HHS Public Access

Author manuscript

Int Psychogeriatr. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Int Psychogeriatr. 2015 December ; 27(12): 2059–2067. doi:10.1017/S1041610215001106.

Change in agitation in Alzheimer's disease in the placebo arm of a 9-week controlled trial

Paul B. Rosenberg, M.D.[1] **[Associate Professor of Psychiatry and Behavioral Sciences]**, **Lea T. Drye, PhD**[2] **[Assistant Scientist]**, **Anton P. Porsteinsson, MD**[3] **[William B. and Sheila Konar Professor of Psychiatry, Director, Alzheimer's Disease Care, Research and Education Program (AD-CARE)]**, **Bruce G. Pollock, MD, PhD**[4] **[Vice President Research and Director, Campbell Family Mental Health Research Institute, Professor and Director of the Division of Geriatric Psychiatry, Faculty of Medicine]**, **D.P. Devanand, M.D**[5] **[Professor of Psychiatry and Neurology, Director, Division of Geriatric Psychiatry]**, **Constantine Frangakis, PhD**[6] **[Professor of Department of Biostatistics]**, **Zahinoor Ismail, MD**[7] **[Clinical Associate Professor of Psychiatry and Neurology, Assistant Professor of Psychiatry]**, **Christopher Marano, MD**[1] **[Assistant Professor of Psychiatry and Behavioral Sciences]**, **Curtis L. Meinert, PhD**[6] **[Professor of Epidemiology and Biostatistics]**, **Jacobo E. Mintzer, MD, MBA**[8] **[Executive Director, Professor, Staff Physician]**, **Cynthia A. Munro, PhD**[9] **[Associate Professor]**, **Gregory Pelton, MD**[5] **[Assistant Professor]**, **Peter V. Rabins, MD**[1] **[Professor of Psychiatry and Behavioral Sciences]**, **Lon S. Schneider, MD**[10] **[Professor of Psychiatry, Neurology, and Gerontology]**, **David M. Shade, JD**[2] **[Associate Scientist]**, **Daniel Weintraub, MD**[11] **[Associate Professor]**, **Jeffery Newell**[12] **[Ph.D. Student]**, **Jerome Yesavage, MD**[13] **[Director Aging Clinical Research Center, Associate Chief of Staff for Mental Health]**, **Constantine G. Lyketsos, M.D., M.H.S.**[1] **[Elizabeth Plank Althouse Professor, Interim Director, Division of Geriatric Psychiatry and Neuropsychiatry, Chair]**, and **for the CitAD Research Group**

Paul B. Rosenberg: prosenb9@jhmi.edu

[1]Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins School of Medicine, Johns Hopkins Bay view Medical Center, 5300 Alpha Commons Dr. #429, Baltimore, MD 21224, Phone: (410) 550 9883, Fax: (410) 550 1407

[2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 911 S. Ann St, Baltimore, MD 21231

[3]University of Rochester School of Medicine and Dentistry, 435 East Henrietta Road, Rochester, N.Y. 14620

[4]Campbell Institute, CAMH, University of Toronto, Toronto, ON, Canada, University of Toronto, Centre for Addiction and Mental Health, 33 Russell Street, Toronto, ON M5S 2S1

[5]College of Physicians and Surgeons, Columbia University, 1051 Riverside Drive, Unit 126, New York, NY 10032

Correspondence to: Paul B. Rosenberg, prosenb9@jhmi.edu.

Conflict of Interest: None.

Clinicaltrials.gov identifier: NCT00898807

[6]Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., E3642, Baltimore, MD, 21205-2179

[7]Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada, University of Toronto, Toronto, ON, Canada, 1403 29 Street NW, Calgary Canada, T2N 2T9

[1]Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins University School of Medicine, Johns Hopkins Bayview Medical Center, 5300 Alpha Commons Drive, 4th floor, Baltimore, MD 21224

[6]Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., W5010, Baltimore, MD, 21205-2179

[8]Clinical Biotechnology Research Institute, Roper St. Francis Healthcare, Charleston SC, Department of Health Studies, Medical University of South Carolina, Charleston SC, Ralph H. Johnson VA Medical Center, Charleston SC, 316 Calhoun Street, 5th Floor- CBRI, Charleston, SC 29401

[9]Department of Psychiatry and Behavioral Sciences, Department of Neurology, Johns Hopkins Bayview and Johns Hopkins School of Medicine, 600 N. Wolfe St., Meyer 218, Baltimore, MD 21287-7218

[12]Clinical Science, University of Southern California, Culture and Mental Health Lab, 3620 McClintock Ave., Los Angeles, CA 90089-1011

[5]Clinical Psychiatry and Neurology, Division of Geriatric Psychiatry, New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, 1051 Riverside Drive, Unit 126, New York, New York 10032-2695

[1]Johns Hopkins School of Medicine, Johns Hopkins Hospital, Meyer 279, 600 North Wolfe Street, Baltimore, MD 21287

[10]Keck School of Medicine, University of Southern California, 1540 Alcazar St, CHP-216, Los Angeles, CA

[2]Departments of Medicine (Pulmonary) and Epidemiology (Center for Clinical Trials), Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St Rm 5025-D, Baltimore, MD 21205

[11]Psychiatry and Neurology, Perelman School of Medicine at the University of Pennsylvania, Parkinson's Disease Research, Education and Clinical Center (PADRECC), Mental Illness Research, Education and Clinical Center (MIRECC), Philadelphia Veterans Affairs Medical Center, 3615 Chestnut Street, #330, Philadelphia, PA 19104-2676

[13]Director Mental Illness Research Education and Clinical Center, VA Palo Alto Health Care System, Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Mail Code 151-Y, 3801 Miranda Avenue, Palo Alto, California 94304

[1]Johns Hopkins School of Medicine, Department of Psychiatry, Johns Hopkins Bayview Medical Center, 5300 Alpha Commons Dr. #429, Baltimore, MD 21224

Abstract

Background—Placebo responses raise significant challenges for design of clinical trials. We report changes in agitation outcomes in the placebo arm of a recent trial of citalopram for agitation in Alzheimer's disease (AD).

Methods—In the Citalopram for Agitation in Alzheimer's Disease (Cit AD) study, all participants and caregivers received a psychosocial intervention and 92 were assigned to placebo for 9 weeks. Outcomes included Neurobehavioral Rating Scale agitation subscale (NBRS-A), modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (CGIC), Cohen-Mansfield Agitation Inventory (CMAI), the Neuropsychiatric Inventory (NPI) Agitation/Aggression domain (NPI A/A) and Total (NPI-Total) and ADLs. Continuous outcomes were analyzed with mixed-effects modeling and dichotomous outcomes with logistic regression.

Results—Agitation outcomes improved over 9 weeks: NBRS-A mean (SD) decreased from 7.8 (3.0) at baseline to 5.4 (3.2), CMAI from 28.7 (6.7) to 26.7 (7.4), NPI A/A from 8.0 (2.4) to 4.9 (3.8), and NPI-Total from 37.3 (17.7) to 28.4 (22.1). The proportion of CGI-C agitation responders ranged from 21 to 29% and was significantly different from zero. MMSE improved from 14.4 (6.9) to 15.7 (7.2) and ADLs similarly improved. Most of the improvement was observed by 3 weeks and was sustained through 9 weeks. The major predictor of improvement in each agitation measure was a higher baseline score in that measure.

Conclusions—We observed significant placebo response which may be due to regression to the mean, response to a psychosocial intervention, natural course of symptoms, or nonspecific benefits of participation in a trial.

Keywords

Alzheimer's disease; Agitation; Randomized Clinical Trial; Neuropsychiatric symptoms

Introduction

Neuropsychiatric symptoms (NPS) are highly prevalent in Alzheimer's disease (AD) (Steinberg et al., 2008; Gonfrier et al., 2012). Agitation and aggression are among the most common and distressing NPS in AD(Lyketsos et al., 2011; 2002; 2000). Current recommendations for management are to start with non-pharmacologic strategies (Gauthier et al., 2010; APA Work Group on Alzheimer's Disease and other Dementias et al., 2007; Kales et al., 2014), but many patients do not respond sufficiently to these strategies. Clinicians frequently prescribe psychotropic medications off-label as there are no medications with FDA-approved indications for agitation in AD. Antipsychotics are widely used and there is some evidence for efficacy (Pollock et al, 2002; Pollock et al, 2007), but there are concerns about their side effect profiles, particularly their increased mortality risk (Kales et al., 2007; Schneider, Dagerman and Insel, 2005; Kales et al., 2012). We recently reported improved agitation outcomes with use of the selective serotonin reuptake inhibitor citalopram when compared with placebo in the Citalopram for Agitation in Alzheimer's Disease trial (CitAD)(Porsteinsson et al., 2014)

Placebo responses are common in neuropsychiatric trials and it is essential to understand factors affecting placebo in order to detect specific drug effects. Several recent trials for agitation in AD report clinical improvement on placebo (Trzepacz et al., 2013; Herrmann et

al., 2013; Fox et al., 2012; Sommer et al., 2009) consistent with a meta-analysis of antipsychotic trials (Schneider et al., 2006), but there are few data on predictors of placebo response. To compare agitation in AD with another diagnosis, placebo responses in trials of major depressive episode are substantial and in the range of 40-50% (Khan et al., 2012). Understanding the magnitude and inherent variance of placebo response is crucial to planning future intervention trials, particularly for sample size estimation and understanding clinical covariates of response.

To this end we examined outcomes in the placebo arm of CitAD, hypothesizing that there we would observe decreased agitation and improved functional outcomes over the 9-week observation period. All CitAD participants regardless of treatment assignment received a standardized psychosocial intervention adapted from prior trials for NPS (Martin et al., 2006; Drye et al., 2012) to provide standard of care for non-pharmacologic interventions. Thus, any changes in outcomes observed in the placebo arm might (or might not) be due to the effects of this psychosocial intervention.

Methods

The CitAD study design and results have been published (Drye et al., 2012; (Porsteinsson et al., 2014). Briefly, CitAD was a randomized, double-blind, placebo-controlled trial comparing 9 weeks of citalopram (target dose 30 mg) to placebo in participants with AD and agitation. CitAD is listed on clinicaltrials.gov with the identifier: NCT00898807. Participants were eligible for inclusion if they had a diagnosis of AD (McKhann et al., 1984), Mini-Mental State Exam (MMSE) 5-26(M. F. Folstein, S. E. Folstein and McHugh, 1975), with Neuropsychiatric Inventory (NPI)Agitation/Aggression rated as occurring 1) very frequently, or 2) frequently with moderate or marked severity (Cummings et al., 1994). Primary outcome measures were 9-week change in the Neurobehavioral Rating Scale agitation subscale (NBRS-A) (Levin et al., 1987) and the ratings at 9 weeks on the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC) (Schneider et al., 1997). Secondary outcomes included Cohen-Mansfield Agitation Inventory (14-item short form)(CMAI) (Cohen-Mansfield, 1996), NPI-Total and NPI-Agitation/Aggression subscale, Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)(Galasko et al., 1997), and MMSE. Participants assigned to placebo received pills containing inert material with identical appearance to active drug, with a target dose of three pills daily (equivalent to target dose of citalopram 30 mg daily). All participants and caregivers received a standardized psychosocial intervention as previously described (Drye et al., 2012). Outcomes were assessed at baseline and after 3, 6, and 9 weeks of study treatment. If agitation could not be adequately controlled with psychosocial intervention (see below) up to .5 mg daily of lorazepam and/or 50 mg of trazodone nightly were allowed as rescue medications. Antipsychotics and other antidepressants were not allowed in the trial, but due to protocol deviations 2 participants received antipsychotics and one received a trazodone dose higher than 50 mg nightly.

Psychosocial intervention

We used a psychosocial intervention in this trial to ensure a high standard of dementia care and to reduce the variability of dementia care between sites. Study caregivers and patients regardless of treatment assignment received the CitAD standardized psychosocial intervention, which consisted of three components: a 20 – 30 minute counseling session at each of the scheduled study visits, provision of educational materials, and 24-hour availability for crisis management assistance.

The counseling sessions were conducted by a trained study clinician and include design of a supportive care plan during the randomization visit. Counseling sessions included development and review of support care plans, emotional support, counseling regarding caregiving skills and problem-solving, as well as referrals and educational materials where appropriate. This intervention has been used for a similar purpose in two prior multi-center trials, one for depression in AD (Rosenberg et al., 2010) and the other for apathy in AD(Rosenberg et al., 2013). The only outcome data on the intervention is indirect, as it has not been formally tested vs. a comparator intervention in any trial.

Data Analysis

These analyses are exclusive to participants randomized to placebo. For continuous outcomes, mean weekly slope was estimated using mixed effects regression, with a random intercept for participant. All available data were included in the model; likelihood based models do not require complete data and are one of the preferred analysis methods for longitudinal data with missing values that are assumed to be missing at random (National Research Council, 2010). Approximately 10% of the enrolled participants did not complete the study. Negative slope values indicate improvement on the agitation or NPI out comes, but worsening on the MMSE and ADCS-ADL. The p-values tested the hypothesis that the mean slope is zero (i.e., no change over time). For CGIC, the p-values were for z-tests that the proportion of responders at week 9 was zero. Potential covariates included baseline clinical covariates and demographics, NBRS, CGIC, CMAI, NPI, ADLs, and psychosis (presence of delusions or hallucinations). Continuous risk factors were categorized into tertiles at baseline. For continuous outcomes, the effect of baseline covariateson rate of change for the outcome variable was assessed by adding an interaction of time X risk factor into the mixed model and estimating the F-statistic, comparing the model with the interaction term (time by risk factor) to a model without the interaction term. For the CGIC, response was defined as moderate or marked improvement, and potential predictors of response were tested using logistic regression. The adjusted mixed and logistic models controlled for gender, race, years of education, and the baseline scale score (not applicable for CGIC) based on prior reports that demographic variables are associated with NPI scores in observational studies (Steinberg et al., 2006). No other adjustment variables were included because of the small sample size. We chose to adjust for the baseline scale score because it was the risk factor that was consistently associated with response across the unadjusted models for the different outcome variables. Unadjusted models are presented in supplementary material. Sensitivity analyses for the CGIC outcome were performed using multiple imputation of missing outcome values. In order to compare the magnitude of changes on placebo in CitAD to comparable trials, we calculated the standardized mean

change for selected outcomes as: (post-treatment value – pre-treatment value)/(pre-treatment standard deviation)(Morris, 2000).

Results

92 CitAD participants were assigned to placebo and had evaluable data over 9 weeks. Baseline clinical characteristics have been previously published {Porsteinsson: 2014 ks} mean age (SD) was 79 (8) years, 41% were female, just under half had education beyond high school, mean (SD) MMSE score was 14.4 (6.9), and mean (SD) dementia duration was 5 (4) years.

Table 1 shows changes in agitation and functional outcomes over 9 weeks of study treatment. There were significant improvements in agitation outcomes: NBRS-A decreased 31%, NPI-Total decreased 24%, and NPI-Agitation decreased 39%, and CMAI 7%. MMSE increased (indicating improvement) and ADCS-ADL scores decreased (indicating worsening) as well. mADCS-CGIC response varied from 21% to 29% and was significantly different from zero (indicating improvement) at all time points. The largest decline in NBRS-agitation scores was between baseline and week 3 (change of -2.0 points, 95% CI: -2.7, -1.4, $p < 0.0001$). There was no difference in NBRS-agitation scores between weeks 3 and 6 (change of 0.1 points, 95% CI: -0.6, 0.8, $p = 0.71$) or between weeks 6 and 9 (change of -0.4 points, 95% CI: -1.1, 0.3, $p = 0.27$).

The effect of baseline clinical characteristics on agitation outcomes after adjustment for baseline covariates are presented in Supplementary Table 1; the results were similar in unadjusted models (data not shown). NBRS-A decreased more in participants who were female, non-white, non-Hispanic, and in the highest tertile of baseline NBRS-A. CMAI decreased more in participants who were female, in the highest tertile of baseline CMAI, and with baseline delusions. CGIC response was more likely in participants in the highest tertile of baseline NBRS-A. Sensitivity analyses of the CGIC outcome using multiple imputation led to the same conclusions (data not shown). NPI-Agitation/Aggression decreased more in participants in the highest tertile of baseline NPI-Agitation/Aggression.

Supplementary Table 2 shows the effect of baseline clinical characteristics on other outcomes after adjustment for covariates. NPI-Total decreased more in participants who were in the highest baseline tertile of NPI-Total and lowest baseline tertile of MMSE. There were no baseline clinical factors affecting MMSE outcome. ADCS-ADL declined more in participants who were in the middle tertile of baseline ADCS-ADL.

Discussion

We observed decreased severity of three agitation measures and improvement in MMSE over 9 weeks placebo group of the CitAD trial. The effect was evident at 3 weeks and remained stable at weeks 6 and 9. For all agitation measures the greatest improvement was in participants most symptomatic at baseline. This observation combined with the above, that the improvement leveled by week 3, suggests that the improvement was largely due regression to the mean. This is supported by the finding that improvement in each agitation measure was not predicted by baseline severity in other measures, suggesting that these

measures target different characteristics of agitation. Alternatively, these improvements could be due to benefits of the psychosocial intervention, nonspecific benefit from participating in a trial, or represent the natural clinical course of these symptoms. The relatively rapid response argues against these explanations, however, as one would expect the benefit of a psychosocial intervention to increase with repetition and therefore over the course of the trial. The improvement in MMSE may have been due to practice effects or to improvement in ability to focus as agitation decreased, since a disease-modifying effect on AD itself is unlikely in a short 9-week timeframe. Regardless of mechanism, these observations of short-term improvement in agitation may help inform future study of interventions in this field.

We observed a decline in activities of daily living (ADLs) on placebo. The magnitude appears relatively small, with the mean ADL score declining from 41.1 to 39.6. While we cannot ascribe causality, this may have been due to changes in rater bias (whether research staff or caregivers), with raters becoming less optimistic over repeated ratings. There is evidence for bias in caregiver ratings of depression in AD decreasing over the course of a 12-week trial (Rosenberg, Mielke and Lyketsos, 2005), suggesting that caregivers become more objective in mood ratings with repetition or over time; we may have observed a similar effect on ADL ratings.

The reduction in agitation varied by measure, and was considerably larger for NBRS-A, NPI-Agitation/Aggression, and NPI-Total than CMAI. Over the 9 weeks of observation of CitAD participants on placebo we observed standardized mean changes in NBRS-A of 0.80, NPI-Agitation/Aggression of 1.38, NPI-Total of 0.73, and CMAI of 0.30. These changes are comparable to prior trials: we calculate standardized mean changes of 0.57 for CMAI and 0.43 for NPI-Total in the placebo arm of a 12-week controlled trial of memantine in nursing home residents by Fox et al. (Fox et al., 2012), 0.36 for NPI-NH (total)in the placebo arm of a 24-week trial controlled trial of memantine in outpatients by Herrmann et al.(Herrmann et al., 2013), 1.40 for NPI-NH (total)in the placebo arm of an 8-week trial of oxcarbazepine by Sommer et al. (Sommer et al., 2009), and 0.73 for the NPI-4-A/A factor in a 12 week trial of mibamptor by Trzepacz et al. (Trzepacz et al., 2013). Overall CMAI appears to have a smaller placebo response than the other agitation measures which is a desirable attribute. The differences between the standardized mean changes between trials appear to be driven more by differences in variance rather than mean change of measures. Another reason for this observation may be the relatively low baseline CMAI scores, leaving less range for improvement than the other measures. The standardized mean changes we observed are similar to results from prior trials, reinforcing the reliability of estimates of placebo response of agitation in AD with a relatively large dataset. These data can be used to inform sample size estimates for future trials in this field.

We report that the placebo response in several neuropsychiatric, cognitive, and functional measures was statistically significant. Given the substantial standardized mean changes noted above, we believe this is likely to be clinically significant. Additionally, we found that baseline agitation severity for each agitation measure predicted response of that measure alone, and that most of the response was present by week 3. Taken together, these observations suggest that future trials of interventions for agitation in AD will need to

account for this magnitude of response in estimates of sample size. Given the challenges of providing sufficient statistical power for hypothesis-testing, the design of future trials may need to involve innovative study designs such as sequential parallel comparison or other adaptive trial designs (Baer and Ivanova, 2013) that offer the possibility of improving statistical power. There is a need for further development and validation of agitation measures with the objective of reducing possible regression to the mean (Gitlin et al., 2014). The effect of non-pharmacologic interventions needs to be systematically studied (Gitlin, Kales and Lyketsos, 2012)

Among this study's strengths are its rigorous methods, use of a psychosocial intervention to enhance “usual care”, and most importantly observation of outcomes within a clinical trial setting which is most relevant to future trials. The most significant limitation is its inability to distinguish the effects of regression to the mean from improvements due to psychosocial intervention, the course of illness, or the nonspecific benefit or time effect of being enrolled in a trial, because there these are observational data of participants assigned to placebo. The psychosocial intervention has not been formally studied and it is possible that we are reporting on its effect rather than a pure “placebo” effect. Another limitation is the relatively short-term assessment of outcomes, although the 9-week duration of this trial is similar to comparable trials in the field. It is possible that with a longer observation period we might observe cycles of agitation in AD that would need to be better characterized to observe change.

These observations indicate that within an RCT context with masked treatment allocation, an environment with high expectations for improvement, agitation in AD improves significantly (both clinically and statistically) in the placebo group over 9 weeks of observation, typically by 3 weeks after baseline, likely due to regression toward the mean. Given the relatively good agreement between these and prior results, these estimates of placebo response can be used to inform the design of future trials of agitation in AD including novel trial designs (Baer and Ivanova, 2013).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: This work was supported by NIA and NIMH, R01AG031348 and in part by NIH P50, AG05142 (USC, LSS).

Role of the Sponsors: The NIA and NIMH had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

References

Rabins, PV.; Blacker, D.; Rovner, BW.; Rummans, T.; Schneider, LS.; Tariot, PN.; Blass, DM.; Steering Committee on Practice Guidelines. McIntyre, JS.; Charles, SC.; Anzia, DJ.; Cook, IA.; Finnerty, MT.; Johnson, BR.; Nininger, JE.; Schneidman, B.; Summergrad, P.; Woods, SM.; Berger, J.; Cross, CD.; Brandt, HA.; Margolis, PM.; Shemo, JPD.; Blinder, BJ.; Duncan, DL.; Barnovitz, MA.; Carino, AJ.; Freyberg, ZZ.; Gray, SH.; Tonnu, T.; Kunkle, R.; Albert, AB.; Craig,

TJ.; Regier, DA.; Fochtmann, LJ. APA Work Group on Alzheimer's Disease and other Dementias. The American journal of psychiatry. Second. 2007. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias; p. 5-56.

Baer L, Ivanova A. When should the sequential parallel comparison design be used in clinical trials? Clinical Investigation. 2013

Cohen-Mansfield J. Conceptualization of agitation: results based on the Cohen-Mansfield Agitation Inventory and the Agitation Behavior Mapping Instrument. International psychogeriatrics / IPA. 1996; 8(Suppl 3):309–15. discussion 351–4. [PubMed: 9154580]

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994; 44(12):2308–2314. [PubMed: 7991117]

Drye LT, Ismail Z, Porsteinsson AP, Rosenberg PB, Weintraub D, Marano C, Pelton G, Frangakis C, Rabins PV, Munro CA, Meinert CL, Devanand DP, Yesavage J, Mintzer JE, Schneider LS, Pollock BG, Lyketsos CG. CitAD Research Group. Citalopram for agitation in Alzheimer's disease: Design and methods. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2012; 8(2):121–130.10.1016/j.jalz.2011.01.007

Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research. 1975; 12(3):189–198. [PubMed: 1202204]

Fox C, Crugel M, Maidment I, Auestad BH, Coulton S, Treloar A, Ballard C, Boustani M, Katona C, Livingston G. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. PloS one. 2012; 7(5):e35185–e35185.10.1371/journal.pone.0035185 [PubMed: 22567095]

Galasko DD, Bennett DD, Sano MM, Ernesto CC, Thomas RR, Grundman MM, Ferris SS. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer disease and associated disorders. 1997; 11(Suppl 2):S33–S39. [PubMed: 9236950]

Gauthier S, Cummings J, Ballard C, Brodaty H, Grossberg G, Robert P, Lyketsos C. Management of behavioral problems in Alzheimer's disease. International psychogeriatrics / IPA. 2010; 22(3):346–372.10.1017/S1041610209991505 [PubMed: 20096151]

Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA : the journal of the American Medical Association. 2012; 308(19):2020–2029.10.1001/jama.2012.36918 [PubMed: 23168825]

Gitlin LN, Marx KA, Stanley IH, Hansen BR, Van Haitsma KS. Assessing neuropsychiatric symptoms in people with dementia: a systematic review of measures. International psychogeriatrics / IPA. 2014:1–44.10.1017/S1041610214001537

Gonfrier S, Andrieu S, Renaud D, Vellas B, Robert PH. Course of neuropsychiatric symptoms during a 4-year follow up in the REAL-FR cohort. The journal of nutrition, health & aging. 2012; 16(2): 134–137.

Herrmann N, Gauthier S, Boneva N, Lemming OM, Lemming OM. A randomized, double-blind, placebo-controlled trial of memantine in a behaviorally enriched sample of patients with moderate-to-severe Alzheimer's disease. International psychogeriatrics / IPA. 2013; 25(6):919–927.10.1017/S1041610213000239 [PubMed: 23472619]

Kales HC, Gitlin LN, Lyketsos CG, Lyketsos CG. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. Journal of the American Geriatrics Society. 2014; 62(4):762–769.10.1111/jgs.12730 [PubMed: 24635665]

Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, Cunningham F, Schneider LS, Blow FC. Risk of mortality among individual antipsychotics in patients with dementia. The American journal of psychiatry. 2012; 169(1):71–79.10.1176/appi.ajp.2011.11030347 [PubMed: 22193526]

Kales HC, Valenstein M, Kim HM, McCarthy JF, Ganoczy D, Cunningham F, Blow FC. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. The American journal of psychiatry. 2007; 164(10):1568–76. quiz 1623. 10.1176/appi.ajp.2007.06101710 [PubMed: 17898349]

Khan A, Faucett J, Lichtenberg P, Kirsch I, Brown WA. A systematic review of comparative efficacy of treatments and controls for depression. PloS one. 2012; 7(7):e41778.10.1371/journal.pone.0041778 [PubMed: 22860015]

Levin HS, High WM, Goethe KE, Sisson RA, Overall JE, Rhoades HM, Eisenberg HM, Kalisky Z, Gary HE. The neurobehavioural rating scale: assessment of the behavioural sequelae of head injury by the clinician. Journal of neurology, neurosurgery, and psychiatry. 1987; 50(2):183–193.

Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, Cedarbaum J, Brashear R, Miller DS. Neuropsychiatric symptoms in Alzheimer's disease. 2011:532–539.10.1016/j.jalz.2011.05.2410

Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA : the journal of the American Medical Association. 2002; 288(12):1475–1483. [PubMed: 12243634]

Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. The American journal of psychiatry. 2000; 157(5):708–714. [PubMed: 10784462]

Martin BK, Frangakis CE, Rosenberg PB, Mintzer JE, Katz IR, Porsteinsson AP, Schneider LS, Rabins PV, Munro CA, Meinert CL, Niederehe G, Lyketsos CG. Design of Depression in Alzheimer's Disease Study-2. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2006; 14(11):920–930.10.1097/01.JGP.0000240977.71305.ee [PubMed: 17068314]

McKhann, G.; Drachman, D.; Folstein, M.; Katzman, R.; Price, D.; Stadlan, EM. Neurology. 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease; p. 939-944.

Morris SB. Distribution of the standardized mean change effect size for meta-analysis on repeated measures. The British journal of mathematical and statistical psychology. 2000; 53(Pt 1):17–29. [PubMed: 10895520]

Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG. Effect of Citalopram on Agitation in Alzheimer Disease. JAMA : the journal of the American Medical Association. 2014; 311(7):682.10.1001/jama.2014.93 [PubMed: 24549548]

Rosenberg PB, Drye LT, Martin BK, Frangakis C, Mintzer JE, Weintraub D, Porsteinsson AP, Schneider LS, Rabins PV, Munro CA, Meinert CL, Lyketsos CG. DIADS-2 Research Group. Sertraline for the treatment of depression in Alzheimer disease. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2010; 18(2):136–145.10.1097/JGP.0b013e3181c796eb [PubMed: 20087081]

Rosenberg PB, Lanctôt KL, Drye LT, Herrmann N, Scherer RW, Bachman DL, Mintzer JE. Safety and efficacy of methylphenidate for apathy in alzheimer's disease: a randomized, placebo-controlled trial. The Journal of clinical psychiatry. 2013; 74(8):810–816.10.4088/JCP.12m08099 [PubMed: 24021498]

Rosenberg PB, Mielke MM, Lyketsos CG. Caregiver assessment of patients' depression in Alzheimer disease: longitudinal analysis in a drug treatment study. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2005; 13(9):822–826.10.1176/appi.ajgp.13.9.822 [PubMed: 16166413]

Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA : the journal of the American Medical Association. 2005; 294(15):1934–1943.10.1001/jama.294.15.1934 [PubMed: 16234500]

Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg B, Schmitt FA, Grundman M, Thomas RG, Ferris SH. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. Alzheimer disease and associated disorders. 1997; 11(Suppl 2):S22–32. [PubMed: 9236949]

Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup TS, Sultzer DL, Weintraub D, Lieberman JA. CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. The New England journal of medicine. 2006; 355(15):1525–1538.10.1056/NEJMoa061240 [PubMed: 17035647]

Sommer OH, Aga O, Cvancarova M, Olsen IC, Selbaek G, Engedal K. Effect of oxcarbazepine in the treatment of agitation and aggression in severe dementia. Dementia and geriatric cognitive disorders. 2009; 27(2):155–163.10.1159/000199236 [PubMed: 19182483]

Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, Breitner JCS, Steffens DC, Tschanz JT. Cache County Investigators. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. International journal of geriatric psychiatry. 2008; 23(2):170–177.10.1002/gps.1858 [PubMed: 17607801]

Trzepacz PT, Cummings J, Konechnik T, Forrester TD, Chang C, Dennehy EB, Willis BA, Shuler C, Tabas LB, Lyketsos C. Mibampator (LY451395) randomized clinical trial for agitation/aggression in Alzheimer's disease. International psychogeriatrics / IPA. 2013; 25(5):707–719.10.1017/S1041610212002141 [PubMed: 23257314]

Description of Author's Roles

Author Contributions: Dr. Rosenberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Porsteinsson, Drye, Pollock, Devanand, Frangakis, Meinert, Mintzer, Munro, Rabins, Rosenberg, Schneider, Shade, Weintraub, Yesavage, Lyketsos.

Acquisition of data: Porsteinsson, Pollock, Devanand, Ismail, Marano, Mintzer, Pelton, Rosenberg, Schneider, Weintraub, Yesavage.

Analysis and interpretation of data: Porsteinsson, Drye, Pollock, Devanand, Frangakis, Ismail, Marano, Meinert, Mintzer, Munro, Newell, Pelton, Rabins, Rosenberg, Schneider, Shade, Weintraub, Lyketsos.

Drafting of the manuscript: Rosenberg, Lyketsos, Devanand, Porsteinsson, Schneider, Mintzer, Weintraub, Drye.

Statistical analysis: Drye, Frangakis, Meinert, Shade.

Obtained funding: Porsteinsson, Drye, Pollock, Devanand, Frangakis, Meinert, Mintzer, Munro, Rabins, Rosenberg, Schneider, Weintraub, Yesavage, Lyketsos.

Administrative, technical, and material support: Porsteinsson, Drye, Rabins, Shade, Lyketsos.

Study supervision: Porsteinsson, Drye, Pollock, Devanand, Frangakis, Meinert, Mintzer, Rosenberg, Pelton, Schneider, Shade, Weintraub, Yesavage, Lyketsos.

Appendix

Steering Committee voting members (responsibilities: study design and conduct): Resource center representatives: Constantine Lyketsos, MD, MHS (chair) Dave Shade, JD (vice chair)

Clinical center directors: D.P. Devanand, MD Jacobo Mintzer, MD, MBA Paul Rosenberg, MD Bruce G. Pollock, MD, PhD Anton Porsteinsson, MD Lon S. Schneider, MD Jerome Yesavage, MD Daniel Weintraub, MD

Research group: Resource centers (responsibility: study administration): *Chair's Office, Johns Hopkins Bayview and Johns Hopkins School of Medicine, Baltimore:* Constantine Lyketsos, MD, MHS (chair) Allison Carlson (lead coordinator) Dimitri Avramopoulos, MD, PhD (study geneticist) Cynthia Munro, PhD (study neuropsychologist) Peter Rabins, MD, MPH (conflict of interest officer) Annie Roche

Coordinating Center, Johns Hopkins Bloomberg School of Public Health, Baltimore: Dave Shade, JD (director), Anne Shanklin Casper, MA, CCRP (lead coordinator) Lea Drye, PhD, Constantine Frangakis, PhD Gabrielle Jenkin, Curtis Meinert, PhD Hao-Min Pan, Susan Tonascia, ScM Ozlem Topaloglu, PhD Matthew Toepfner, Vijay Vaidya, MSc, MPH

Project Office, National Institute on Aging, Bethesda: Laurie Ryan, PhD (project officer)

Clinical centers (responsibility: data collection): *Johns Hopkins Bayview and Johns Hopkins School of Medicine, Baltimore:* Paul Rosenberg, MD (director), Julia Pedroso, RN, MA (lead coordinator), Alyssa Bergey, MA Allison Carlson Carol Gogel, RN Christopher Marano, MD Jamie Pollutra, RN Lynn Smith, MA Martin Steinberg, MD

Columbia University Medical Center, Columbia: D.P. Devanand, MD (director) Corazon de la Pena (lead coordinator) Gregory H. Pelton, MD

Medical University of South Carolina, Charleston: Jacobo Mintzer, MD, MBA (director) Nicholas Gregory (lead coordinator) Olga Brawman-Mintzer, MD Allison Moroni Amanda Watts Shenequia Lucas Marilyn Stuckey, RN Amy Gandy Markeeta Hatchell, RN

University of Pennsylvania School of Medicine, Philadelphia: Daniel Weintraub, MD (director) Jamie Czerniakowski (lead coordinator) Suzanne DiFilippo, RN Eugenia Mamikonyan Joel Streim, MD

University of Rochester School of Medicine, Rochester: Anton Porsteinsson, MD (director) Bonnie Goldstein, MS, NP (coordinator) Susan Salem-Spencer, RN, MSN (coordinator) Nancy Kowalski, MS, RNC, Kimberly S. Martin, RN Jeanne LaFountain, RN Kelly Makino, Kelly Stear Andrew Porter Asa Widman

Stanford University School of Medicine: Jerome Yesavage, MD (director) Jeff Newell (lead coordinator) Wes Ashford, MD, Karen Bratcher, RN Steven Chao, MD, Jennifer Kaci Fairchild, PhD Leah Friedman, PhD, Gerald Georgette, RN Emily Gere, Ellen Kim, Vyjeyanthi Periyakoil, MD Arthur Traum, MD, Alda Vicencio, RN Deryl Wicks

University of Toronto: Bruce G. Pollock, MD, PhD, FRCPC (director) Dielle Miranda (lead coordinator) Robert Bies, PhD Amer Burhan, MD Phil Gerretsen, MD Zahinoor Ismail, MD Benoit H. Mulsant, MD, MS Minh-Quan Nguyen, HBsc Tarek Rajji, MD, David Tang-Wai, MD

University of Southern California Keck School of Medicine: Lon S. Schneider, MD (director) Maurcio Becerra (lead coordinator) Karen Dagerman, MS Sonia Pawluczyk, MD Bryan Spann, DO, PhD Liberty Teodoro, RN

Data Safety and Monitoring Board members (responsibility: review of accumulating data on safety and efficacy) *Voting* Kristine Yaffe, MD (chair) Stephan Arndt, PhD Jeffrey Cummings, MD

Non-voting Lea Drye, PhD Constantine Lyketsos, MD Laurie Ryan, MD, Dave Shade, JD

Table 1

a Agitation outcomes over time in the placebo group

		Neurobehavioral Rating Scale (NBRS) - agitation subscore			Cohen-Mansfield Agitation Inventory (CMAI)			CGIC agitation responders	Neuropsychiatric Inventory (NPI) agitation subscale		
Raw scores											
Visit	**N***	**Mean**	**SD**		**Mean**	**SD**		**n (%)**	**Mean**	**SD**	
Enrollment	92	7.8	3.0		28.7	6.7		n/a	8.0	2.4	
Week 3	84	5.7	3.1		26.9	6.7		24 (29%)	4.9	3.1	
Week 6	84	5.8	3.6		27.0	7.4		18 (21%)	4.9	3.6	
Week 9	83†	5.4	3.2		26.7	7.4		21 (26%)	4.9	3.8	
*Estimate** of change*											
		Slope	95% CI	p-value	Slope	95% CI	p- value	p- value	Slope	95% CI	p-value
		-0.23	(-0.30, -0.16)	<0.001	-0.20	(-0.33, -0.06)	0.004	<0.001	-0.31	(-0.39, -0.23)	<0.001

*Number of participants in the placebo group with data

†Two participants were missing week 9 NBRS agitation and CGIC agitation. The N for these two outcomes is 81.

**For continous outcomes, mean weekly slope is estimated using mixed effects regression with a random intercept for participant. Negative slope values indicate improvement for NBRS, CMAI and NPI agitation. The p-value is for the test of the hypothesis that the slope is zero (i.e., no change over time). For CGIC, the p-value is for a Z test that the proportion of responders at week 9 is zero.

		Neuropsychiatric			Mini Mental State			ADCS		
Raw scores										
Visit	**N***	**Mean**	**SD**		**Mean**	**SD**		**Mean**	**SD**	
Enrollment	92	37.3	17.7		14.4	6.9		41.1	18	
Week 3	84	26.1	16.1		14.9	7.3		40.8	18	
Week 6	84	27.6	21.0		15.5	7.3		40.0	18	
Week 9	83†	28.4	22.1		15.7	7.2		39.6	18	
*Estimate** of change*										
		Slope	95% CI	p-value	Slope	95% CI	p-value	Slope	95% CI	p-value
		-0.87	(-1.29, -0.46)	<0.001	0.11	(0.05, 0.18)	0.001	-0.17	(-0.32, -0.02)	0.02

*Number of participants in the placebo group with data

†Two participants were missing week 9 NBRS agitation and CGIC agitation. The N for these two outcomes is 81.

** Mean weekly slope is estimated using mixed effects regression with a random intercept for participant. Negative slope values indicate improvement for NPI. Positive slope values indicate improvement for MMSE and ADCS-ADL. The p-value is for the test of the hypothesis that the slope is zero (i.e., no change over time).