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Sedation Mediates Part of Citalopram's Effect on Agitation in Alzheimer's Disease

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Contributions

Jeffery Newell and **Jerome A. Yesavage** formulated the research question, wrote the first draft of the manuscript and interpreted the findings.

Helena C. Kraemer was responsible for the analysis methodology and interpretation of findings.

Leah Friedman, **Joy L. Taylor**, **Michelle Madore**, **Steven Z. Chao**, and **Paul B. Rosenberg** contributed to critical revisions of the manuscript.

Cynthia A. Munro, **D.P. Devanand**, **Lea T. Drye**, **Jacobo E. Mintzer**, **Bruce G. Pollock**, **Anton P. Porsteinsson**, **Lon S. Schneider**, **David M. Shade**, **Daniel Weintraub**, and **Constantine G. Lyketsos** were responsible for the supervision of the study and data collection at given site.

Art Noda conducted the data analysis, contributed to the interpretation of results and critical revisions of the manuscript.

All authors approved the final version of the manuscript.

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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.

Graphical Abstract

Keywords

agitation; sedation; citalopram

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 NBRSA 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 $r = 0.41$; $p < .0001$).

3. Results

Of the 186 subjects enrolled in the CitAD study, 162 had complete data for NBRSA 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. Figure 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 NBRSA 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 Figure 2. In this figure both Citalopram and Placebo groups show that large increases in sedation are associated with larger improvements in agitation. The lines are nearly parallel as the M by T interaction is small. The differences between the two treatment groups show that, as a whole, the Citalopram participants are more sedated than their Placebo counterparts.

4. Discussion

We found evidence that the effects of citalopram on agitation were mediated in part by sedating effects of the medication as evidenced by increased measures of fatigue and somnolence at Week 3 of the trial. A weakness of this analysis is that the measure of sedation was relatively unsophisticated. Although review of the literature did not reveal any similar formal mediator analyses, it has long been observed that psychotropic medication with sedative effects may account for some of the benefit of such medications on agitation

(Jacobson 2014; Maher et al. 2011; Brodaty et al. 2003; Seitz et al. 2013; Soto et al. 2014; Gallagher & Herrmann 2014; Tariot et al. 2011). The current study appears to be the first that has statistically demonstrated that this relationship exists between antidepressants and agitation in patients with dementia. One would expect that similar analyses could be performed on other datasets involving clinical trials of other types of psychotropic medications for agitation in dementia patients. Despite these significant findings we note that sedation explains only 11% of the variance ($R^2=0.11$) in change in agitation in these patients, with a significant, but modest effect size of 0.16 (95% CI: 0.08 to 0.22) (Kraemer 2014). Thus other factors are required to explain the majority of effects of citalopram on agitation in patients with Alzheimer's disease.

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Author Declaration

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

Mr. Newell, Dr. Yesavage, Dr. Taylor, Dr. Kraemer, Dr. Friedman, Dr. Madore, Dr. Chao, and Mr. Noda: NONE.

Dr. Munro reports receipt of grant funding from the NIH, NIA, and NIMH; payment for expert testimony from various law firms, the Office of the Federal Public Defender, and the US Attorney's Office; and payment for lectures for Episcopal Ministries.

Dr. Rosenberg reports receipt of a grant to his institution from NIA; grants from Janssen, Eli Lilly, Pfizer, and Functional Neuromodulation; consultancy for Janssen, GLG, Vindico, Abbvie, Lundbeck, and Elan; development of educational presentations for Eli Lilly; and receipt of a fee for travel accommodations for meetings from Eli Lilly.

Dr. Devanand reports grant funding from the National Institute of Aging and the Department of Defense, and has served on the scientific advisory boards of AbbVie and Lundbeck and Intracellular Therapeutics.

Dr. Drye reports receipt of a grant to her institution from NIH, NIA, and NIMH.

Dr. Mintzer is a grant recipient for Takeda, Pfizer, Merck, Genentech, Eli Lilly, Transition Therapeutics, ADCS, Roche, Avanir, and Grifols. These companies are developing different drugs for Alzheimer's disease. Dr. Mintzer is also a majority owner of BioPharma Connex, a company that currently has active contracts with Avanir, Roche, and Eli Lilly for either facilitating recruitment or neuroimaging operations facilitation in Latin America. Finally, Dr. Mintzer is the VP of Medical Affairs at NeuroQuest, a company developing a biomarker for Alzheimer's disease.

Dr. Pollock reports receipt of grants to his institution from NIH; he was previously (until 2008 and 2010, respectively) on the advisory board of Lundbeck Canada and the faculty of the Lundbeck International Neuroscience Foundation.

Dr. Porsteinsson reports receipt of a grant to his institution from AstraZeneca, Avanir, Baxter, Biogen, BMS, Eisai, Elan, EnVivo, Genentech/Roche, Janssen Alzheimer Initiative,

Medivation, Merck, Pfizer, Toyama, Transition Therapeutics, the National Institutes of Health (NIH), the National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), and the Department of Defense; paid consultancy for Elan, Janssen Alzheimer Initiative, Lundbeck, Pfizer, and TransTech Pharma; membership on data safety and monitoring boards for Quintiles, Functional Neuromodulation, and the New York State Psychiatric Institute; participation on a speaker's bureau for Forest; and development of educational presentations for CME Inc and PVI.

Dr. Schneider reports, from 3 years prior to and during the course of this study, receipt of grants and clinical trials support from NIH, Abbott, AstraZeneca, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, Novartis, Pfizer, Roche; paid consultancy, including data monitoring committees, adjudication committees, for Abbott, Abbvie, AC Immune, AstraZeneca, Baxter, Bristol Myers Squibb, Elan, Eli Lilly, Forest Laboratories, Forum, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, Merz, Novartis, Orion, Otsuka, Pfizer, Roche, Servier, Takeda, Toyama/FujiFilm, Zinfandel.

Mr. Shade reports receipt of a grant to his institution and support for travel to meetings for NIA and NIMH.

Dr. Weintraub has received research funding or support from Michael J. Fox Foundation for Parkinson's Research, National Institutes of Health, Novartis Pharmaceuticals, Department of Veterans Affairs, Avid Radiopharmaceuticals, and Alzheimer's Disease Cooperative Study; honoraria from Biotie, Teva Pharmaceuticals, Otsuka, UCB, Clintrex LLC, and the CHDI Foundation; license fee payments from the University of Pennsylvania for the QUIP and QUIP-RS; royalties from Wolters Kluweland; and fees for legal consultation for lawsuit related to antipsychotic prescribing in a patient with Parkinson's disease.

Dr. Lyketsos reports receipt of a grant to his institution from NIMH, NIA, Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, Glaxo-Smith-Kline, Eisai, Pfizer, Astra-Zeneca, Lilly, Ortho-McNeil, Bristol-Myers, Novartis, National Football League, Elan, Functional Neuromodulation, Transition Therapeutics. Payment as consultant or advisor Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, Avanir, Zinfandel, BMS, Abvie, Janssen, Orion, Otsuka, Servier, Astellas; and royalties from Johns Hopkins Press and Oxford University Press.

Highlights

- Clinical trial found benefit of citalopram for agitation in Alzheimer's disease
- We examined if effect of treatment drug on agitation was mediated by its sedating effect
- We found that benefit of citalopram was mediated by a significant but small sedative effect
- Other unknown factors explain majority of effects of Citalopram on agitation.

Figure 1. Mean Change in NRS-A (top), Fatigue (middle), and Somnolence (bottom) across Time for Placebo and Citalopram Groups, with Standard Error bars. Dashed line for Citalopram (n=82), and solid line for Placebo (n=80).

Figure 2.

Effect of Change in Sedation versus Change in Agitation Across Placebo and Citalopram Groups.

Both Citalopram and Placebo groups show that large increases in sedation are associated with larger improvements in agitation as reflected by the two nearly parallel lines. The differences between the two treatment groups are that as a whole the Citalopram patients are more sedated than the Placebo patients as reflected by the Star's position offset to the right. The vertical line with arrows represents the raw effect and also includes the mediation effect. The bold portion of line to the arrows represents the effect of treatment had there been no mediating effect of sedation change. Thus the dotted portion of the line represents the mediating effect of sedation change.