Journal of Psychiatric Research 79 (2016) 4–7

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Principal components analysis of agitation outcomes in Alzheimer's disease

Jerome A. Yesavage [a, b, c, *], Joy L. Taylor [a, b], Leah Friedman [b], Paul B. Rosenberg [d], Laura C. Lazzeroni [b], Jeannie-Marie S. Leoutsakos [d], Lisa M. Kinoshita [a], Mark J. Perlow [a], Cynthia A. Munro [d], D.P. Devanand [e, f], Lea T. Drye [g], Jacobo E. Mintzer [h, i], Bruce G. Pollock [j], Anton P. Porsteinsson [k], Lon S. Schneider [l], David M. Shade [g], Daniel Weintraub [m, n], Constantine G. Lyketsos [d], Art Noda [b], for the CitAD Research Group

[a] Department of Veterans Affairs Health Care System, Palo Alto, CA, 94304, United States
[b] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, 94305, United States
[c] Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, 94305, United States
[d] Department of Psychiatry and Behavioral Sciences, Johns Hopkins Bayview Medical Center, Johns Hopkins School of Medicine, Baltimore, MD, 21205, United States
[e] Division of Geriatric Psychiatry, New York State Psychiatric Institute, New York, NY, 10032, United States
[f] College of Physicians and Surgeons of Columbia University, New York, NY, 10032, United States
[g] Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 21205, United States
[h] Clinical Biotechnology Research Institute, Roper St. Francis Healthcare, Charleston, SC, 29401, United States
[i] Ralph H. Johnson VA Medical Center, Charleston, SC, 29401, United States
[j] Campbell Institute, CAMH, University of Toronto, Toronto, Ontario, M5S 2S1, Canada
[k] University of Rochester School of Medicine and Dentistry, Rochester, NY, 14642, United States
[l] University of Southern California Keck School of Medicine, Los Angeles, CA, 90089, United States
[m] Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, 19104, United States
[n] Department of Veterans Affairs, Philadelphia, PA, 19104, United States

ARTICLE INFO

Article history:
Received 16 February 2016
Received in revised form
5 April 2016
Accepted 14 April 2016

Keywords:
Agitation
Alzheimer's disease
Principal component analysis

ABSTRACT

Background: We developed a composite measure of agitation as a secondary outcome of change over time in the Citalopram for Agitation in Alzheimer's disease study (CitAD). CitAD demonstrated a positive effect of citalopram on agitation on the Neurobehavioral Rating Scale agitation subscale (NBRS-A). CitAD included additional agitation measures such as the Cohen-Mansfield Agitation Inventory and the Neuropsychiatric Inventory.
Methods: We performed principal components analyses on change in individual item of these scales for the same, original CitAD subjects.
Results: The first principal component accounted for 12.6% of the observed variance and was composed of items that appear to reflect agitation. The effect size for citalopram calculated using this component was 0.53 (95% CI 0.22–0.83) versus 0.32 for the NBRS-A (95% CI 0.01–0.62).
Conclusions: Results suggest that a composite measure of change in agitation might be more sensitive than change in a single primary agitation measure.

Published by Elsevier Ltd.

1. Introduction

Agitation is a common and disturbing symptom in many Alzheimer Disease patients and its pharmacological treatment has often been inadequate (Antonsdottir et al., 2015). Given the prohibitive costs of additional clinical trials, the purpose of this work is to test the hypothesis that a composite measure of agitation based on a principal component analysis (PCA) of change in individual items from standard agitation measures provides more sensitivity to change after psychotropic medication treatment than a single global agitation measure. For this analysis we used data of change over time on relevant measures from the Citalopram for Agitation

* Corresponding author. Palo Alto VA Health Care System, 3801 Miranda Avenue (151Y), Palo Alto, CA, 94304, USA.
E-mail address: yesavage@stanford.edu (J.A. Yesavage).

http://dx.doi.org/10.1016/j.jpsychires.2016.04.004
0022-3956/Published by Elsevier Ltd.

in Alzheimer's Disease study (CitAD; Porsteinsson et al., 2014). In prior work we found that PCAs of measures such as the Mini Mental State Examination (MMSE) differ depending upon whether the PCA is performed on data from a single time point or from data reflecting change in individual items over time (Brooks et al., 1993; Tinklenberg et al., 1990). The present work performs a similar analysis on measures of agitation (Porsteinsson et al., 2014).

The CitAD study demonstrated a significant positive effect of citalopram on agitation of 0.93 points on the Neurobehavioral Rating Scale agitation subscale (NBRS-A: p = 0.04; Cohen's d = 0.32; possible range of scores: 0–18 points; Levin et al., 1987). The original study included secondary measures of agitation such as the Cohen-Mansfield Agitation Inventory (CMAI; Cohen-Mansfield, 1996) and the Neuropsychiatric Inventory (NPI; Cummings et al., 1994), thus providing the opportunity to perform PCAs on change on all relevant individual items of these scales over the course of the study. This allows the possibility of determining if there are candidate composite measures that might be more sensitive to change after psychotropic medication treatment than the single CitAD primary agitation measure, the NBRS-A.

2. Methods

2.1. Participants

Participants in CitAD had a diagnosis of AD with the Neuropsychiatric Inventory (NPI) Agitation/Aggression subscale rated as occurring 1) very frequently, or 2) frequently marked moderate or severe (Cummings et al., 1994). Primary outcome measures were 9-week change in the NBRS-A (Levin et al., 1987) and the 9-week rating on the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC; Schneider et al., 1997). Participants received either placebo or active drug with a target dose of three pills a day (a target dose of citalopram 30 mg daily). All participants and caregivers received a psychosocial intervention as previously described (Drye et al., 2012) that involved counseling, emotional support and problem solving.

2.2. Statistics

The de-identified data set available for the CitAD study was used in these analyses. This dataset contains no protected health information (PHI), and thus provides no risk of confidentiality loss. Our criterion for determining if there were a candidate composite measure of change in agitation that might be more sensitive to treatment effects than the CitAD primary agitation measure, the NBRS-A (Levin et al., 1987), was to determine if the resulting new measure demonstrated a larger effect size on the same subjects than did the NBRS-A alone. All subjects with complete data for the CMAI (14 items) and NPI (12 items) at time of enrollment (baseline) and week 9 (end of treatment) were included in the analysis (N = 167). Difference scores from end of treatment minus baseline were computed.

2.2.1. Standardized scores of individual scale items

The difference scores were standardized to mean = 0 and the standard deviation = 1 across all 167 subjects with complete data. Standardization allows us to compare scores across two different metrics: the CMAI and the NPI.

2.2.2. Principal components analysis

These 26 items were included in a PCA for all 167 subjects (regardless of treatment assignment). Analyses were performed using SAS software, version 9.4 (Cary, NC) using the SAS procedure PROC FACTOR (with the method = prin option). Sample size for the original effect size was calculated using the equation of Smithson (Smithson, 2001).

2.2.3. Bootstrapping

To calculate confidence limits for calculated effect sizes of various measures of agitation, 2000 bootstrap samples were drawn from the 167 complete CitAD cases. Bootstrapping is a statistical procedure in which random sampling and replacement of items in a dataset is used to estimate how confident one is of a particular result. For each bootstrap sample in this study, effect sizes for NBRS, CMAI, and NPI were calculated by taking the difference in change scores between treatment groups and dividing by the standard deviation of those changes scores for both groups combined. For the unstandardized effect size for NPI, the items were reverse coded such that 0 = no and 1 = yes. For creation of composites with other scales, the NPI z-score was multiplied by −1 in order to be in the same direction as the other two scales. The z-score composite change score was calculated as the mean of the three individual change z-scores, which in turn were the mean z-scores for the individual items. The composite z-score effect size was then calculated in the same way as the individual unstandardized scale effect sizes. Similarly, the z-score composites were calculated from just the CMAI and NPI. A principal components analysis was performed on the standardized change scores for the CMAI and NPI items, and component scores for the first component were calculated, and again effect sizes were calculated in the standard way. Finally, confidence intervals were calculated from bootstrap samples. Effect size here is the mean effect size across the 2000 draws, and the confidence interval is constructed from the 2.5th and 97.5th percentiles of the effect sizes from the 2000 draws. For both the original and bootstrap effect sizes, the necessary sample size was calculated assuming an independent samples *t*-test with 0.80 power and 0.05 alpha. This procedure was repeated for the lower and upper bounds of the confidence interval.

3. Results

The first step in this process was to determine the PC structure

Table 1
Eigenvalues of the correlation matrix for 26-item principal components analysis.

Item	Eigenvalue	Proportion of variance	Cumulative proportion
1	3.27	0.126	0.126
2	1.95	0.075	0.202
3	1.64	0.063	0.264
4	1.43	0.055	0.319
5	1.38	0.053	0.372
6	1.33	0.051	0.423
7	1.23	0.047	0.471
8	1.15	0.044	0.515
9	1.13	0.044	0.559
10	1.08	0.042	0.600
11	0.99	0.038	0.638
12	0.97	0.038	0.676
13	0.89	0.034	0.710
14	0.82	0.031	0.741
15	0.79	0.030	0.772
16	0.76	0.029	0.801
17	0.73	0.028	0.829
18	0.68	0.026	0.855
19	0.61	0.023	0.879
20	0.57	0.022	0.900
21	0.54	0.021	0.921
22	0.47	0.018	0.939
23	0.44	0.017	0.956
24	0.43	0.016	0.973
25	0.37	0.014	0.987
26	0.33	0.013	1.000

Forbidden

You don't have permission to access this resource.
