Outcomes of Late-Life Anxiety Disorders During 32 Weeks of Citalopram Treatment

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Background: Anxiety disorders are common in later life, but little is known about the long-term benefits and risks of pharmacotherapy.

Method: 30 patients aged 60 years and older, with a DSM-IV anxiety disorder, entered a 32-week trial of citalopram. Data gathered at baseline and follow-up included anxiety symptoms using Hamilton Rating Scale for Anxiety (HAM-A) scores, quality of life using the Medical Outcomes Study 36-item Short Form (SF-36), and sleep using the Pittsburgh Sleep Quality Index (PSQI). Data analysis consisted of mixed-effect repeated measures models of HAM-A scores and pre-post comparison of SF-36 and PSQI scores.

Results: 30 persons entered treatment; most (27/30) had a primary DSM-IV diagnosis of generalized anxiety disorder (2 had panic disorder; 1 had posttraumatic stress disorder). Three subjects discontinued study medication due to side effects, 5 were terminated because of nonresponse, and 5 dropped out of the study for other reasons; thus, 17 subjects (57%) completed 32 weeks of treatment. Subjects' HAM-A scores improved significantly, with continuing improvements up until about 20 weeks of treatment. On the basis of a criterion of reduction in HAM-A to < 10 during the trial, 60% (18/30) of subjects were responders. Those who completed the 32-week trial had significant improvements in sleep and quality of life—including social functioning, vitality, mental health, and role difficulties due to emotional problems.

Conclusions: In this 32-week study of citalopram for elderly persons with anxiety disorders, 60% responded. Those who received a full course of treatment experience significant improvements in quality of life and sleep quality.

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Anxiety disorders in old age are common and impair quality of life. Generalized anxiety disorder (GAD) has an estimated prevalence of 4% to 7% among older adults in the community.[1–3] It is associated with lower health-related quality of life[4] and increased health care utilization.[5] Other disorders such as panic disorder and posttraumatic stress disorder (PTSD) are less common[6] but are frequently seen in clinical samples.[7] Little is known about the appropriate management of anxiety disorders in elderly persons. The acute efficacy of antidepressants has been demonstrated for geriatric anxiety disorders.[8–10] However, anxiety disorders are chronic, with symptom duration of years to decades, in older adults[11]; thus, short acute trials are unlikely to establish the clinical value and risk-benefit ratio of pharmacotherapy treatment for these disorders. Almost no study has examined pharmacotherapy beyond the acute (4 to 6 weeks) period in this population; in contrast, durability of antidepressant response has been studied in depressed elderly.[12,13]

Accordingly, we examined the course of late-life anxiety disorder during 32 weeks of protocolized treatment with citalopram. Because prior studies of anxious depression in the elderly have shown a delayed response to antidepressants for this patient group,[13,14] we hypothesized that most subjects would show a similarly delayed response. We also hypothesized that continued citalopram

pharmacotherapy would result in a durable response associated with improvements in quality of life.

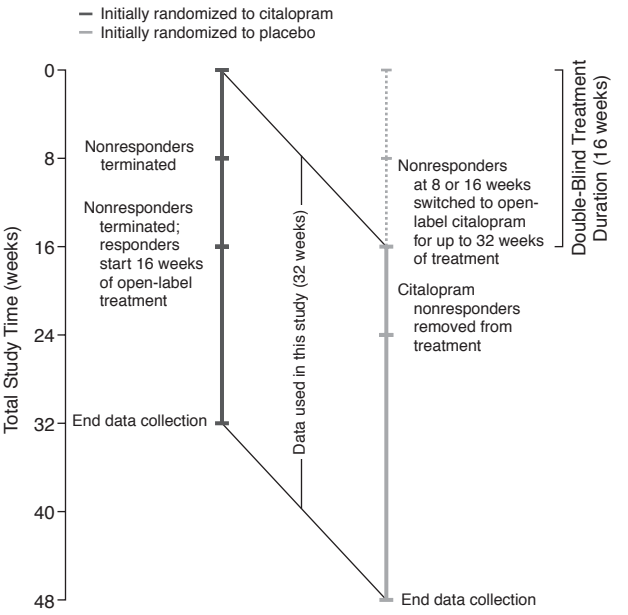
METHOD

Adults aged 60 years and older were recruited via advertisements and referrals in an urban area. All participants gave written informed consent for the study, which was approved by the University of Pittsburgh's Institutional Review Board. Trained raters supervised by geriatric psychiatrists conducted interviews with participants, which included the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID),[15] Hamilton Rating Scale for Anxiety (HAM-A),[16] and Hamilton Rating Scale for Depression (HAM-D).[17] Subjects had to meet diagnostic criteria for a DSM-IV anxiety disorder without receiving a diagnosis of a current major depressive episode or presenting with dementia, history of psychosis, unstable medical illness, or active alcohol or substance abuse. They were also required to have a score of 17 or greater on the HAM-A assessment, reflecting at least moderate anxiety symptoms. Interrater reliability was maintained for the HAM-A and SCID via yearly retraining.

This analysis is based on a previously reported placebo-controlled trial of citalopram[10] followed by open-label citalopram treatment (Figure 1). Subjects were initially randomly assigned to citalopram or placebo under double-blind conditions for up to 16 weeks. However, after 8 weeks, the blind was broken for nonresponders. Nonresponders who were on citalopram treatment were removed from the study. Nonresponders who were on placebo were switched to citalopram and treated openly for up to 32 weeks. Subjects who responded during the initial 8 weeks were treated under double-blind conditions for 16 weeks. At that time, the blind was broken. Patients who were on citalopram therapy were treated openly for up to 16 additional weeks. Patients who were only on placebo (i.e., were never switched to citalopram) were removed from the study. Thus, in this analysis, we include data from subjects initially randomly assigned to citalopram who received it for up to 32 weeks (16 weeks blinded followed by 16 weeks open-label) and from subjects initially randomly assigned to placebo, who also received citalopram for up to 32 weeks (all open-label); we exclude data from the placebo phase of the analysis. An examination of these 2 groups ensured that they did not differ in terms of trajectory of response during citalopram treatment; therefore, we concluded that they could be combined into 1 group for this analysis.

With the exception of stable dosing of lorazepam (maximum 2 mg/day) in those who were already taking benzodiazepines prior to study entry, other psychotropic medications were disallowed at least 2 weeks prior to the initiation of citalopram treatment. Subjects were seen weekly during the first 4 weeks on citalopram, every 2 weeks for the remainder of the first 16 weeks, and then every 4 weeks during the last 16 weeks. Citalopram dosing started at 10 mg/day and increased to 20 mg/day after 1 week. Subjects who did not respond by 4 weeks were increased to a dose of 30 mg/day, and those who did not respond by 8 weeks could be increased to 40 mg/day. Adherence to medication use was determined by subject report, which was confirmed by pill count.

Figure 1. 32-Week Treatment Design With Retention[a]



[a]Solid bold lines indicate data used in the present analysis.

Because we did not wish to keep nonresponders indefinitely in the study, the specific predetermined termination time points were defined based on the Clinical Global Impressions-Improvement (CGI-I) scale.[18] Subjects needed to have at least minimal improvement (CGI-I = 3 or less) at 8 and 12 weeks and much improvement (CGI-I = 2 or less) by 16 weeks; otherwise, they were removed from the study at those respective time points.

At all visits, subjects were assessed with the HAM-A and, at baseline and week 32, with the Pittsburgh Sleep Quality Index (PSQI)[19] and the Medical Outcomes Study 36-item Short Form Health Survey (SF-36).[20] At all visits, participants were asked about side effects by an open-ended question.

Statistical Analysis

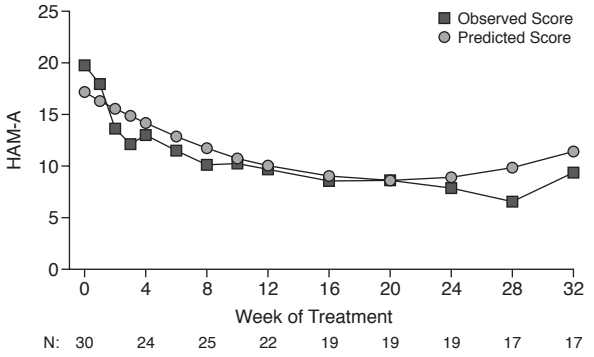
Because our first aim was to examine the course of symptom improvement, we tested several models for fit with HAM-A scores. A mixed model with linear and quadratic terms was the best fit based on observation of the data and examination of the residuals. We also examined response on psychic and somatic items from the HAM-A. Psychic items were anxious mood, tension, fears, concen-

Table 1. Baseline Demographic and Clinical Information on Citalopram-Treated Subjects (N = 30)

Characteristic	Value
Age, y	
Mean (SD)	69 (6)
Range	60–86
Sex, N (%)	
Female	19 (63)
Male	11 (37)
Race, N (%)	
African American	2 (7)
White	28 (93)
Education, y	
Mean (SD)	14 (2.6)
Range	10–20
HAM-A score	
Mean (SD)	19.9 (5.1)
Range	11–30
HAM-D score	
Mean (SD)	12.0 (3.1)
Range	8–22
Mini-Mental State Examination score	
Mean (SD)	28.6 (1.9)
Range	22–30

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

Figure 2. Improvements in HAM-A Scores During 32 Weeks of Treatment[a]



[a]Decline in HAM-A scores as estimated by the model, as well as raw means, displayed.
Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

tration, depressed mood, and behavior at the interview; somatic items were insomnia, muscular and sensory complaints, and cardiovascular, respiratory, gastrointestinal, genitourinary, and autonomic symptoms. For those who completed 32 weeks of treatment, we compared baseline and endpoint SF-36 subscales and PSQI scores using paired t tests.

RESULTS

Demographic and clinical information of all patients at baseline is shown in Table 1. Participants meeting criteria for study participation received a principal diagnosis of GAD (N = 27), panic disorder (N = 2), or posttraumatic stress disorder (N = 1). Of the 30 participants receiving citalopram treatment, 3 (10%) of 30 were removed from the study due to adverse events: sedation after 1 dose, tremors after 1 week, and sedation after 16 weeks. Five participants (17%) withdrew consent for reasons unrelated to side effects. Five participants (17%) were removed from the study at either 8 or 16 weeks in accordance with the study design because they did not show at least minimal improvement (CGI-I = 3 or less) at 8 weeks and much improvement (CGI-I = 2 or less) at 16 weeks. Thus, 17 (57%) of 30 participants showed much improvement and went on to complete 32 weeks of treatment. Mean (SD) final citalopram dose was 21.8 (8.6) mg (median = 20 mg; range, 10–40 mg).

On the basis of a criterion of reaching a HAM-A < 10 during the trial, 18 (60%) of 30 subjects were responders, which included 3 subjects who subsequently dropped out due to side effects. A survival analysis showed a median time-to-response of 55 days. A comparison of baseline severity showed a significant difference between responders versus nonresponders. The mean baseline HAM-A score of responders was 18.1 (SD 3.5), and the mean HAM-A score of nonresponders and dropouts was 23.1 (SD 6.1) ($t = 2.48$, $df = 28$, $p = .03$). Medication adherence was high in the sample: only 5 subjects (3 responders and 2 nonresponders) reported missing even 1 dose.

The predicted HAM-A scores in the quadratic fit model (which utilized data for all 30 participants) showed a steady improvement in anxiety-related symptoms up to a 20-week treatment period. Figure 2 shows HAM-A changes over time in observed cases and predicted scores from the model. The nadir of HAM-A scores for the group was week 20; the mean predicted HAM-A score at this time point was 8.7, a significant improvement from the HAM-A baseline predicted group score of 17.2 ($F = 73.43$, $df = 1,27$; $p < .001$). We then examined changes in the psychic and somatic subscales from the HAM-A. The HAM-A psychic subscale–predicted group score improved from 8.8 at baseline to 4.0 at week 20 ($F = 61.7$, $df = 1,27$; $p < .0001$). The HAM-A somatic items showed a similar decrease over time from a subscale-predicted group score of 8.5 at baseline to 4.6 at week 20 ($F = 41.7$, $df = 1,27$; $p < .0001$).

Finally, the 17 participants who completed the 32-week trial showed significant improvements in the following SF-36 subscales: mental health, social functioning, role limitations due to emotional problems, and vitality. Sleep quality, as measured by the PSQI, also improved significantly in this group (Table 2).

DISCUSSION

This is one of the few reports describing anxiety disorder pharmacotherapy in elderly persons, and, to our

Table 2. Changes in Quality of Life From the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and in Sleep Quality From the Pittsburgh Sleep Quality Index (PSQI) in Study Completers (N = 17)[a]

	Baseline			Week 32			t Test[b]	
Scale	Mean	SD	Min/Max	Mean	SD	Min/Max	(df = 16)	p
SF-36								
Mental component	39.0	10.1	17.0/56.2	50.6	10.2	22.3/65.2	4.76	.0002
Physical component	50.2	8.7	29.5/62.1	47.4	9.4	22.7/56.9	–1.39	.18
Bodily pain	60.9	25.3	22/100	70.1	21.2	22/100	1.59	.13
General health perceptions	70.1	19.3	30/97	71.9	16.3	40/97	0.58	.57
General mental health	50.6	16.9	16/80	72.7	17.6	32/96	5.57	.0001
Physical functioning	80.6	17.6	45/95	77.6	20.4	25/100	–1.05	.31
Role limitations due to emotional problems	51.0	41.0	0/100	76.5	32.8	0/100	3.05	.01
Role limitations due to physical health	67.6	38.3	0/100	70.6	36.7	0/100	0.28	.79
Social functioning	78.7	23.7	25/100	90.4	18.5	50/100	2.39	.04
Vitality	48.5	14.0	15/75	58.5	18.1	20/90	2.85	.02
Pittsburgh Sleep Quality Index[c]	8.9	3.3	4/17	5.4	3.0	1/11	–3.76	.002

[a]Increasing SF-36 scores indicate quality of life improvements; *decreasing* PSQI scores indicate sleep quality improvements.
[b]Test statistics based on 32-week and baseline comparisons.
[c]df = 15 due to missing baseline PSQI measure in 1 subject.

knowledge, the duration of the trial is the longest to date. Some limitations should be noted. First, the study design (for ethical reasons) prevented a full evaluation of response, as some people removed by study design (e.g., at week 8 or 16 because of nonresponse) may have eventually become responders; therefore, our response rate and completion rate may be artificially low. The removal of subjects for nonresponse also may have affected the analytic results using the mixed effect model, though the data do meet the missing-at-random assumption of this model and this was the best option for using all available data in this analysis. Also, the size of our study group was small, and subjects in general were medically healthy and cognitively intact. Finally, our data are open-label, and the response rate cannot be definitively attributed to citalopram, although we have also published separate analysis of the portion of this trial conducted under randomized placebo-controlled conditions that demonstrated the efficacy of citalopram.[10]

Notwithstanding these limitations, our data suggest that citalopram is reasonably well-tolerated and is associated with significant improvement in anxiety symptoms, with a completion rate of the 32-week trial of 57% and a response rate (in an intent-to-treat analysis) of 60%. Additionally, trial completers had significant improvements in sleep and several aspects of quality of life. Nonresponders had a higher baseline HAM-A score than responders. This is not surprising, as research in geriatric depression has suggested that higher anxiety scores predict slower, or lower, response rate.[13,14] Additionally, those with higher HAM-A scores had "farther to go" to achieve response, which may have reduced response rate. The sample size had insufficient power for an examination of all possible predictors of response, and future research needs to examine more fully what predicts response in geriatric anxiety.

The response rate of 60% is fairly typical of recent pharmacotherapy studies.[9,21–23] This improvement was significant in both psychic and somatic anxiety symptoms, which has also been noted in young adults treated with selective serotonin reuptake inhibitors (SSRIs).[24] The completion rate of 57% is partly due to study dropouts because of side effects; while the dropout rate was not high for an anxiety disorder treatment trial, it is a reflection that some anxious elderly cannot tolerate SSRIs, even if they are responding to treatment and receive frequent follow-up visits. The advantage of following 32 weeks of treatment is that it allows examination of the trajectory of anxiety improvement. The median time to response of 8 weeks that we found suggests that many elderly persons will require an extended trial of more than 8 weeks to demonstrate response. Indeed, the peak response in this trial was seen at 20 weeks of treatment, which is consistent with other data showing that anxious elderly often need an extended period of treatment to improve.[14] This is an important point for clinicians, who need to inform their patients when a peak response to pharmacotherapy might be expected. These findings are also of importance for research in geriatric anxiety disorders, as acute trials that are 8 weeks or less may not be sufficient to examine the full range of response.

We found improvements in several related areas of quality of life: social functioning, mental health function, role limitations due to emotional concerns, and vitality. Some of these areas have been demonstrated to improve in older anxious adults with effective psychotherapy as well.[24,25] Our finding is a reminder that an examination of symptom change is only a small part of the overall effects of a treatment; a demonstration of quality of life benefit is necessary as well. In this study, an improvement in quality of life with treatment points to an overall benefit to anxious elderly treated with an SSRI. Additionally, we found that sleep quality improves with treatment of geriatric anxiety—an important consideration given that sleep impairment is often a major concern for anxious patients.

More research is needed that examines the effects of long-term treatment of geriatric anxiety disorders. In contrast to research in geriatric depression, in which relapse, recurrence, and long-term quality of life changes have been examined within protocolized treatment,[11,26] no such studies have been carried out in geriatric anxiety. As a result, it is less clear to clinicians what the goals of long-term treatment of geriatric anxiety are. Concepts of treatment phases familiar in the depression field, i.e., acute, continuation, and maintenance treatment (to achieve response or recovery, and prevent recurrence, respectively),[27] are not widely used in anxiety disorders research despite similarities between depression and anxiety disorders such as GAD. While our trial is the longest to date in this population, it is not of sufficient length or size to fully examine durability of symptomatic response, stabilization of quality of life, or prevention of other sequelae (such as disability, cognitive impairment, or major depressive disorders or other psychiatric comorbidities). Because all of these outcomes may be clinical goals of long-term management of geriatric anxiety disorders, they are worthy of further study.

Drug names: citalopram (Celexa and others), lorazepam (Ativan and others).

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