Why Include Cognitive Measures?
A Systematic Review and Meta-Analysis of Agitation Trials in Individuals with Dementia

Heather G. Belanger, Ph.D.,[1-2] Kavita Gohil, DrPH,[1] Jeffrey Finman, Ph.D.,[1] Gary G. Kay, Ph.D.[1]

[1]Cognitive Research Corporation, St Petersburg, FL; [2]Depts. of Psychiatry & Behavioral Neurosciences and Psychology, University of South Florida, Tampa, FL

Introduction

Randomized controlled trials have investigated the potential of various medications to treat agitation in dementia. Many such trials include measures of cognitive performance. It is unclear whether cognition is significantly impacted in these trials.

PURPOSE OF THIS STUDY

The purpose of this review and meta-analysis was to determine the extent to which various agents used to treat agitation may impact cognitive performance in these trials.

Method

SEARCH STRATEGY & SELECTION CRITERIA

Electronic databases, including PubMed, EMBASE, International Pharmaceutical Abstracts (IPA), clinicaltrials.gov, and the Cochrane Central Register of Controlled Trials (CENTRAL), were systematically searched from inception to April 22, 2023, using a combination of keywords and Medical Subject Headings (MeSH) terms including dementia, agitation/aggression, and trials. We also conducted a manual search by screening the reference lists of the included studies and recent reviews.

We included placebo-controlled trials of pharmaceuticals that recruited individuals with dementia specifically for agitation/aggression issues and that included standardized cognitive assessment. Trials testing medications specifically designed to treat cognition (e.g., acetylcholinesterase inhibitors) were excluded.

DATA ANALYSIS

Effect sizes were calculated using standardized mean differences (SMD) using R software, Version 4.0.3. Publication bias was assessed using funnel plots and Egger's test of funnel plot asymmetry. Heterogeneity among studies was assessed with the I^2 statistic. Interpretation of the I^2 was made by assigning attributes of low, moderate, and high to the values of 0 to 25%, 50 to 75%, and more than 75%, respectively.[1] Fixed effect meta-analysis was to be used if there was no substantial heterogeneity. The random effects model was to be used if heterogeneity was present. The random effects model utilized the DerSimonian-Laird method for evaluation of within-study variance. Study methodology was pre-registered with Prospero (CRD42023414140).
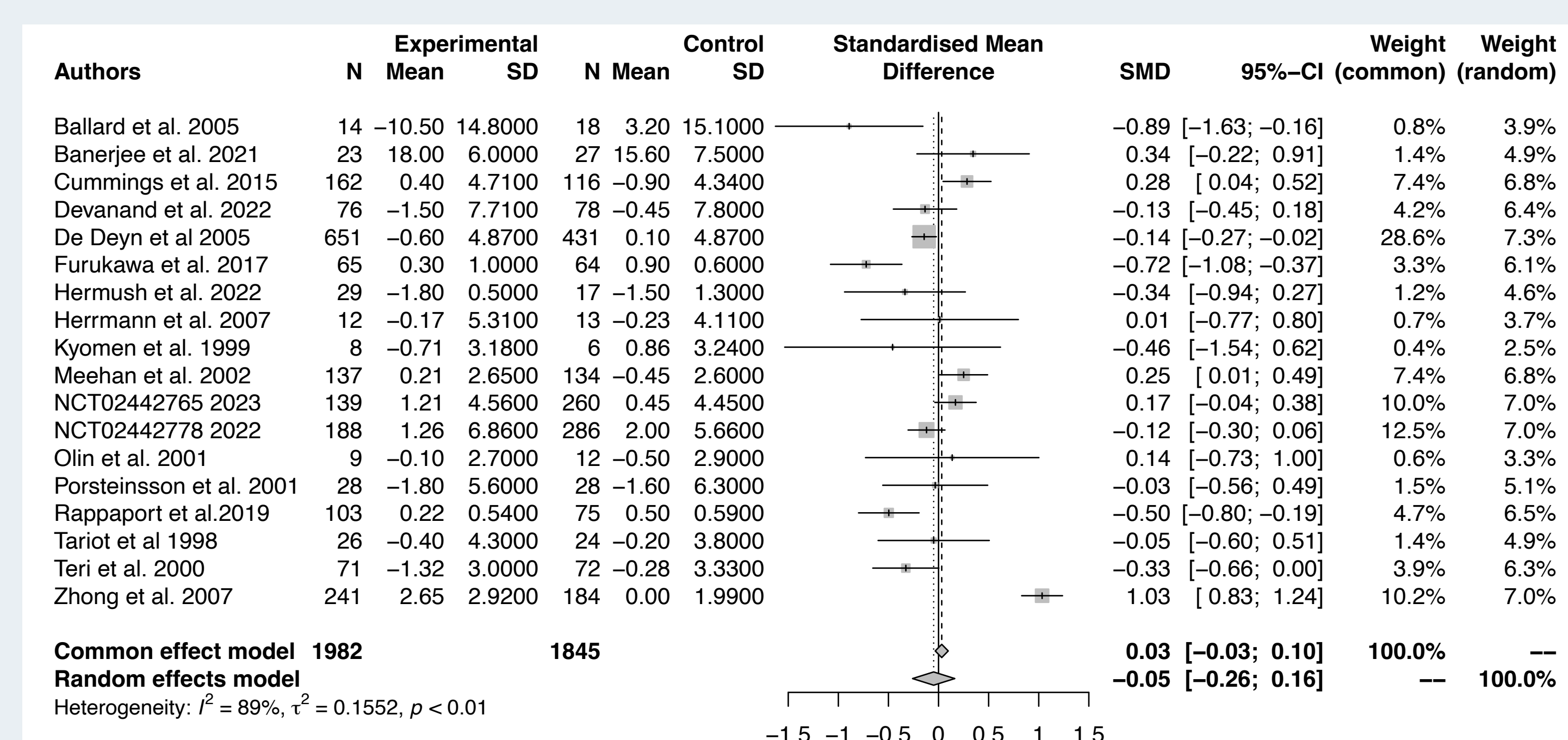
Results

OVERALL EFFECT SIZE

- Of the 138 full-text articles reviewed in detail, 18 met inclusion/exclusion criteria.
- Based on I^2 (89%), heterogeneity was high so random effects models were used.
- Egger's test did not reveal the presence of funnel plot asymmetry, intercept = -0.88, t = -0.62, p = 0.54.
- The overall *effect of agitation treatment on cognitive performance* was **not** statistically significant, SMD = -0.05 [-0.26; 0.16].

Conclusions

Medications investigated for treatment of agitation in dementia show no significant effect on cognition.

Including measures of cognition in agitation trials for dementia appears to unnecessarily burden participants and increase study costs.

Authors	N	Experimental Mean	SD	N	Control Mean	SD	Standardised Mean Difference	SMD	95%-CI	Weight (common)	Weight (random)
Ballard et al. 2005	14	-10.50	14.8000	18	3.20	15.1000		-0.89	[-1.63; -0.16]	0.8%	3.9%
Banerjee et al. 2021	23	18.00	6.0000	27	15.60	7.5000		0.34	[-0.22; 0.91]	1.4%	4.9%
Cummings et al. 2015	162	0.40	4.7100	116	-0.90	4.3400		0.28	[0.04; 0.52]	7.4%	6.8%
Devanand et al. 2022	76	-1.50	7.7100	78	-0.45	7.8000		-0.13	[-0.45; 0.18]	4.2%	6.4%
De Deyn et al. 2005	651	-0.60	4.8700	431	0.10	4.8700		-0.14	[-0.27; -0.02]	28.6%	7.3%
Furukawa et al. 2017	65	0.30	1.0000	64	0.90	0.6000		-0.72	[-1.08; -0.37]	3.3%	6.1%
Hermush et al. 2022	29	-1.80	0.5000	17	-1.50	1.3000		-0.34	[-0.94; 0.27]	1.2%	4.6%
Herrmann et al. 2007	12	-0.17	5.3100	13	-0.23	4.1100		0.01	[-0.77; 0.80]	0.7%	3.7%
Kyomen et al. 1999	8	-0.71	3.1800	6	0.86	3.2400		-0.46	[-1.54; 0.62]	0.4%	2.5%
Meehan et al. 2002	137	0.21	2.6500	134	-0.45	2.6000		0.25	[0.01; 0.49]	7.4%	6.8%
NCT02442765 2023	139	1.21	4.5600	260	0.45	4.4500		0.17	[-0.04; 0.38]	10.0%	7.0%
NCT02442778 2022	188	1.26	6.8600	286	2.00	5.6600		-0.12	[-0.30; 0.06]	12.5%	7.0%
Olin et al. 2001	9	-0.10	2.7000	12	-0.50	2.9000		0.14	[-0.73; 1.00]	0.6%	3.3%
Porsteinsson et al. 2001	28	-1.80	5.6000	28	-1.60	6.3000		-0.03	[-0.56; 0.49]	1.5%	5.1%
Rappaport et al.2019	103	0.22	0.5400	75	0.50	0.5900		-0.50	[-0.80; -0.19]	4.7%	6.5%
Tariot et al 1998	26	-0.40	4.3000	24	-0.20	3.8000		-0.05	[-0.60; 0.51]	1.4%	4.9%
Teri et al. 2000	71	-1.32	3.0000	72	-0.08	3.3300		-0.33	[-0.66; 0.00]	3.9%	6.3%
Zhong et al. 2007	241	2.65	2.9200	184	0.00	1.9900		1.03	[0.83; 1.24]	10.2%	7.0%
Common effect model	**1982**			**1845**				**0.03**	**[-0.03; 0.10]**	**100.0%**	**---**
Random effects model								**-0.05**	**[-0.26; 0.16]**	**---**	**100.0%**

Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.1552$, $p < 0.01$

-1.5 -1 -0.5 0 0.5 1 1.5

MODERATORS

The effect sizes did not significantly differ based on type of cognitive test used.

- MMSE (n = 14)
  SMD = 0.01 [-0.02, 0.14]
- ADAS-COG (n = 3)
  SMD = 0.12 [-0.10, 0.35]

The effect sizes did not significantly differ based on duration of trial.

- 24 hours up to 6 weeks (n = 10)
  SMD = -0.08 [-0.30, 0.13]
- 6 – 16 weeks (n = 3)
  SMD = 0.00 [-0.33, 0.32]

References

1. Higgins JP, Thompson SG, Deeks JJ, Altman DG.
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Disclosures

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