeted for evaluation either by staff referral or by findings from systematic screening. Potential subjects whose decision-making capacity was adequate were given complete descriptions of the study and asked for written informed consent as approved by the University of Pennsylvania Institutional Review Board. For those with impairments in decision making, we required assent from the subject and written informed consent from a health care proxy. For all subjects, participation required approval from the individuals' primary care physician.

Potential subjects were evaluated by research nurses with extensive experience in geriatric psychiatry; diagnostic assessments were conducted through clinical assessments using inclusive DSM-IV criteria.[22] Inclusion criteria included significant dysphoria with a score ≥ 10 on the Geriatric Depression Scale (GDS)[23] and/or a rating > 2 on item 1 (depressed mood) of the Hamilton Rating Scale for Depression (HAM-D)[24]; diagnosis of major depressive episode, minor depression, dementia with depression, or dysthymic disorder; score > 12 on the 17-item HAM-D; duration of symptoms > 1 month; score on the Blessed Memory Information Concentration test < 21[25,26]; and being judged as likely to remain in the nursing facility for at least 3 months. Exclusion criteria included histories of mania or schizophrenia; current psychosis; current substance abuse; treatment with psychotropic drugs within 2 weeks (other than as-needed use of oxazepam, lorazepam, or temazepam); history of adverse reactions to sertraline or venlafaxine or nonresponse to these medications at doses of at least 100 mg/day and 150 mg/day, respectively; communication disorders that precluded study assessments; weight loss judged to present a danger to the patient; suicidal risk; or unstable medical disorders or terminal conditions judged likely to lead to death within 6 months.

Treatment

All subjects received placebo under single-blind conditions for a period of 1 week, and those who continued to meet inclusion and exclusion criteria were randomized to receive either sertraline in doses up to 100 mg/day or immediate-release venlafaxine in doses up to 150 mg/day, both given in divided doses. The sertraline group received 25 mg/day for week 1, and then the dose was increased, as tolerated, to 50 mg/day for weeks 2 through 5, and 100 mg/day for weeks 6 through 10. The venlafaxine group received 18.75 mg/day in week 1, and then the dose was increased, as tolerated, to 37.5 mg/day for week 2, 75 mg/day for week 3, 112.5 mg/day for week 4, and 150 mg/day for weeks 5 through 10.

Assessments

Subjects were evaluated at the start of the study, after completion of 1 week on single-blind placebo, and weekly under double-blind conditions for assessment of

depressive symptoms, cognition, functional status, and potential adverse effects of treatment. Cognitive status was evaluated with the Mini-Mental State Examination (MMSE).[27] Medical comorbidity was quantified with the Cumulative Illness Rating Scale (CIRS),[28,29] using information derived from review of medical records, physical examination of the patient, and discussion with the patient, family, and primary care physician. Kappas for interrater reliability for each item were 0.6 or greater. Instruments for evaluating functional status included the Physical Self Maintenance Scale (PSMS) and the Instrumental Activity of Daily Living scale (IADL).[30] Kappas for interrater reliability were 0.8 or greater for each item on these scales. Assessments of depression symptomatology included the 21-item HAM-D[24]; the Cornell Scale for Depression in Dementia (used in both cognitively intact and impaired individuals)[31]; nurse-rated Clinical Global Impressions-Improvement scale,[32] which rated symptoms on a 7-point scale ranging from very much better to very much worse; and the 30-item GDS.[23] Subjective side effects were evaluated with the Asberg scale,[33] modified to include additional items related to side effects of SSRIs. The endpoints considered were the 10-week assessments for subjects who completed the protocol, assessments conducted at the time of termination when it was caused by worsening depression, and the final depression assessments that were not confounded by adverse events when these led to early termination. The HAM-D and the Cornell scale were scored using rules that counted symptoms as present when it was not possible to determine whether they were related to depression or physical illness; interrater reliability was greater than 0.9. Vital signs (blood pressure and pulse) were determined at all study visits. Electrocardiograms were obtained at baseline, at the end of week 4, and at study termination.

Analyses

Most statistical analyses used SPSS for Windows, version 10.1 (SPSS, Inc., Chicago, Ill.), augmented with random coefficient and mixed effects repeated measures linear analyses performed with SAS V8 Proc Mixed (SAS Institute, Cary, N.C.). To estimate the effects of treatment over time in all subjects and in completers, we analyzed mixed effects models with random intercepts, slopes, quadratic, and cubic polynomial terms for visit. Visit number was centered to reduce the correlation between the estimates of these polynomial effects. The tests of the population means of the random slopes, quadratic, and cubic terms served as tests of group differences with respect to trends and curvature across time. To further investigate any consequences of informative dropout, we employed linear models extensions of the informative dropout models described by Ten Have and colleagues.[34]

RESULTS

Subjects

Sixty-seven nursing home residents consented to participation in this study and 52 were randomized (25 to sertraline and 27 to venlafaxine). Attrition between consent and randomization occurred in 15 individuals; 5 were judged to be medically unstable or terminally ill, 5 improved either to simplification of their medication regimens or to administration of single-blind placebo, 2 withdrew consent, 2 were terminated from the study for administrative reasons, and 1 left the facility. The 52 subjects who were randomized included 23 women and 29 men; 12 subjects were African American and 40 were white.

The mean age of the subjects was 82.5 years (range, 61–99 years). Thirteen of the subjects had MMSE scores between 12 and 18, 21 between 18 and 24, and 18 between 24 and 30. Among subjects, 80.8% were diagnosed with major depressive disorder, and the rest with dysthymic disorder, minor depression, or depression (not otherwise specified). A total of 48.1% were taking an antidepressant medication at the time of screening or referral, 19.2% were taking an SSRI, and 1.9% were taking venlafaxine. Medical comorbidity was frequent, with 83% of the subjects having cardiac disease of at least moderate severity; 58%, vascular disease; 69%, hypertension; 38%, hematopoietic disease; 42%, respiratory disease; 67%, eye, ear, nose, or throat disease; 48%, upper gastrointestinal disease; 73%, lower gastrointestinal disease; 12%, hepatobiliary disease; 27%, renal disease; 67%, genitourinary disease; 75%, musculoskeletal-integumentary disease; 44%, neurologic disease; and 37%, endocrine disease. The mean (SD) number of systems affected for each subject was 7.4 (2.1), and the mean severity of each condition was 1.55 (0.41), that is, between mild and moderate. As indicated in Table 1, the patients randomized to venlafaxine included more African Americans than those who received sertraline, but there were no other differences between groups. The differences between agents presented below remained significant when the African American subjects were excluded and analyses were conducted in the white subsample alone. Therefore, they cannot be attributed to the higher proportion of African Americans in the venlafaxine group.

Attrition

As shown in Table 2, attrition in these subjects was related to serious adverse events (3 subjects assigned to sertraline and 9 subjects assigned to venlafaxine), withdrawal related to side effects (1 for sertraline and 4 for venlafaxine), withdrawal of consent (0 for sertraline and 2 for venlafaxine; both of which occurred in the context of high levels of anxiety and irritability), and discontinuation for administrative reasons (1 for sertraline and 2 for

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants[a]

Variable	Sertraline (N = 25)	Venlafaxine (N = 27)	F	p Value
Age, mean (SD)	83.8 (9.8)	81.2 (10.8)	0.784	.380
Rating scale score, mean (SD)				
CIRS	1.53 (0.42)	1.57 (0.39)	0.134	.716
PSMS	15.7 (3.9)	14.7 (3.6)	1.051	.310
IADL	12.7 (2.8)	13.7 (2.6)	1.910	.174
MMSE	21.9 (4.9)	22.0 (5.4)	0.001	.976
				Exact p
Sex, F	14 (56)	9 (33)		.162
Race, white	23 (92)	17 (63)		.020
Diagnosis of MDD	19 (76)	23 (85)		.492
Prior treatment with antidepressants	13 (52)	12 (44)		.782
SSRI	6 (24)	4 (15)		.492
Venlafaxine	1 (4)	0 (0)		.481
Facility type				
Nonprofit	13 (52)	11 (41)		.718
For-profit	3 (12)	4 (15)		
VA	9 (36)	12 (44)		

[a]Values shown as N (%) unless otherwise noted.
Abbreviations: CIRS = Cumulative Illness Rating Scale, IADL = Instrumental Activity of Daily Living scale, MDD = major depressive disorder, MMSE = Mini-Mental State Examination, PSMS = Physical Self Maintenance Scale, SSRI = selective serotonin reuptake inhibitor, VA = Veterans Administration.

Table 2. Clinical Conditions Associated With Termination and Interruption of Treatment

Event	Subject No.	Drug	Week	Description of Event
Serious adverse events	1	V	3	Cerebrovascular accident
	2	V	1	Hypertension, decreased renal function, delirium
	6	V	3	Rapid atrial fibrillation, worsened CHF
	7	S	7	Pneumonia, hyponatremia, delirium
	13	V	7	UTI, anemia, hyponatremia, thrombocytopenia
	14[a]	S	2	Worsened CHF
	22	V	6	Cerebrovascular accident
	31	V	3	UTI, delirium
	33	S	6	Chest pain, delirium
	37	S	6	Psychosis
	43	V	7	Worsening interstitial lung disease
	46	V	2	CHF, urosepsis
	49	V	3	Delirium, fall with fractured knee
Side effects	19	V	2	Nausea
	26	V	9	Anxiety
	48	S	4	Bradycardia, anxiety, fatigue
	52	V	5	Fall, anxiety
	53	V	2	Fall, agitation, t-wave inversion on ECG
Withdrawn consent	15	V	2	(Increased irritability was described by the patient)
	25	V	2	(Increased irritability was described by the patient)

[a]Interrupted treatment.
Abbreviations: CHF = congestive heart failure, ECG = electrocardiogram, S = sertraline, UTI = urinary tract infection, V = venlafaxine.

venlafaxine who were terminated from the study at the time of the interim analysis). In addition, 1 subject (assigned to sertraline) had treatment interrupted as a result of worsening of preexisting heart failure that was judged to be unrelated to study medication; this subject was restarted on medication (without breaking the blind) upon return to the nursing home after a brief hospitalization. All of the serious adverse events were judged by the investigators as probable reflections of intercurrent medical events that were only possibly related to study medication. However, when the blind was broken, both contingency table analyses and survival analyses demonstrated greater attrition in patients assigned to venlafaxine (Table 3).

Side Effects

Assessment of subjective side effects with a modified Asberg scale demonstrated no significant differences between medications in the total symptom burden as evaluated at 1 week, the time of each subject's maximum symptomatology, or at endpoint. However, there were significant differences in individual symptoms. At 1 week, there were greater reports of fatigue and palpitations in those receiving sertraline and greater reports of urinary difficulties in those receiving venlafaxine. At both the time of maximum symptoms and endpoint, there were greater reports of gastrointestinal symptoms in those receiving sertraline. Evaluation of the effects of treatment on blood pressure demonstrated no significant differences between groups (Table 4). Systolic blood pressure increased from baseline measures of 125.9 mm Hg (SD 23.8 mm Hg) for sertraline and 129.0 (16.9) mm Hg for venlafaxine to maximum subsequent values of 146.1 (25.9) mm Hg and 146.2 (17.3) mm Hg, respectively (F [interaction] = 0.582, p = .45). Diastolic blood pressure increased from 67.9 (14.4) mm Hg and 70.9 (12.6) mm Hg to 77.8 (13.8) mm Hg and 81.7 (13.2) mm Hg, respectively (F [interaction] = 0.156, p = .70). Electrocardiograms were available in 45 subjects. Analyses comparing changes from baseline to the last available measures demonstrated no significant group differences in QT, QTc, QRS, or PR intervals. However, there was a significant interaction between time and group for heart rate (F = 6.98; p = .012). Baseline heart rate (SE) was 78.4 (2.8) b.p.m. with sertraline and 74.6 (3.1) b.p.m. with venlafaxine, while final heart rates were 70.9 (2.8) and 76.7 (3.0) b.p.m., respectively.

Effects on Depressive Symptoms

Repeated-measures analysis of the impact of treatment on depressive symptoms suggested marginal interactions between time and medication favoring sertraline in intent-to-treat analyses. Since the intent-to-treat findings in favor of sertraline could be attributed to earlier dropouts

Table 3. Reasons for Early Termination and Withdrawal From the Study

Analysis	Events, N/Total N		Contingency Table Fisher Exact p	Event History (KM)	
	Sertraline	Venlafaxine		Log Rank Statistic	p
Termination due to SAE	3/25	9/27	.101	5.28	.022
Termination or interruption due to SAE	4/25	9/27	.205	3.41	.065
Termination due to SAE or withdrawal due to SE	5/25	12/27	.019	8.08	.005
Termination due to SAE or withdrawal due to SE or withdrawn consent	5/25	15/27	.004	10.04	.002

Abbreviations: KM = Kaplan-Meier, SAE = serious adverse event, SE = side effect.

Table 4. Number of Subjects Who Exhibited a Change in Blood Pressure During Treatment With Sertraline or Venlafaxine

Interval	Sertraline	Venlafaxine
Diastolic		
Baseline to last observation[a]		
≤ –10 mm	9	6
No change	13	15
≥ 10 mm	3	6
Baseline to maximum[b]		
≤ –10 mm	0	0
No change	14	12
≥ 10 mm	11	15
Systolic		
Baseline to last observation[c]		
≤ –10 mm	8	5
No change	9	12
≥ 10 mm	8	10
Baseline to maximum[d]		
≤ –10 mm	0	0
No change	6	8
≥ 10 mm	19	19

[a] $\chi^2 = 1.67$, p = .43.
[b] $\chi^2 = 0.69$, p = .41.
[c] $\chi^2 = 1.27$, p = .53.
[d] $\chi^2 = 0.21$, p = .65.

in the venlafaxine-treated patients, analyses of completers were conducted to determine whether there were any indications of earlier responses in patients who were treated with venlafaxine (Table 5). Although we recognize that the small sample size of completers (20 for sertraline and 10 for venlafaxine) severely limits the power for detection of group differences, we were interested in these analyses to probe for signals that there might be differences in the efficacy of these medications that could counterbalance the apparent differences in tolerability demonstrated above. One set of completer analyses was based on measures of clinical global improvement. For sertraline-treated patients, 50% were very much improved, 25% much improved, 20% slightly improved, and 5% very much worse. For venlafaxine, 20% were very much improved, 60% much improved, and 20% unchanged. ($\chi^2 = 10.23$, p = .04). Thus, these analyses again provided no evidence for more complete responses to venlafaxine.

In regression models that considered group, time, time squared, time cubed, and interactions of group with time, time squared, and time cubed, we found significant effects of time, and marginal trends for the group × time and group × time squared interactions. However, these interaction effects were not significant (p > .20) when such models were fitted to all follow-up data for all subjects regardless of whether they were completers. Similar nonsignificant results occurred with the inclusion of parameters to adjust for informative dropout. Inspection of the best fit to the models for completers (Figure 1) suggested that there may have been a lag in response for venlafaxine relative to sertraline. There were no suggestions for superiority of venlafaxine in either the completeness or the rapidity of response. The suggested lag in venlafaxine responses may have been related to a relatively slow titration up to the target dose of 150 mg/day. However, in the context of lag that was probably related to slow titration, findings of decreased tolerability demand even greater concern.

DISCUSSION

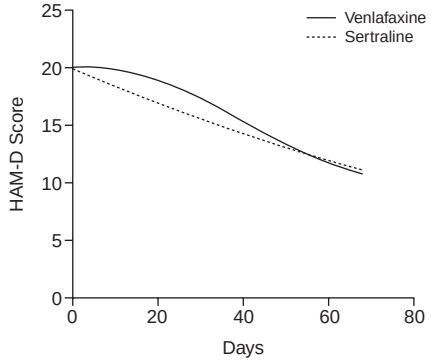
The research reported here was conducted to test the hypothesis that venlafaxine, an antidepressant with noradrenergic and serotonergic uptake inhibition activity, would have greater efficacy than sertraline, a selective serotonin reuptake inhibitor, while exhibiting comparable safety and tolerability. Contrary to this hypothesis, our findings demonstrated that venlafaxine was less well tolerated and that it may have been less safe than sertraline for use in frail elderly nursing home residents. Although this study was conducted primarily to test the hypothesis that older patients may respond more rapidly or more completely to venlafaxine than to SSRIs, the data from this study provided no evidence to support this phenomenon, even in those who completed an acute course of treatment. Indeed, the findings demonstrated greater rates of termination and withdrawal from treatment for patients taking venlafaxine. Prior to breaking the blind, the adverse events were, in general, judged to be only possibly related to study medication. Nevertheless, the increased

Table 5. Depression Symptom Outcomes[a]

	Sertraline		Venlafaxine			p
Analysis/Measure	Baseline	Endpoint	Baseline	Endpoint	F	Value
Intent to treat						
HAM-D	20.2 (3.4)	12.2 (5.1)	20.3 (3.7)	15.7 (6.2)	3.45	.069
GDS	16.9 (6.2)	13.4 (7.6)	17.1 (5.8)	16.3 (7.4)	2.13	.151
Cornell	20.9 (4.4)	12.4 (6.3)	20.2 (4.1)	16.2 (6.8)	7.65	.008
CGI	N/A	2.3 (1.5)	N/A	3.0 (1.3)	2.83	.098
Completer						
HAM-D	20.4 (3.4)	11.0 (4.7)	20.2 (3.2)	11.4 (4.4)	0.07	.795
GDS	17.1 (6.8)	12.3 (7.9)	15.1 (5.7)	13.2 (7.3)	0.64	.429
Cornell	20.0 (4.3)	11.1 (5.7)	19.1 (4.7)	11.7 (4.2)	0.59	.450
CGI	N/A	1.9 (1.2)	N/A	2.2 (1.0)	0.44	.515

[a]All values represent mean (SD).
Abbreviations: CGI = Clinical Global Impressions scale, Cornell = Cornell Scale for Depression in Dementia, GDS = Geriatric Depression Scale, HAM-D = Hamilton Rating Scale for Depression, N/A = not applicable.

Figure 1. Change in Hamilton Rating Scale for Depression (HAM-D) Scores as a Function of Time (days)



rate of terminations associated with serious adverse events and side effects in patients randomized to venlafaxine relative to sertraline implicates venlafaxine as a causal factor in these adverse events.

Given the small sample size for this study, the absence of any signal suggesting superiority of venlafaxine over sertraline cannot be taken as evidence against hypotheses that norepinephrine reuptake inhibition can contribute to antidepressant responses in frail older patients. The findings on safety and tolerability were not anticipated. They became apparent during an interim analysis conducted as part of the planned data and safety monitoring program for this study. Although the previous literature on the use of venlafaxine in the elderly is limited, it does, in general, support the safety of its use in older patients. Thus, a recent report that analyzed the efficacy and safety of extended-release venlafaxine in the older patients who participated in research conducted by the manufacturer for generalized anxiety disorder noted that rates of treatment-emergent adverse events, adverse events leading to treatment discontinuation, and total study withdrawals in older adults were comparable to those for younger patients.[35] A recent review of the use of venlafaxine as an antidepressant in older patients[20] identified 3 double-blind comparisons and 4 open-label studies in older patients. This review summarized findings by stating that all of the studies support the safety and efficacy of venlafaxine in older adults with major depression.[36–42]

However, additional information comes from the report of the largest of these studies, a double-blind, placebo-controlled trial of immediate-release venlafaxine versus fluoxetine and placebo for the treatment of major depression in healthier, young-old individuals.[37] It presented only limited data on the overall dropout rate, stating only that it was similar across groups (at 24%–36%). However, the results indicate that 29% of the patients taking venlafaxine dropped out due to adverse events, versus 19% of those taking fluoxetine and 9% of those taking placebo. Dropouts due to serious adverse events were 6%, 3%, and 2%, respectively. The mean age for the patients in the anxiety studies[35] was 66 years, while that for the placebo- and fluoxetine-controlled study in depression[37] was 71 years. Taken together, these studies suggest a trend for decreased tolerability of venlafaxine with increasing age. Thus, the findings in older nursing home residents may represent an amplification of effects that began to appear, albeit in moderated form, in research on older patients with depression living in the community.

Discussion of these findings raises questions about what type of mechanism might be responsible for the greater number of heterogeneous adverse events observed in subjects randomized to venlafaxine. The only observation from this study that may be informative in this regard is the significant interaction for heart rate between drug assignment and time. Heart rate decreases in patients taking sertraline, but it increases in those taking venlafaxine. This observation is consistent with findings from studies in young adult volunteers demonstrating that venlafaxine can indirectly augment peripheral sympathetic autonomic activity,[43,44] while sertraline may suppress it.[45] Although the effect size for the difference between agents in this study is small, and unlikely to be clinically significant, this finding is consistent with noradrenergic effects of

venlafaxine at these doses in this population. It suggests the hypothesis that the lower tolerability of venlafaxine may be related to its noradrenergic actions. It is difficult to evaluate the extent to which older findings in tricyclic antidepressants with significant noradrenergic reuptake inhibition are relevant. Because the tricyclics have other potentially toxic effects (e.g., quinidine-like antiarrhythmic and muscarinic blocking activities), the experience with these agents may lead to an overestimation of problems. Moreover, because they also have α-adrenergic blocking activity that may compensate for some of the effects of noradrenergic reuptake inhibition, the rates of toxic effects from tricyclic antidepressants may underestimate the impact of noradrenergic reuptake inhibition in the frail elderly.

Experience with reboxetine, a selective noradrenergic reuptake blocker, may support the hypothesis of enhanced noradrenergic activity leading to decreased tolerability. Studies of younger nondepressed subjects have demonstrated that reboxetine augments sympathetic "tone," leading to peripheral hyperadrenergic symptoms including orthostatic intolerance (increased pulse rate without a drop in blood pressure upon standing) as well as sweating, piloerection, and sleeplessness.[46] This effect may lead to more clinically significant events in patients who are old and frail. In fact, an open-label study of reboxetine for older depressed outpatients, average age 80.1 years, reported that 4 of the 12 had significant cardiovascular events.[47] The findings reported here lead to the hypothesis that the toxicity associated with noradrenergic reuptake inhibition is amplified by aging and/or by psychiatric-medical comorbidity; it is offered to guide clinical practice, to further research on venlafaxine, and to inform the development of newer antidepressants.

Strengths of this study are its inclusion of heterogeneous older adults, typical of nursing home residents, and its conduct in a large number of nursing facilities. Limitations include the lack of a placebo control, the relatively small sample size, and the lack of evidence for any clear mechanism underlying the effects of interest. In the absence of a placebo control, it is, in principle, not possible to evaluate the extent to which the findings reflect increased adverse events with venlafaxine or a decrease in intercurrent medical events with sertraline. Nevertheless, the difference between agents is clinically relevant. As discussed above, it is possible that the effects may be related to noradrenergic uptake inhibition by venlafaxine. However, it is, in principle, possible that the decreased tolerability of venlafaxine may be related to symptoms that occur during states of withdrawal after missed doses[48]; however, this possibility is not supported by review of the timing of events and their association with nonadherence. Nevertheless, it may be relevant that this study was conducted with immediate-release venlafaxine, and it is possible that the extended-release form will be better tolerated.

The findings presented here have clear implications for the care of nursing home residents. Recent findings have suggested that the substantial numbers of nursing home residents with depression may be nonresponsive or partially responsive to treatment with SSRIs. A recent expert consensus panel on the treatment of late-life depression supported the use of venlafaxine as an alternative first-line antidepressant for severe depression and as an agent of choice for those who do not respond to SSRIs.[15] However, for the frail elderly, it may be prudent to avoid venlafaxine until more evidence about safety is available. The next stratum of recommendations from the expert consensus panel included bupropion, mirtazapine, and the tricyclic antidepressant nortriptyline. However, only limited data about the safety and efficacy of the first 2 of the agents are available in this population. Although the efficacy of nortriptyline in nursing home residents has been established through 2 randomized clinical trials,[21,49] drug-disease interactions and concerns about the safety of tricyclic antidepressants in older patients place limits on its utility. Thus, in spite of widespread use of antidepressants in nursing homes, there must be questions about what constitutes optimal treatment.

There are also more general implications to these observations. The unexpected findings on the decreased tolerability of venlafaxine raise concerns about whether other medications that appear safe in mixed-age adults and healthier older patients in the community may be poorly tolerated in the frail elderly. Although there may be substantial public health benefits from systematic testing of drugs that are to be used in these populations, the FDA regulations do not provide requirements or incentives for such research. An alternative may be to develop specific approaches to surveillance for the safety and tolerability of medications in the nursing home population. If, as suggested by the findings reported here, there are medications that appear to be safe in the community elderly that are less well tolerated in the frail elderly, the conduct of such surveillance should be a high priority, both for providers and for those federal agencies that fund and regulate the care of the elderly.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa), fluoxetine (Prozac and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), nortriptyline (Aventyl, Pamelor, and others), oxazepam (Serax and others), paroxetine (Paxil), sertraline (Zoloft), temazepam (Restoril and others), venlafaxine (Effexor).

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