# Sedation mediates part of Citalopram's effect on agitation in Alzheimer's disease

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## ABSTRACT

Background: We found a benefit of citalopram for agitation in the Citalopram for Agitation in Alzheimer's Disease study (CitAD), and wondered if this was mediated by a sedative effect. CitAD was a randomized, placebo-controlled, double-blind, parallel group trial conducted at 8 academic centers in the United States and Canada from August 2009 to January 2013. One hundred sixty-two participants with probable Alzheimer's disease (AD) and clinically significant agitation were analyzed in this study. Participants received a psychosocial intervention and were randomized to receive either citalopram or placebo (approximately half assigned to each group). Participants were rated on the Neurobehavioral Rating Scale Agitation subscale and measures of sedation (i.e., fatigue and somnolence).
Methods: Using the MacArthur Foundation procedures for documenting a mediator effect, we performed a secondary analysis examining whether sedation mediates the effect of treatment on agitation outcome.
Results: We found a statistically significant mediating effect of sedation on agitation outcomes, but the magnitude of the effect was small, only explaining 11% of the variance in agitation, with a significant, but modest effect size of 0.16 (95% CI: 0.08 to 0.22).
Conclusions: The benefit of citalopram was partly due to sedation but largely due to other mechanisms of action.

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## 1. Introduction

The purpose of this work is to determine if the sedative effects of citalopram mediate changes in agitation in patients with

Alzheimer's disease. A mediator of change is "… an intervening variable that may account (statistically) for the relationship between the independent and dependent variable (Kazdin, 2007)." The current work performs a mediator analysis using data of change over time on measures from the Citalopram for Agitation in Alzheimer's Disease study (CitAD) (Porsteinsson et al., 2014). CitAD was a multicenter double-blind, randomized clinical trial assessing the different impact of a placebo and citalopram on agitation in individuals with probable Alzheimer's disease (AD) and significant agitation. The CitAD study demonstrated a significant effect of citalopram in reducing agitation, as measured by the Neurobehavioral Rating Scale Agitation subscale (NBRS-A (Levin et al., 1987)). Citalopram has known sedating effects (Jacobson, 2014). Although review of the literature did not reveal any similar formal mediator analyses on citalopram or related medications, comments have been made for many years that the antidepressants, antipsychotics, and anticonvulsants all have sedative effects, and that this may account for the benefit of such medications on agitation in dementia (Jacobson, 2014; Kraemer et al., 2008; McKhann et al., 1984; Drye et al., 2012). In the parent study, a modest decrease in the Mini Mental State Examination (Folstein et al., 1975) was observed that might have resulted from the sedating effects of citalopram. Because CitAD included measures of sedation (fatigue and somnolence), we were able to perform a mediator analysis on change in agitation to determine if the effect of citalopram on agitation could be explained by its effects on sedation.

## 2. Methods

### 2.1. Study procedures

De-identified data from the CitAD study were used in these analyses. The study protocol was approved by the Institutional Review Board or research ethics board at each clinical or coordinating center. All participants and informants provided written informed consent prior to participation in the study.

Inclusion criteria were Probable AD as identified using NINCDS-ADRDA (McKhann et al., 1984) criteria and required participants to have a MMSE score of 5–28, as well as clinically significant agitation. The primary measure of agitation was the NBRS-A scale. Participants were excluded if they had a major depression or psychosis requiring antipsychotic treatment. A patient caregiver was required to supervise medication use and participate in assessments. Medications for the treatment of Alzheimer disease (such as cholinesterase inhibitors) at stable doses within the month preceding randomization were permitted. Withdrawal of psychiatric medications other than predefined rescue medications was required. Adequate previous treatment or contraindication to citalopram was exclusionary. Prolonged QT interval on an electrocardiogram was added later as an exclusion.

The CitAD study was a multicenter, randomized, placebo-controlled, double-blind, two-armed, parallel group clinical trial. Participants received either citalopram or placebo capsules. Target citalopram dose was 30 mg/day, titrated from a starting dose of 10 mg with dose changes based on clinical response and tolerability.

Measures of sedation were obtained by multiple ratings of symptoms and adverse effects at the pre-treatment baseline and after every three weeks of treatment, on a "Symptom Checklist". The ratings of fatigue and somnolence were on a four-point scale (1 = None; 2 = Mild; 3 = Moderate; 4 = Severe). Further information regarding the CitAD study design, methods and attrition are documented in a previous publication (Drye et al., 2012).

### 2.2. Statistics

The current analysis follows the MacArthur Foundation procedures for documenting a mediator effect on agitation (Kraemer et al., 2008). In summary, these procedures include three basic requirements:

1. Temporal precedence, i.e., change in the mediator (M), sedation, occurs prior to, or at the same time as change in the outcome, agitation (Baseline to Week 3 for sedation versus Baseline to Week 9 for agitation).
2. Correlation, i.e. there is a significant correlation between treatment choice (T) and change in the mediator (M) variable.
3. To show mediation, a regression analysis with change in agitation as the dependent measure is required. Independent variables include T, M, and their interaction. In other words, if either M or the T by M interaction (or their combination) is statistically significant, mediation has been demonstrated.

We constructed a composite sedation measure centered at the mean score for all participants. Difference scores (end of week 3 minus baseline) were computed for the somnolence and fatigue measures. These 2 items were included in a principal components analysis for 162 subjects (regardless of treatment assignment) that generated a single sedation factor. The analysis was performed with SAS 9.4 software (Cary, NC) using PROC FACTOR (with the method = prin option). Somnolence and fatigue were significantly correlated with one another (Spearman r = 0.41; p < 0.0001).

## 3. Results

Of the 186 subjects enrolled in the CitAD study, 162 had complete data for NBRS-A at Baseline and Week 9, and somnolence and fatigue at Baseline and Week 3, and therefore were analyzed for this study. Our analyses followed the three-step MacArthur Foundation procedures for showing a mediator effect outlined in the Methods above:

1. To meet the temporal precedence requirement, the change in the mediator (Baseline to Week 3) preceded the change in the outcome (Baseline to Week 9).
2. Fig. 1 presents plots of the mean agitation, fatigue and somnolence across time for the Placebo and Citalopram groups. Examination of the changes in the sedation indicators in this Figure suggested a substantial increase in sedation at Week 3 in the citalopram group that was attenuated by Weeks 6 and 9. We therefore chose these measures as our indicators of change in sedation from Baseline to Week 3. There was a significant correlation between choice of treatment (Citalopram) and increase in sedation (Spearman r = 0.20; p < 0.05).
3. Mediation was supported by a regression analysis with change in agitation as the dependent measure. Independent variables included treatment choice (T or citalopram versus placebo), M (change in sedation from baseline to week 3), and the M by T interaction. Treatment was coded as +1/2 (Citalopram) and −1/2 (Placebo). There was a significant change in NBRS-A scores by treatment ($\beta = -1.55$; SE: 0.51; t value: −3.01; p < 0.005; $R^2 = 0.11$). Though the M by T interaction was not significant ($\beta = -0.32$; SE: 0.45; t value: −0.73; p = 0.47), the significant main effect of M is sufficient to demonstrate a mediation effect. These relationships are also presented in Fig. 2. In this figure both Citalopram and Placebo groups show that large increases in sedation are associated with larger improvements is agitation. The lines are nearly parallel as the M by T interaction is small. The differences between the two treatment groups show that, as