Geriatric Depression Treatment in Nonresponders to Selective Serotonin Reuptake Inhibitors

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Background: Up to a third of elderly patients with major depressive disorder are treatment resistant, yet little objective evidence is available to guide the clinician in managing these patients. We report here our experience with elderly subjects with prospectively defined treatment-resistant depression in 2 separate research studies: one entailing an augmentation strategy, the other a change to venlafaxine extended release (XR).

Method: Fifty-three elderly subjects with major depressive disorder according to DSM-IV criteria who failed treatment with paroxetine plus interpersonal psychotherapy received 1 to 3 trials of augmentation with bupropion sustained release, nortriptyline, or lithium. Successively fewer subjects entered each sequential trial of augmentation. Twelve subjects subsequently received venlafaxine XR monotherapy. Response to treatment was defined as a 17-item Hamilton Rating Scale for Depression score of < 10 for 3 weeks.

Results: Sixty percent of subjects (N = 32) responded to some form of augmentation, with 45% (24/53), 31% (5/16), and 43% (3/7) responding to the first, second, and third augmentation trials, respectively. The mean time to response after starting the first augmentation trial was 6.0 (SD = 5.8) weeks. Forty-two percent (N = 5) of the venlafaxine XR–treated subjects responded with the mean time to response of 6.4 (SE = 0.9) weeks. Adverse effects leading to treatment discontinuation and falls were more common in the augmentation subjects than in the venlafaxine XR subjects.

Conclusion: We observed similar rates and speed of response with an augmentation strategy and a strategy of switching to venlafaxine XR in elderly subjects with prospectively defined treatment-resistant major depressive disorder. Venlafaxine XR was generally better tolerated than the augmentation strategies. Further investigation of venlafaxine XR as a preferred strategy for treatment-resistant geriatric depression is warranted.

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Late-life depression is a prevalent condition, especially among the chronically ill elderly.[1] The impetus for developing effective treatments for late-life depression is clear: late-life depression is associated with disability,[2] increased morbidity, and increased mortality related both to comorbid medical conditions[3] and to suicide.[4] The newer antidepressants are generally better tolerated and have fewer side effects among the elderly than do tricyclic antidepressants. Nevertheless, up to a third of older depressed patients do not fully respond to antidepressant trials of adequate dose and duration[5,6] and thus can be considered to be treatment resistant. Such patients are left with significant residual disability and decreased quality of life.

Several general pharmacologic strategies have been proposed for the management of treatment-resistant depression. One strategy is to augment the initial antidepressant monotherapy with another antidepressant[7] or with another agent such as lithium,[8] thyroid hormone,[9] atypical antipsychotics,[10] mood stabilizers/anticonvulsants,[11] or dopamine agonists,[12] including stimulants.[13] Another strategy is to switch to another antidepressant altogether.[7] Ven-

lafaxine may be a particularly useful agent in this regard. Unfortunately, the evidence supporting these strategies is limited in all age groups. Lithium augmentation is the most rigorously studied of these strategies. Nevertheless, a recent meta-analysis of strategies for treatment-resistant depression demonstrated that even the evidence supporting lithium augmentation is not robust.[8] Furthermore, while a few studies have assessed the efficacy of a second treatment step following failure of a first step, there are virtually only a handful of studies involving a limited number of subjects that have assessed a third or fourth treatment step in those who failed a first and second treatment step.[14,15]

Hence, most guidelines that exist to guide clinicians in the pharmacologic management of treatment-resistant depression, especially for geriatric patients, are not based on evidence but rather on the opinion of experts.[16] A recent expert consensus statement on the pharmacologic treatment of late-life depression identified bupropion sustained release (SR), lithium, and tricyclic antidepressants (TCAs) as the 3 most popular augmenting agents for treating geriatric patients who did not respond to a selective serotonin reuptake inhibitor (SSRI). Additionally, this survey identified venlafaxine extended release (XR) and bupropion SR as preferred antidepressants to switch to for geriatric patients with depression who do not respond to SSRIs.[17]

The potential advantages and disadvantages of augmenting and switching strategies have been described.[7,18] Switching drugs may be a simpler approach that includes fewer side effects and drug interactions. On the other hand, augmenting an antidepressant may maintain any partial symptom remission as well as lead to a more rapid response. In the only comparison of these 2 strategies, Posternak and Zimmerman[19] demonstrated a similar response rate for switching (45%) versus augmenting (56%) strategies in a naturalistic open-label study investigating treatment-resistant depression in a mixed-age sample.

We report here our experience in managing elderly subjects with treatment-resistant depression in 2 separate research studies. In the first study, depressed elderly subjects who did not respond to an adequate trial of paroxetine monotherapy were augmented with 1 of 3 possible medications (bupropion SR, nortriptyline, or lithium carbonate) over 1 to 3 sequential augmentation trials. Subjects who failed augmentation were then switched to venlafaxine XR monotherapy in the second study. This post hoc analysis compares the rates and speed of treatment response as well as the side effects associated with both strategies.

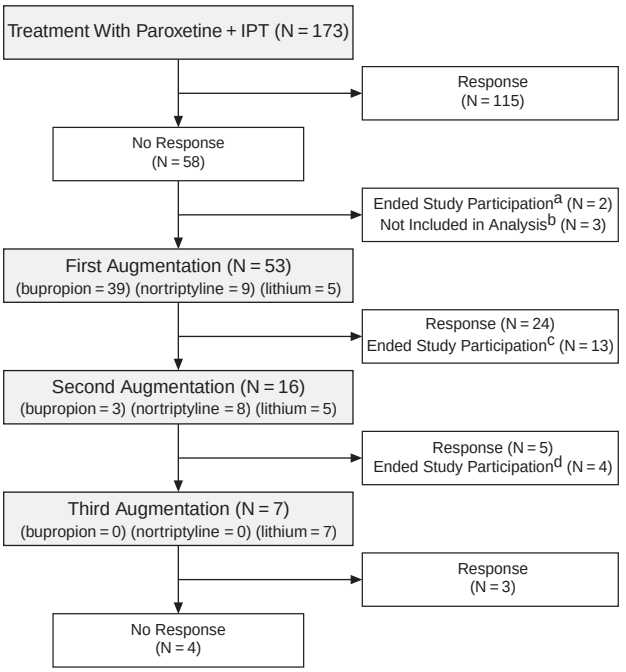
METHOD

Subjects

The subjects included in this post hoc analysis were participants in the acute treatment phase of the Maintenance Therapies in Late-Life Depression study—a National Institute of Mental Health–sponsored study[20] of therapies to prevent recurrence of late-life depression. All subjects were experiencing a DSM-IV major depressive episode prior to entering the acute treatment phase of this study during which they received treatment with paroxetine pharmacotherapy combined with interpersonal psychotherapy (IPT)[20] (Figure 1). Fifty-eight subjects failed to achieve or sustain remission with combined IPT and paroxetine therapy. Fifty-three of these 58 subjects subsequently received IPT and paroxetine plus an augmenting medication (bupropion SR, nortriptyline, or lithium carbonate) in an attempt to achieve remission. These 53 subjects constitute the "augmentation group." Three subjects who failed to respond to paroxetine monotherapy and 9 who failed to respond to paroxetine plus augmentation therapy were subsequently treated in an open study of venlafaxine XR. These 12 subjects constitute the "switch group."

All subjects were aged 69 years or older, met the Structured Clinical Interview for DSM-IV (SCID) criteria[21] for

Figure 1. Progression of Elderly Subjects With Major Depressive Disorder Through Augmentation Therapy (N = 53)



[a]Reason for study termination: entered venlafaxine XR study.
[b]Not included due to protocol violation.
[c]Reasons for study termination: severe medical illness (N = 2), development of psychotic depression (N = 1), severe agitation (N = 1), subject withdrawal of consent (N = 2), study design (N = 4), entered venlafaxine XR study (N = 3).
[d]Reasons for study termination: subject withdrawal of consent (N = 1), entered venlafaxine XR study (N = 3).
Abbreviations: IPT = interpersonal psychotherapy, XR = extended release.

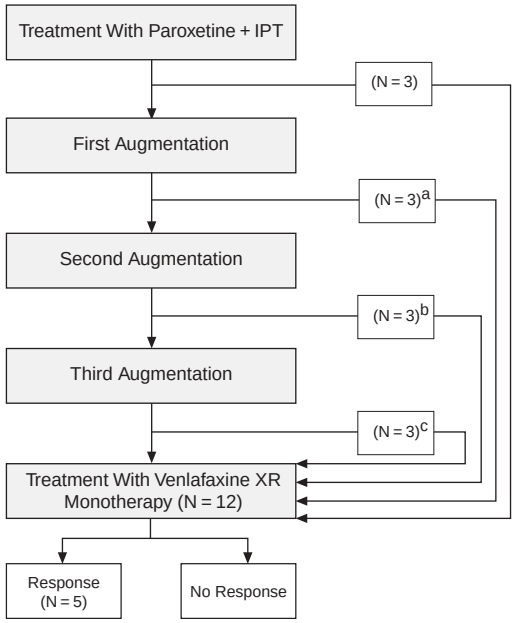
a major depressive episode without psychotic features, had a Mini-Mental State Examination[22] score > 15, and did not have bipolar disorder or a history of substance abuse in the preceding 3 months. Subjects were required to have a baseline 17-item Hamilton Rating Scale for Depression (HAM-D-17)[23] score of > 15 prior to starting treatment with IPT and paroxetine monotherapy and a baseline HAM-D-17 score of > 11 prior to starting venlafaxine XR. Cognitive function was characterized by the Mattis Dementia Rating Scale[24] and the Executive Function Inventory.[25] Total medical burden was quantified using the Cumulative Illness Rating Scale-Geriatric version (CIRS-G).[26] Serum electrolyte levels, renal function, complete blood counts, thyroid-stimulating hormone (TSH) levels, folate levels, and vitamin B_{12} levels were measured, and electrocardiograms were obtained prior to starting treatment. Subjects were excluded for bradycardia (< 50 bpm), hyponatremia (sodium level < 130 mEq/L), or clinical hypothyroidism. Subjects received explanations about research procedures and potential risks and benefits and provided written informed consent according to university institutional review board procedures.

Treatment Procedures

This study was conducted at a university-based geropsychiatric clinic. Subjects were initially treated acutely with pharmacotherapy and weekly IPT, as described by Szanto et al.[20] Paroxetine was started at 10 mg/day and titrated to 40 mg/day as indicated. Response was defined as 3 consecutive weekly HAM-D-17 scores of < 10. Subjects who achieved response were changed to bi-weekly appointments. Relapse after response was defined by (1) 2 consecutive HAM-D-17 scores > 10 at bi-weekly appointments and (2) the return of a major depressive episode by SCID criteria. Remission was defined as 16 consecutive weeks of HAM-D-17 scores < 10. Recurrence after remission was defined by (1) a HAM-D-17 score > 10 and (2) the return of a major depressive episode by SCID/DSM-IV criteria.

Fifty-three subjects who failed to respond to paroxetine monotherapy or relapsed after initial response to paroxetine monotherapy went on to receive 1, 2, or 3 trials of augmentation therapy with bupropion SR, nortriptyline, or lithium carbonate. These 53 subjects constitute the augmentation group. The choice of augmenting agent was based on the subject's medical condition and preference (e.g., subjects with cardiac conduction problems were not treated with nortriptyline). Lithium carbonate and nortriptyline doses were titrated as tolerated to maintain plasma levels of 0.5 to 0.7 mEq/L and 80 to 120 ng/L, respectively. Doses of bupropion SR ranged from 50 to 450 mg/day based on tolerability and clinical response. Subjects who either did not respond to or could not tolerate the first augmenting agent received a second trial with a different augmenting agent, similarly followed by a third augmenting trial if indicated. Twenty subjects returned to paroxetine monotherapy between augmentation trials or after failing all 3 trials. Response to augmentation was defined using the same criteria as for IPT plus paroxetine.

Figure 2. Progression of Elderly Subjects With Major Depressive Disorder to Venlafaxine Extended Release (XR) Monotherapy (N = 12)



[a]Two subjects did not respond to the first augmentation; 1 subject recurred after initial remission.
[b]One subject did not respond to the second augmentation; 2 subjects recurred after initial remission.
[c]Two subjects did not respond to the third augmentation; 1 subject recurred after initial remission.
Abbreviation: IPT = interpersonal psychotherapy.

Twelve subjects whose depression failed to improve with IPT and paroxetine with or without augmentation chose to transfer to a 12-week open-label study of venlafaxine XR. (Figure 2) These subjects constitute the switch group. Three subjects (25%) had relapsed or recurred after initial treatment with paroxetine monotherapy and IPT and subsequently declined augmentation. Nine (75%) of the 12 subjects had received augmentation therapy, with 5 subjects experiencing a relapse and the other 4 a recurrence. Of these 9 subjects who received augmentation, 6 (67%) returned to paroxetine monotherapy for a median duration of 12.3 weeks (range, 2.4–25.0 weeks) after discontinuing augmentation but prior to switching to venlafaxine XR monotherapy. Venlafaxine XR was started at 37.5 mg/day and titrated to a maximum dose of 300 mg/day based on the subject's response and tolerance to the medication. IPT was not part of this study protocol but was continued if the subject requested therapy. Response to venlafaxine XR was defined as 2 consecutive HAM-D-17 scores < 10 at bi-weekly clinic

visits and, hence, approximated the 3-week criterion used for subjects receiving IPT and paroxetine with or without augmentation.

The HAM-D-17 and UKU Side Effect Rating Scale[27] were completed and vital signs were obtained at each clinic visit. Subjects were also asked at each visit whether or not they had experienced a fall since the last research clinic visit. A fall was not formally defined for the subject. All reported events were recorded regardless of the cause to which the subject attributed the fall (e.g., syncope, incoordination, environmental barrier) or the sequela of the fall (e.g., no injury, cut, fracture).

Statistical Analysis

Descriptive statistics were used to summarize both the demographic characteristics and the treatment experience of the 2 groups. Comparison of the 2 groups was not made using statistical tests as the 2 groups were not independent and were small in size. Speed to remission was assessed using Kaplan-Meier survival analysis.

RESULTS

Table 1 summarizes the demographic and clinical characteristics of both groups. Subjects in the switch group had a longer duration of their index depressive episode and lower HAM-D-17 scores when compared with the augmentation group. This latter difference is because some of the subjects in the switch group had experienced some limited reduction in depressive symptoms after treatment with IPT and paroxetine with or without augmentation, although only 1 subject had a HAM-D-17 score of < 15 at the time of starting treatment with venlafaxine XR. The switch group subjects appeared to be more medically compromised, in terms of having more medical diagnoses and more severe medical illness as rated by the CIRS-G, than did the subjects in the augmentation group. However, the 2 groups were similar in terms of median TSH levels, vitamin B_{12} levels, and folate levels. Approximately 13% (N = 7) of the augmentation group and 17% (N = 2) of the switch group met criteria for subclinical hypothyroidism as measured by TSH levels prior to starting treatment with IPT and paroxetine. Nine percent (N = 5) and 2% (N = 1) of augmentation group subjects had low levels of vitamin B_{12} and folate, respectively, at the beginning of treatment compared with none of the switch group subjects. All subjects with hypothyroidism and/or low vitamin B_{12}/folate levels were treated at the initiation of paroxetine and IPT and were euthyroid with normal vitamin levels when augmentation was started.

Experience With Augmentation

The augmentation group consisted of 53 subjects who failed treatment with IPT and paroxetine monotherapy

Table 1. Demographic and Clinical Measures at Baseline of the Augmentation (N = 53) and Switch (N = 12) Groups in Depressed Elderly Patients Unresponsive to Paroxetine + Interpersonal Psychotherapy

Variable	Augmentation Group (N = 53)	Switch Group (N = 12)[a]
Age, y		
Mean (SD)	76.2 (5.7)	78.8 (7.2)
Median	76	78.5
Range	69–90	71–94
Female, N (%)	33 (62.3)	6 (50.0)
White, N (%)	48 (90.6)	12 (100)
CIRS-G total score		
Mean (SD)	9.8 (4.0)	12.0 (5.1)
Median	9	12
Range	2–19	5–20
CIRS-G count		
Mean (SD)	5.8 (2.1)	6.6 (2.3)
Median	5	7
Range	2–12	3–10
Thyroid-stimulating hormone level, μIU/mL		
Mean (SD)	2.7 (2.5)	2.6 (1.9)
Median	1.9	2.2
Range	0.4–16.2	0.8–6.5
Serum vitamin B_{12} level, pg/mL		
Mean (SD)	520 (288.7)	511.7 (220.8)
Median	423	441
Range	181–1500	229–933
Serum folate level, ng/mL[b]		
Mean (SD)	463.6 (154.1)	547.1 (165.3)
Median	453.5	609
Range	185–821	304–726
Mini-Mental State Examination score		
Mean (SD)	27.9 (2.3)	27.8 (2.0)
Median	28	28
Range	20–30	23–30
Mattis Dementia Rating Scale score		
Mean (SD)	132.2 (9.6)	134.3 (9.1)
Median	134	138
Range	100–142	109–142
Executive Interview score[c]		
Mean (SD)	9.2 (5.1)	8.2 (6.5)
Median	9	7
Range	0–20	1–24
UKU Side Effect Rating Scale total score[d]		
Mean (SD)	20.1 (6.9)	14.9 (7.5)
Median	20	12
Range	7–36	8–34
HAM-D-17 score		
Mean (SD)	21.2 (3.5)	17.5 (3.5)
Median	20	16.5
Range	16–30	11–24
Single episode, N (%)	22 (41.5)	8 (66.7)
Age at first depressive episode, y		
Mean (SD)	59.2 (18.8)	66.6 (19.3)
Median	66	72
Range	11–85	25–93
Duration of index episode, wk		
Mean (SD)	120.2 (224.7)	156.5 (347.4)
Median	39	40.5
Range	3–1248	3–1248

[a]Nine of the 12 switch subjects were first treated in the augmentation algorithm and are therefore included in the 53 augmentation subjects.
[b]Augmentation group: N = 48; switch group: N = 10.
[c]Augmentation group: N = 47.
[d]Switch group: N = 11.
Abbreviations: CIRS-G = Cumulative Illness Rating Scale-Geriatric version, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Table 2. Medication Doses and Duration of Treatment for the Augmentation (N = 53) and Switch (N = 12) Groups in Depressed Elderly Patients Unresponsive to Paroxetine + Interpersonal Psychotherapy[a]

Augmentation Trial	Medication	N	Treatment Duration, Median (range), wk	Maximum Dose, Median (range), mg/d
First trial	Bupropion	39	5.6 (0.3–30)	200 (50–400)
	Nortriptyline	9	17 (0.2–28.7)	35 (10–50)
	Lithium	5	7 (1–22.3)	300 (225–300)
Second trial	Bupropion	3	8.1 (0.6–14.7)	175 (100–300)
	Nortriptyline	8	7.8 (3–26.4)	20 (10–35)
	Lithium	5	6 (4–15.9)	300 (150–300)
Third trial	Bupropion	0	NA	NA
	Nortriptyline	0	NA	NA
	Lithium	7	6.9 (1–18)	300 (150–450)
Switch trial	Venlafaxine XR	12	12.0 (8.7–12)	244 (150–300)

[a]Nine of the 12 switch subjects were first treated in the augmentation algorithm and are therefore included in the 53 augmentation subjects.
Abbreviations: NA = not applicable, XR = extended release.

after a median treatment duration of 10.7 (range, 2.0–27.7) weeks with a median maximal dose of paroxetine of 40 mg/day (range, 20–40 mg/day).

Figure 1 illustrates the treatment course and response characteristics for the augmentation group as they progressed through sequential trials of augmentation. Successively fewer subjects entered each subsequent trial of augmentation due to either responding to treatment or the subject's decision to leave the study. Twenty-four (45%) of 53 subjects responded to the first augmentation trial. Sixteen subjects received a second augmentation trial, of whom 5 (31%) responded. Finally, 7 subjects received a third augmentation trial, of whom 3 (43%) responded. Overall, 32 (60%) of the original 53 patients responded to some form of augmentation. The rate of response to augmentation was not different in subjects who initially responded (and then relapsed) with IPT and paroxetine monotherapy compared with those who never responded. The mean time to response after starting the first augmentation trial was 6.0 (SD = 5.8) weeks. Five subjects relapsed after originally responding to the first or second augmentation trial, 2 (40%) of whom responded to an additional augmentation trial.

Table 2 summarizes the doses and treatment duration of the augmentation agents added to paroxetine monotherapy. The median (range) cumulative duration of augmentation therapy was 7.3 (0.1–30.0) weeks. Subjects remained in the first, second, and third trials of augmentation for a median duration of 7.3 (range, 0.1–30.0), 7.3 (range, 0.6–26.4), and 6.9 (range, 1.0–18.0) weeks, respectively.

Twenty of 53 subjects in the augmentation group returned to paroxetine monotherapy for a median duration of 7.9 weeks (range, 1.0–45.0 weeks). Nine of 12 subjects who returned to paroxetine monotherapy and IPT after their first augmentation trial responded, whereas 1 of 3 subjects did so after the second augmentation trial. None of the 4 subjects who returned to paroxetine monotherapy after discontinuation of their third augmentation trial responded. Subjects who did not respond after a return to treatment with paroxetine monotherapy and IPT tried another augmentation medication, left the study, or switched to venlafaxine XR monotherapy.

Thirty-two (60%) of the 53 subjects in the augmentation group discontinued an augmentation trial. As each subject could receive up to 3 trials of augmentation, there were 49 occasions when an augmentation trial was discontinued. Adverse effects contributed to 32 instances (65%) that an augmentation trial was discontinued, involving 27 (51%) of the 53 subjects. Of the specific augmentation strategies, bupropion SR was associated with the highest rate of discontinuation due to adverse events (50%; 21/42) compared with 24% (4/17) and 41% (7/17) for nortriptyline and lithium, respectively. Dizziness, tremors, and unsteadiness were the main reasons for discontinuation of any augmentation trial. Twenty (38%) of 53 subjects receiving an augmentation therapy experienced one or more falls (range, 1–5 falls). For the specific augmentation strategies, the rate of falls was 36% (15/42), 18% (3/17), and 29% (5/17) for bupropion, nortriptyline, and lithium augmentation, respectively.

Experience With Switching to Venlafaxine XR

The switch group consisted of 12 subjects who received treatment with venlafaxine XR monotherapy after failing treatment with IPT and paroxetine with or without augmentation. Figure 2 illustrates the treatment course and outcomes for these subjects. Three subjects each entered after failing paroxetine monotherapy and each possible augmentation trial. Overall, 5 (42%) of 12 subjects responded to venlafaxine XR. Subjects were treated with venlafaxine XR for a maximum of 12 weeks (range, 8.7–12 weeks). The median maximum dose of venlafaxine was 244 mg/day (range, 150–300 mg/day). The mean time to response after starting venlafaxine XR was 6.4 (SE = 0.9) weeks.

The rate of response to venlafaxine XR varied on the basis of the number of previous treatment trials and the response to prior treatment. The response rate was 67% (4 of

6 subjects) for those subjects who received venlafaxine XR after receiving IPT with paroxetine monotherapy or with paroxetine plus 1 augmentation trial, 33% (1 of 3 subjects) for those subjects who received IPT with paroxetine plus a second augmentation trial, and 0% (0 of 3 subjects) for those subjects who received venlafaxine XR after receiving all 3 trials of augmentation. Similarly, when examined on the basis of response to prior treatment, 4 (57%) of the 7 switch subjects who had experienced a response and subsequent relapse responded to venlafaxine XR, whereas only 1 (20%) of the 5 switch subjects who did not experience a response to IPT and paroxetine with or without augmentation responded to venlafaxine XR treatment.

One (8%) of the 12 subjects in the switch group discontinued venlafaxine XR due to an adverse event (orthostatic hypotension). One additional subject discontinued venlafaxine XR prior to completing the 12-week trial after withdrawing consent. Three (25%) of 12 subjects taking venlafaxine XR experienced 1 or more falls (range, 1–2 falls).

DISCUSSION

In one of the few analyses to consider sequential management of treatment-resistant depression in later life, we observed similar rates and speed of response with an augmentation strategy and a switching strategy in elderly depressed subjects who failed to respond or to sustain a response to initial treatment with paroxetine and IPT. Thirty-one percent to 45% of subjects responded to each separate trial of paroxetine plus augmentation or to venlafaxine XR monotherapy. The aggregate response rate for subjects who progressed through all 3 trials of augmentation was 60%. Since compliance was good overall (data not shown), it is unlikely that failure to respond to either strategy was due to noncompliance with study medication. Adverse effects, mainly tremors, dizziness, and unsteadiness, led over half (51%) of subjects to discontinue a trial of paroxetine plus augmentation. The rate of discontinuation due to adverse effects was lower for venlafaxine XR monotherapy (8%; N = 1). Similarly, the incidence of falls may be lower with venlafaxine XR monotherapy (25%) than with paroxetine plus augmentation (38%), although the design of this study prevents us from making definite causal inferences. We have previously reported a high rate of falls when paroxetine and bupropion are combined in depressed elderly subjects based on an analysis of a subset of the subjects reported here.[28]

The strengths of this study include the use of a reliable and valid method for diagnosing depression, the prospective definition of treatment resistance, and the use of validated instruments to monitor depressive symptoms throughout the study. These factors have been highlighted by Fava[29] as important in treatment-resistance research. There are several limitations in the study design to the extent of any comparisons or conclusion about either treatment strategy.

First, this was a post hoc analysis of 2 open-label studies that lacked control groups. Second, the number of subjects receiving the second or third augmentation trial in the augmentation group or receiving venlafaxine XR in the switch group was small. Third, the sequential nature of subjects' participation in the studies, although useful for reducing variability in subjects' characteristics and treatment histories, created overlapping groups, e.g., most of the venlafaxine XR–treated subjects had failed at least 1 augmentation trial. Thus, the subjects in the switch group could be considered more treatment resistant because they failed more treatment trials than did the subjects in the augmentation group even though their baseline HAM-D-17 scores were lower.

Fourth, the venlafaxine XR subjects were a mix of subjects who had experienced no response, relapse after initial response, or recurrence after a period of remission during paroxetine therapy. Fifth, there were important differences between the design of the studies through which the 2 groups were treated, including more frequent clinic visits and treatment with IPT for those subjects receiving paroxetine with or without augmentation. IPT has demonstrated efficacy in geriatric depression,[30] and its absence may have reduced the potential for success with venlafaxine XR monotherapy.

Sixth, the availability of alternative augmentation medications may have lowered the threshold of study clinicians and subjects alike to discontinue 1 augmentation trial and try a different augmentation agent. This may help to explain the high discontinuation rate (51%) associated with augmentation trials in comparison with venlafaxine XR (8%). Seventh, while medication noncompliance was low in both studies (data not presented), it was assessed by self-report only. Finally, the information available to characterize the 2 groups medically was limited, hence restricting the comparisons that can be made about the tolerability and safety of the 2 treatment strategies.

Placing our results in the context of the current literature is difficult due to the variability in criteria for treatment response and remission as well as treatment resistance. In addition, there is a paucity of studies in late-life treatment-resistant depression. Our result that 31% to 45% of subjects respond to augmentation is consistent with previously reported response rates in mixed-age samples.[31] Our finding that the likelihood of response to venlafaxine XR monotherapy decreases with the number of previously attempted treatment trials is also consistent with other reports.[32] This finding, along with the related finding that response with subsequent relapse to prior treatment was associated with response to venlafaxine XR, suggests that it might be a characteristic of the sub-

ject, rather than of the specific treatment intervention, that is most closely related to treatment response.

Regarding the success of augmentation in the elderly, our results are consistent with that of Flint and Rifat,[14] who reported that 35% of elderly depressed subjects who had failed an adequate trial of nortriptyline responded to lithium augmentation. In adults with treatment-resistant depression, lithium augmentation has been shown to have an efficacy rate of 30% to 50%,[33] but may be less efficacious in the elderly.[34,35] It is important to note, however, that the majority of studies of lithium augmentation paired lithium with a non-SSRI antidepressant. There is concern that a lithium-SSRI combination may be less effective and poses a greater risk of adverse effects than a lithium-tricyclic antidepressant combination.[7] Combined bupropion and SSRI therapy had a remission rate of 70% in an open-label trial[36] and 54% in an augmentation trial involving a prospectively defined treatment-resistant nongeriatric sample.[37] Heterocyclic antidepressant augmentation of fluoxetine in a mixed-age sample led to a 35% response.[38] In treatment-resistant samples of mixed-age subjects, venlafaxine monotherapy has demonstrated a response rate of 16% to 69%.[39–42] While several of these studies used venlafaxine immediate release (IR) formulation, venlafaxine XR has comparable efficacy in depression relative to venlafaxine IR.[43]

The high rate of discontinuation with the augmentation trials relative to venlafaxine XR may be attributable to medication tolerability. The specific combination of bupropion and paroxetine is a risk factor for falls,[28] and the combination of lithium and an SSRI is also associated with an increased risk of adverse events.[7] In elderly depressed patients, the theoretical advantage of synergizing 1 antidepressant with another medication needs to be balanced with concerns of potential negative effects. Interestingly, the efficacy of venlafaxine XR is likely due to its combined serotonergic and noradrenergic action, similar to the efficacy of SSRI and TCA combinations. Generally, it is believed that venlafaxine XR has a favorable side-effect profile in the elderly.[44–46] However, this belief was recently challenged by Oslin and colleagues.[47] They conducted a 10-week, randomized, controlled trial comparing venlafaxine and sertraline in frail, elderly, depressed nursing home residents under double-blind conditions. In this trial, venlafaxine was associated with increased side effects and serious adverse events (typically cardiovascular or cerebrovascular in origin) and was no more efficacious and less well tolerated than sertraline.[47] It is unclear whether this finding in frail nursing home residents can be generalized to all elderly, regardless of health status.

Our results, while not definitive, appear to indicate modest efficacy of both augmentation and switching therapies for treatment-resistant geriatric depression. The high rate of discontinuation related to adverse effects and the possible increased risk of falls with paroxetine plus augmentation therapy in comparison with venlafaxine XR monotherapy is an important consideration for clinicians and researchers alike. We believe that controlled evaluation of the utility of venlafaxine XR monotherapy as a preferred strategy for treatment-resistant geriatric depression is warranted.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

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