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Time to response to citalopram treatment for agitation in Alzheimer's disease

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Abstract

Background—Agitation is a common and significant problem in Alzheimer's disease (AD). In the recent Citalopram for Agitation in Alzheimer's Disease (CitAD) study, citalopram was efficacious for the treatment of AD agitation. Here we examined the time course and predictors of response to treatment.

Methods—Response in CitAD was defined as a modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC) score of 1 or 2, or a Neurobehavioral Rating Scale agitation subscale (NBRS-A) score reduction ≥50% from baseline. “Stable early

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response” was defined as meeting the aforementioned criteria at both weeks 3 and 9, “late response” was response at week 9 but not at week 3, and “unstable response” was response at week 3 but not at week 9.

Results—In the primary analyses, citalopram was superior to placebo on both the CGIC and the NBRs-A response measures. There were little between-group differences in response rates in the first three weeks of the study (21% vs 19% on the CGIC). Citalopram patients were more likely than placebo patients to be a late responder (18% vs. 8% on CGIC, Fisher’s exact $p=0.09$; 31% vs. 15% on NBRs-A, Fisher’s exact $p=0.02$). Approximately half (45–56%) of citalopram responders at end-of-study achieved response later in the study, compared with 30–44% of placebo responders.

Discussion—Treatment with citalopram for agitation in AD needs to be at least nine weeks in duration to allow sufficient time for full response, and study duration is an important factor to consider in the design of clinical trials for agitation in Alzheimer’s disease.

INTRODUCTION

Agitation is common, persistent, and associated with adverse consequences for patients with Alzheimer’s disease (AD). To date, pharmacologic treatments have not been consistently effective (1) and there is a known mortality risk from antipsychotic treatment (2). The primary objectives of the Citalopram for Agitation in Alzheimer’s Disease Study (CitAD) were to evaluate the efficacy and safety of citalopram for agitation in patients with AD (3;4).

In brief, CitAD was a multicenter, randomized, placebo-controlled, double-blind, parallel group trial of patients with probable AD and clinically significant agitation conducted at eight academic centers in the United States and Canada(4). Participants were randomized to receive a psychosocial intervention plus either citalopram ($n=94$) or placebo ($n=92$) for nine weeks. Dosing began at 10 mg/d with planned titration to 30 mg/d over three weeks, with lower doses allowed if tolerability was an issue. The primary outcome measures were the Neurobehavioral Rating Scale, agitation subscale (NBRs-A) and the modified Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC). The study enrolled 186 participants (citalopram=94, placebo=92). Mean age was 78 years, 46% were women, 65% were white and non-Hispanic, 89% were community dwelling, and the mean duration of AD was 5 years. About two-thirds took cholinesterase inhibitors, and just over 40% memantine. Over 90% of both groups completed the 9-week trial, and about 80% remained on treatment. At week 9, 78% of the sample was receiving 30 mg citalopram daily and 15% were receiving 20 mg citalopram daily. In terms of outcomes, citalopram was superior to placebo on both primary outcome measures, but was associated with an increased QTc interval on ECG, and higher rates of fever and mild gastrointestinal adverse events.

In clinical practice clinicians need to know the general time course of response to a symptomatic therapy. For example, guidelines for antidepressant therapy recommend that if response is absent or minimal after three to four weeks of treatment, consideration should be given to increasing the dose or switching to another antidepressant, while if the depression shows partial improvement by four weeks, treatment should be continued for another 2–4

weeks (5). For late-life depression, a lack of at least partial response by week 4 of an antidepressant course suggests a high likelihood of lack of remission at week 12 (6).

Similar, important treatment decisions apply when managing AD patients with agitation, but there is limited evidence to guide clinical practice (7). Given recommendations to use behavioral interventions (8) and to study other psychotropic medications (e.g., antidepressants (9), cholinesterase inhibitors (10)) for agitation in AD, guidance for use in clinical care is needed. Since agitation is disruptive for both patient and care provider, there is an urgency to produce symptomatic improvement. Thus, clinicians need to balance symptom severity and tolerability from the start of treatment, with an eye toward making adjustments in a timely fashion. However, the pressure to do this must be tempered by evidence about time course of response to a given treatment, to avoid premature medication discontinuation or dose escalation.

Using CitAD data, we performed exploratory analyses to examine the time course of treatment response across the nine study weeks, characterizing patients as stable early responders, unstable responders, or late responders. We also examined clinical predictors of late versus early response.

METHODS

Study design and outcome measures

The methods for CitAD have been published (3). The primary definitions of response were (1) an ADCS-CGIC score of 1 or 2 (“marked improvement” or “moderate improvement”) or (2) an NBRSA score reduction $\geq 50\%$ from baseline to end-of-study, considered separately. Response definitions that incorporated the two outcome measures together were also applied, one more stringent (i.e., responder on *both* CGIC and NBRSA) and the other less stringent (i.e., responder on *either* CGIC or NBRSA, considered together). For the purposes of these analyses, “stable early response” was defined as meeting the aforementioned criteria for response at both weeks 3 and 9. “Late response” was defined as meeting criteria for response at week 9 but not at week 3. Finally, “unstable response” was meeting criteria for response at week 3 but not at week 9.

Statistical analysis

We compared participants with complete data to those without complete data with respect to age, race, sex, baseline scale scores, duration of dementia and use of cholinesterase inhibitors and memantine using logistic regression. In later analyses, we focused on participants with complete data to examine late response and stability of response (n=160). We graphically compared the proportion of participants classified as responders for CGIC and NBRSA at each time point by treatment group, including the exact confidence intervals. To see if there were commonly assessed demographic or clinical variables that predicted late response compared to stable early response, we used logistic regression by first testing for interactions between the treatment group and potential predictors to allow predictors to vary by treatment group, but after finding no interactions (all interaction p-values >0.05), we then combined the treatment groups in analyses and used univariate exact

logistic regression (11) with a score statistic (12) to test for associations and calculate p-values. Each continuous predictor was dichotomized at the median in the logistic models. All reported confidence intervals and p-values are nominal. Adjustment of p-values for multiple comparisons was not performed because the emphasis is on the reporting of point estimates and confidence intervals as opposed to p-values. Given that 20 tests (10 covariates for 2 outcomes) were performed for Table 2, one significant test at the 5% level would be expected by chance alone.

RESULTS

Participants

A total of 186 patients were randomized (citalopram= 94, placebo= 92); 167 (90%) completed the study and provided CGIC and NPRS-A data at week 9 (citalopram= 86, placebo= 81). A total of 163 patients provided these outcome data at both week 3 and week 9 (citalopram= 83, placebo= 80), and 160 at weeks 3, 6 and 9 (citalopram= 80, placebo= 80).

One hundred sixty participants had data at each study visit, with 26 missing data for at least one study visit. Nine participants missed an interim visit (week 3 or 6) but completed the final visit (week 9). Of the 17 participants that missed the week 9 visit, 12 dropped out of the study prior to this point, 4 did not come to the week 9 visit, and 1 died(4). On demographic and clinical variables, participants with complete data differed from those without complete data only with respect to age. Those with incomplete data were more likely to be 80 years of age (Wald $\chi^2 = 3.85$, df=1, OR=2.6, 95% CI=1.0–6.6, p=0.05).

Response at end-of-study

At the end-of-study visit, 33% of all participants were responders based on a score of 1 or 2 on the CGIC (citalopram= 40%, placebo= 26%); 45% were responders based on an NBRSA score reduction of 50% (citalopram= 56%, placebo= 33%). Using the more stringent criterion of response on both, 25% of patients were responders (citalopram= 28%, placebo= 21%), while using the more liberal criterion of response on either the rate was 53% (citalopram= 67%, placebo= 38%).

Time course of responder status

Examining the 160 participants who provided outcome data at all time points (baseline and weeks 3, 6 and 9), stable early response (25% and 19%) and unstable response (10% in both groups) were similar in the two groups using the NBRSA, but late response (compared with all other response categories) was twice as common in the citalopram participants (31% vs. 15%; Fisher's exact p=0.02) (Table 1). More than half (56%) of citalopram participants who were classified as responders based on their NBRSA score at end-of-study were late responders.

Using the CGIC the rates of stable early response were similar for citalopram and placebo (21% vs. 19%), and unstable response was similar and relatively uncommon in the two groups (6% and 9%). 18% of citalopram patients versus 8% of placebo patients were late

responders compared with all other response categories, a nonsignificant difference (Fisher's exact $p=0.09$). Of citalopram participants who were classified as responders on the CGIC at the end-of-study, nearly half (45%) were late responders. There was not a statistically significant between-group difference in participants classified as late versus stable early responders (OR=1.9, 95% CI=0.5–7.7, exact $p=0.41$).

Examining course of response for the two groups in additional detail, cross-sectional rates of CGIC response in the citalopram group (vs. placebo) were 28% (28%) at week 3, 39% (23%) at week 6, and 39% (26%) at week 9 (Figure 1). On the NBRSA, rates of response in the citalopram group were 35% (29%) at week 3, 43% (29%) at week 6, and 56% (34%) at week 9. The NBRSA response rate in the citalopram group was lower for the week 6 visit compared with the week 9 visit (Wald $\chi^2 = 3.83$, $df=1$, OR=0.86, 95% CI=0.75–1.00, $p=0.05$). Given that only a small number of participants exhibited unstable early response, the numbers mean that CGIC scores continued to improve out to six weeks of treatment on the CGIC and out to nine weeks of treatment on the NBRSA.

Baseline predictors of late response versus stable early response

We examined if the potential predictors of late response differed by treatment group using interaction tests; no interactions were statistically significant at the 5% level (data not shown), so all participants (i.e., from both treatment groups) with complete data were used in the initial analysis. For the entire study population, only concomitant memantine use predicted late response versus stable early response (for the CGIC) for at the 5% level (Table 2). The estimated odds of having a late CGIC response for younger patients (those <80 years of age) compared with older patients was OR=3.1, 95% CI=0.9–12.5, exact $p=0.09$; 70% of late responders were <80 years of age, compared with 42% of stable early responders (there was not a significant age difference between those participants receiving versus not receiving memantine).

Examining only citalopram-treated participants and response on the CGIC, there were no variables that predicted late versus early response. The odds ratio for CGIC response for younger patients versus older patients was OR=5.4, 95% CI: 1.0, 41.5, exact $p=0.06$ (such a difference was not seen in the placebo group, data not shown) (Table 3). 79% of late responders were <80 years of age, compared with 39% of stable early responders. Only 21% of participants >80 years old who were responders at end-of-study had not been a responder at week 3; in contrast, 61% of participant <80 years old achieved this after week 3.

DISCUSSION

In these secondary analyses of CitAD study data that included only participants with complete study data, we found that the highest response rate for citalopram compared with placebo in the treatment of AD agitation was evidenced during the final six weeks of the nine-week trial, with citalopram-treated patients more than twice as likely as placebo patients to be a late responder. Approximately half of citalopram responders achieved their response later in the course of the study (i.e., after week 3). In addition, there was a suggestion that younger age predicted later response on citalopram. This suggests that future pharmacologic trials of treatments for agitation in dementia should be at least 9 weeks in

duration, and ideally longer. It also suggests that clinicians should attempt a trial of 9 weeks duration before concluding a lack of response.

Approximately half of citalopram responders responded after week three (compared with approximately one-third of placebo responders), which is the time period when the separation between active and placebo treatment occurred. Although comparisons across studies are difficult due to differences in design and measurement of response, anti-agitation treatment effects for antipsychotics in AD are often reported as early as week two (1;14). The response rate for the citalopram group based on the NBRs-A score increased from 43% to 56% from week 6 to 9 (compared with 29% to 34% for the placebo group), an increase in response rate of 30.2% over the final three weeks of the study.

There was no difference in response rates between active and placebo treatments during the first three study weeks. Possible explanations include (1) citalopram's anti-agitation effect takes more than three weeks to manifest itself; (2) the titration period of three weeks to achieve the final citalopram dose for the study (30 mg/day) delayed its benefit; (3) the minimum therapeutic anti-agitation dose for citalopram is 30 mg/day; and (4) the placebo group responded considerably over the first several weeks, so a differential effect favoring citalopram was not detectable.

Early response for both groups was typically stable. A participant who was a responder at week three had an 80% chance of remaining a responder six weeks later, suggesting that an early response to citalopram for agitation in AD is lasting. A separate, unanswered question is the optimal duration of treatment before considering discontinuation of treatment for agitation in AD. For instance, for a first episode of late-life depression a conservative recommendation is to continue antidepressant treatment for one year before considering discontinuation (13).

Another unanswered question is if additional clinical effects may accrue beyond nine weeks of treatment. Most controlled trials for agitation and psychosis in dementia have been 6–12 weeks in duration, with limited evidence for treatment effects beyond 12 weeks (7).

The difference in response rates between active treatment and placebo were greater on the NBRs-A score compared to the CGIC. This greater sensitivity for the NBRs-A as an instrument was also reflected in the fact that additional response was seen out to nine weeks with NBRs-A, compared with out to only six weeks on the CGIC. The results suggest either greater sensitivity for a rating scale compared with a global impression of change for defining responder status in AD agitation studies, or differences in the ease of achieving responder status on the NBRs-A vs. the CGIC. In practice, clinicians might consider administering a rating scale at baseline and during the course of treatment to best gauge response.

No clinical or demographic variables examined predicted time course of response, other than the use of memantine for the CGIC response, and this association should be interpreted cautiously due to the multiple comparisons and the fact that the association was only present for only one measure of response. It is possible that the small number of participants in each of the subgroups of interest prevented a statistically significant effect from being detected,

and predictors of time course to response should be studied in future studies. For the oldest patients (age ≥ 80 years), a lack of response by week three was a strong indicator that response was not likely to happen with additional treatment, with only 20% of the oldest participants achieving new response after week three. Given that these are the patients most vulnerable to the side effects of psychotropic medications, this finding can inform clinical management.

One limitation of this secondary analysis was the relatively small sample sizes in each of the subgroups, with each responder subgroup involving ≤ 25 participants. In addition, the limited sample sizes made it difficult to examine predictors of different response types. We only included completers so each participant would have a baseline and end-of-study assessment, and it is possible that including all study participants may have altered the findings, although only 10.2% of randomized participants did not complete the study. Finally, as study participants were not followed beyond week 9, we do not know how stable late response is.

These findings have implications for the management of AD patients with clinically significant agitation using citalopram, in that a treatment trial may need to be at least nine weeks to determine if a patient is going to respond. In addition, they can inform the design of future clinical trials for agitation in AD, including decisions regarding study length, frequency and timing of assessments, choice of outcome measures, and variables that might moderate treatment response. Future studies with larger sample sizes and longer treatment duration can more definitively examine the time course and predictors of response to anti-agitation treatments in AD.

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Figure 1. Time course for response on CGIC and NBRSA by treatment assignment^a

^aProportion responding with exact (Clopper Pearson) confidence intervals.

Table 1

Frequencies of response types based on CGIC and NBR-S-A scores

Response categories	Citalopram (% [N]) N=80 total		Placebo (% [N]) N=80 total	
	CGIC	NBR-S-A	CGIC	NBR-S-A
Stable early response	21% (17)	25% (20)	19% (15)	19% (15)
Late response	18% (14)	31% (25)	8% (6)	15% (12)
Unstable response	6% (5)	10% (8)	9% (7)	10% (8)
No response	55% (44)	34% (27)	65% (52)	56% (45)

Table 2
Factors associated with late versus stable early response in entire study population

Baseline variable	Late CGIC response ^d			Late NBR5-A response ^d		
	OR	95% CI	Exact p-value ^b	OR	95% CI	Exact p-value ^b
Age at						
80 yrs	Ref			Ref		
< 80 yrs	3.1	(0.9, 12.5)	0.09	1.8	(0.7, 5.2)	0.29
Gender						
Male	Ref			Ref		
Female	1.8	(0.5, 6.5)	0.46	1.3	(0.5, 3.7)	0.73
Race						
Nonwhite	Ref			Ref		
White	0.7	(0.2, 2.5)	0.74	0.9	(0.3, 2.6)	1.00
MMSE score						
< 13	Ref			Ref		
13	1.5	(0.4, 5.2)	0.70	0.6	(0.2, 1.7)	0.41
CMAI score						
< 25	Ref			Ref		
25	1.1	(0.3, 4.0)	1.00	1.2	(0.4, 3.3)	0.91
NBR5-A score						
< 10	Ref			Ref		
10	0.7	(0.2, 2.8)	0.77	0.7	(0.2, 1.9)	0.55
Duration of AD						
< 4 yrs	Ref			Ref		
4 yrs	2.5	(0.6, 10.7)	0.23	2.1	(0.7, 6.5)	0.19
Cholinesterase inhibitor use						
No	Ref			Ref		
Yes	1.7	(0.5, 6.8)	0.54	1.8	(0.6, 6.0)	0.39
Memantine use						

Baseline variable	Late CGIC response ^d			Late NBRSA response ^d		
	OR	95% CI	Exact p-value ^b	OR	95% CI	Exact p-value ^b
No	Ref			Ref		
Yes	3.7	(1.0, 14.8)	0.05	2.4	(0.8, 7.0)	0.12
Adherence ^c						
< 94%	Ref			Ref		
94%	0.7	(0.2, 2.2)	0.59	0.4	(0.2, 1.2)	0.13

^aVersus stable early response.

^bAnalyses performed using exact logistic regression. The exact p-value is determined using the Score statistic.

^cPercentage of pills (protocol dose) presumed taken based on returned pills.

Table 3

Factors associated with late versus stable early response in citalopram patients

Baseline variable	Late CGIC response ^a		
	OR	95% CI	Exact p-value ^b
Age			
< 80 yrs	Ref		
80 yrs	5.4	(1.0, 41.5)	0.06
Gender			
Male	Ref		
Female	1.6	(0.3, 8.6)	0.72
Race			
Nonwhite	Ref		
White	1.2	(0.2, 7.8)	1.00
MMSE score			
< 13	Ref		
13	1.4	(0.3, 7.8)	0.89
CMAI score			
< 25	Ref		
25	1.4	(0.3, 7.8)	0.89
NBRS-A score			
< 10	Ref		
10	0.5	(0.1, 2.9)	0.60
Duration of AD			
< 4 yrs	Ref		
4 yrs	1.4	(0.3, 7.8)	0.89
Cholinesterase inhibitor use			
No	Ref		
Yes	1.4	(0.3, 7.8)	0.89
Memantine use			
No	Ref		
Yes	3.3	(0.6, 19.6)	0.19
Adherence ^c			
< 94%	Ref		
94%	0.5	(0.1, 2.6)	0.56

^aVersus stable early response.^bAnalyses performed using exact logistic regression. The exact p-value is determined using the Score statistic.^cPercentage of pills (protocol dose) presumed taken based on returned pills.