

Psychostimulants And Non-pharmacological Treatments For Apathy In Alzheimer's: A Systematic Review And Meta-analysis

P1-001

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In AD, psychostimulants outperform placebo in apathy symptoms, while both (pharmacological or non-pharmacological) approaches reduce caregiver burden.

INTRODUCTION

Apathy is a common neuropsychiatric symptom associated with Alzheimer's disease (AD). Treatment and evidence are unclear in regards to pharmacological or non-pharmacological options.

METHODS

We systematically searched Embase, PubMed, and Cochrane databases for randomized controlled trials (RCT) reporting psychostimulants use or non-pharmacological interventions, each compared to placebo, for apathy among AD patients. Outcomes were improvement of MMSE, NPI-apathy subscale, AES (Apathy Evaluation Scale) and Zarit Burden scale (ZBS). Mean Difference (MD) and 95% confidence intervals (CI) were pooled with a random-effects model. Heterogeneity was assessed using I² statistic. Statistical analyses were performed using Review Manager.

RESULTS

We included 12 RCT comprising 640 patients, 182 (28.4%) received pharmacological treatment and 146 (22.8%) received non-pharmacological treatment.

MMSE: Significantly higher in pharmacological treated patients compared to placebo (MD 1.72; 95% CI 0.65 to 2.8; p=0.002; I² = 31%), no difference was found between non-pharmacological treated patients.

AES: Neither pharmacological (MD -5.82) nor non-pharmacological groups (MD -5.52) improved AES apathy scale when compared to placebo.

Study or Subgroup	Intervention			Placebo			Mean difference			Mean difference		
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Weight	IV, Random, 95% CI	Weight	IV, Random, 95% CI
1.1.1 MMSE (Pharmacological)												
ADMET	1.2	2.678049	29	-0.3	2.678049	31	14.1%	1.50 [0.14, 2.86]				
Hermann	-0.58	2.53	13	-1.08	2.81	12	11.0%	0.50 [-1.60, 2.60]				
Methylphenidate for Apathy (Padala)	2.2	2.678049	30	-0.4	2.678049	30	14.1%	2.60 [1.24, 3.96]				
Subtotal (Wald^a)			72			73	39.2%	1.72 [0.65, 2.80]				
Test for overall effect: Z = 3.15 (P = 0.002)												
Heterogeneity: Tau ² (REMLb) = 0.28; Chi ² = 2.99, df = 2 (P = 0.22); I ² = 31%												
1.1.2 MMSE (Non-pharmacological)												
Buettner	0.93	4.501194	48	-0.62	4.551715	29	11.1%	1.55 [-0.54, 3.64]				
Neuromodulation for Apathy (Padala)	1	2.666951	9	0.1	2.656017	10	9.9%	0.90 [-1.50, 3.30]				
Niu	0.81	1.11	16	-0.19	0.66	16	16.6%	1.00 [0.37, 1.63]				
rTMS for Apathy (Padala)	2.9	0.816982	4	-0.6	1.127519	5	14.4%	3.50 [2.23, 4.77]				
Savulich	-1.75	4.501194	21	1.38	4.551715	21	8.8%	-3.13 [-5.87, -0.39]				
Subtotal (Wald^a)			98			81	60.8%	0.96 [-1.00, 2.92]				
Test for overall effect: Z = 0.96 (P = 0.34)												
Heterogeneity: Tau ² (REMLb) = 4.06; Chi ² = 22.58, df = 4 (P = 0.0002); I ² = 88%												
Total (Wald^a)			170			154	100.0%	1.29 [0.14, 2.44]				
Test for overall effect: Z = 2.20 (P = 0.03)												
Test for subgroup differences: Chi ² = 0.45, df = 1 (P = 0.50); I ² = 0%												
Heterogeneity: Tau ² (REMLb) = 1.97; Chi ² = 26.43, df = 7 (P = 0.0004); I ² = 79%												
Footnotes												
^a CI calculated by Wald-type method.												
^b Tau ² calculated by Restricted Maximum-Likelihood method.												

1.1.1 AES (non-pharmacological)

Buettner

Neuromodulation for Apathy (Padala)

rTMS for Apathy (Padala)

Savulich

Subtotal (Wald^a)

Test for overall effect: Z = 1.72 (P = 0.09)

Heterogeneity: Tau² (REMLb) = 37.65; Chi² = 59.24, df = 3 (P < 0.00001); I² = 93%

1.2.2 ZBS (non-pharmacological)

Neuromodulation for Apathy (Padala)

Oliveira

rTMS for Apathy (Padala)

Subtotal (Wald^a)

Test for overall effect: Z = 2.94 (P = 0.003)

Heterogeneity: Tau² (REMLb) = 0.00; Chi² = 1.26, df = 2 (P = 0.53); I² = 0%

1.2.3 NPI (non-pharmacological)

Hermann

Oliveira

Subtotal (Wald^a)

Test for overall effect: Z = 2.46 (P = 0.01)

Heterogeneity: Tau² (REMLb) = 0.30; Chi² = 1.10, df = 1 (P = 0.29); I² = 9%

Total (Wald^a)

Test for overall effect: Z = 1.47 (P = 0.14)

Test for subgroup differences: Chi² = 17.48, df = 2 (P = 0.0002); I² = 88.6%

Heterogeneity: Tau² (REMLb) = 35.80; Chi² = 102.67, df = 8 (P < 0.00001); I² = 90%

Footnotes

^aCI calculated by Wald-type method.

^bTau² calculated by Restricted Maximum-Likelihood method.

CONCLUSIONS

Psychostimulants showed significant benefits in MMSE and NPI-apathy scales compared to placebo, while non-pharmacological interventions showed no such benefit. When assessing caregiver burden, it's shown that either pharmacological or non-pharmacological intervention are superior to no treatment.

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