Received: 14 March 2017 | Accepted: 24 July 2017

DOI: 10.1002/gps.4783

WILEY International Journal of Geriatric Psychiatry

REVIEW ARTICLE

A systematic review of non-pharmacological treatments for apathy in dementia

Christos Theleritis[1] | Kostas Siarkos[1] | Anastasios A. Politis[1] | Everina Katirtzoglou[1] | Antonios Politis[1,2]

[1] Division of Geriatric Psychiatry, First Department of Psychiatry, National and Kapodistrian University of Athens, Athens, Greece

[2] Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University, Baltimore, MD, USA

Correspondence
Antonios Politis, MD, PhD, Division of Geriatric Psychiatry, 1st Psychiatry Dept., University of Athens Medical School Eginition Hopsital, 72-74 Vas. Sofias Avenue, 11528 Athens Greece.
Email: apolitis@med.uoa.gr

Objective: Apathy is one of the most frequent neuropsychiatric symptoms encountered in dementia. Early diagnosis and timely treatment of apathy in dementia are crucial because apathy has been associated with poor disease outcome, reduced daily functioning, and caregiver distress.

Design: Extensive electronic search from the databases included in the National Library of Medicine as well as PsychInfo and Google Scholar for studies which have investigated the effect of non-pharmacological treatments of apathy in dementia. Quality of the studies was appraised.

Results: A total of 1303 records were identified and 120 full-texts assessed. Forty-three unique studies were reviewed. A variety of interventions were found to be effective in reducing apathy in demented patients, particularly when provided in a multidisciplinary manner. However, quantification of the effect was limited by the marked methodological heterogeneity of the studies and the small number of studies where apathy was the primary outcome measure.

Conclusions: Treatment of apathy in dementia is a complex and underexplored field. Certain studies suggest promise for a variety of non-pharmacological interventions. Standardized and systematic efforts primarily focusing on apathy may establish a benefit from individualized treatments for specific disease groups.

KEYWORDS

apathy, dementia, non-pharmacological, systematic review, treatment

1 | INTRODUCTION

Applying the Neuropsychiatric Inventory (NPI), Mega, Cummings, Fiorello, and Gornbein[1] found that 88% of subjects with Alzheimer's disease (AD) had neuropsychiatric symptoms, of which apathy was the most frequent, reported to occur in 27% to 72% of patients.[2-6]

Apathy is also encountered in several neuropsychiatric disorders; it is present in up to 90% of patients with fronto-temporal dementia, dementia with Lewy bodies, progressive supranuclear palsy, 40% of those with cortico-basal degeneration, and 20% of those with Parkinson's disease.[3,7] Some degree of apathy is observed in brain injuries and frontal lobe lesions and is related to lesion location.[7,8]

Apathy has been defined as the absence or lack of feeling, emotion, interest, concern, or motivation not attributable to a decreased level of consciousness, cognitive impairment, or emotional distress.[8] Starkstein, Petracca, Chemerinski, and Kremer[9] proposed the following core features of apathy: diminished motivation, diminished initiative and interest, and blunting of emotions. Recently proposed diagnostic criteria[10] define "apathy" as a loss or diminution of goal-directed behavior, cognition, or emotion, which persists and is accompanied by functional impairment.[11]

In patients with apathy, the capacity of the frontal cortex to select, initiate, maintain, and shift programs of action is undermined.[12] In dementia, Lyketsos, Rosenblatt, and Rabins[13] proposed that apathy is an aspect of executive dysfunction syndrome and is probably caused by damage to frontal-subcortical brain circuits. Indeed, apathy is correlated with neuronal loss, higher tangle counts, white matter hyperintensities, and hypoperfusion in regions involved in frontal-subcortical networks.[2,14] Apathy frequently complicates the course and management of dementia and is prevalent in patients even with milder forms of cognitive impairment in clinic-based[15] and community-based[5,16] samples. Onyike et al[17] proposed that apathy is an early sign of cognitive decline. Consequently, apathy has been associated

The authors Christos Theleritis and Kostas Siarkos have contributed equally to the manuscript

with reduced daily functioning, functional disability, self-neglect, behaviors evoking embarrassment, caregiver distress, and poor outcome.[18,19] Within this context, early diagnosis and effective treatment of apathetic patients with dementia are crucial.

While a prevalent neuropsychiatric syndrome, no specific treatment for apathy in dementia has been approved. Clinical apathy implying motor, cognitive, affective, and behavioral symptoms suggests a benefit may systematically arise when combinations of different treatments are tested.

In a previous review,[20] we searched for effectiveness in apathy of AD throughout treatment modalities. In the present review we expand on the non-pharmacological treatments for apathy in all-cause aging neurodegenerative dementia. Using elastic criteria that allow more studies entering the review, we wished to highlight a more pragmatic picture in the field and to address methodological issues, inform practices, and guide research appropriately.

Key points

- Apathy is one of the most frequent neuropsychiatric symptoms encountered in dementia.
- A variety of nonpharmacological interventions, when provided in a multidisciplinary manner, were found to be effective in reducing apathy in demented patients.
- Standardized and systematic efforts primarily focusing on apathy may establish a benefit from individualized treatments for specific disease groups.

2 | METHODS

2.1 | Inclusion and exclusion criteria

We investigated for answers in this line by extensively searching databases and unrestrictedly including trials, where demented patients diagnosed using widely accepted clinical criteria and structured tools received non-pharmacological interventions in controlled designs and an outcome measure on apathy is reported. Other neuropsychiatric manifestations as well as concomitant psychoactive medications were allowed. Other neurological conditions apart from dementia, eg, drug abuse, severe systematic, or malignant conditions were exclusion criteria.

2.2 | Search strategy and study selection

The most current search was conducted on 28 October 2016. The method we followed was to identify non-pharmacological studies relevant to the treatment of apathy in dementia, from an extensive electronic search from the databases included in the National Library of Medicine for "apathy and dementia", as well as PsychInfo and Google Scholar. Further articles for inclusion were identified by searching the references of retrieved articles and by consulting the Cochrane library. The following keywords were also used: apathy, abulia, amotivation, or passivity, dementia, AD, treatment, management, non-pharmacological, multisensory stimulation (MSS), cognitive stimulation therapy, rehabilitation, music therapy, multisensory behavior therapy (MSBT) —Snoezelen, physical activity, socialization, and reminiscence therapy. Articles that did not report a specific outcome measure of apathy in dementia were excluded. Three authors (CT, KS, EK) have gone through all the abstracts; when there was disagreement between the 3 authors, the issue was resolved by a consensus meeting with the last author (AP). Randomized control trials (RCTs) and case-control studies were chosen to account for certain biases. Included articles were read in full, and their level of evidence and outcome were assessed by all the authors. All care settings were considered for inclusion. We did not search for unpublished studies.

The studies retained for inclusion were classified by their level of evidence following the system of the Oxford Centre for Evidence-Based Medicine.[21] Grades of recommendation were also scored with this classification (Table 1). All RCTs were further evaluated with the use of the PEDro rating scale.[22] It comprises 11 items as follows: participant eligibility criteria and source specified, random allocation of participants to interventions, allocation concealed, intervention groups similar at baseline regarding key outcome measures and important prognostic indicators, blinded subjects, blinded therapists who administered the intervention, blinded assessors who measured at least 1 key outcome, dropouts (attrition bias), intention to treat analysis, reported between group statistical comparisons, and reported measures of variability. Each item was evaluated (items 2 to 11) and added to give a total score. Trials were then qualitatively described according to PEDro scores as follows: a score of 7 or greater was "high" quality, a score of 5 or 6 was "moderate" quality, and a score of 4 or less was "poor" quality.[23]

3 | RESULTS

Search with keywords "apathy" and "dementia" yielded 1303 results. The combination of keywords "apathy" AND "dementia" AND "treatment" yielded 596 results; of "apathy" AND "dementia" AND "non-pharmacological treatment" 120 results (Figure 1). After full-text assessment, 43 results (38 RCTs, 4 case-control design studies,[24-27] and 1 study with retrospective design[28]) were identified that met inclusion criteria for non-pharmacological treatment of apathy in dementia. The studies were 2-fold rated independently by 2 ratters (CT and KS) for their level of evidence. One RCT was in German,[29] and we chose not to include it in Tables 1 and 2 because we are not fluent speakers. Of the 37 RCTs included in Tables 1 and 2, apathy as assessed with NPI (11 times), NPI-NH (twice), AES (6 times), AI (3 times), and DAIR (1 time) was considered a primary outcome in 17 unit cases. In more than a half of them, the intervention had a positive effect to apathy, and the studies were more frequently of "moderate" and "high" quality (OCEBM) with an average PEDro score of 6. Agreement between 2 ratters (CT and KS) was 92.7%.

3.1 | Review of non-pharmacological treatment (Tables 1 and 2)

All studies included a control/comparison group apart the intervention group. In the clustered RCT by Lawton et al,[30] a stimulation retreat model of care (combined staff training, interdisciplinary care planning,

TABLE 1 Randomized controlled trials on non-pharmacological interventions in individuals with apathy in neurodegenerative dementia

Trial	N (experimental/ control)	Mean age (y)	Intervention	Context	Treatment duration (weeks)	Apathy measure (primary measure)	Outcome[b]	Comments
Lawton et al[30]	182 [ITT]	N/A	Trained staff planning interdisciplinary care, activity programming, and family support intervention based on the stimulation-retreat principle of a way of thinking about the care of the dementia resident	NH	48 (1 y)	Interest in externally engaging behaviors (G.D.S., BEHAVE-AD, C-MAI, withdrawal factor of MOSES, AARS)	Greater activity and time use (multivariate $F = 2.51$, $df = 14.272$, $P < 0.01$), whereas passive behavior increased	- high dropout rates - the program was not possible to be fully implemented
Camberg et al[31]	54	82.7	Telephone conversation interactive audio tape, rich in selected memories and emotions based on the individual and the existing knowledge (SimPres®) vs a placebo vs usual care	NHs	17 d over 4 w and 10-d washout period between treatments	"Apathy" anchored to a withdrawal VAS (SOAPD, agitation VAS, withdrawal VAS, PARS, short version C-MAI, MOSES (operationally defined agitation and withdrawn behaviors)	Withdrawn behavior improved significantly more often in SimPres® condition (69%) than in placebo (34%, $P < 0.001$) and usual care (55%, $P < 0.001$) in daily staff observation logs	- pseudo-RCT - 77.2% women - severe dementia
Baker et al[32]	33 (15/18)	78	MSS	Day care centres	4	INTERACT Short/BRS/ BMD (INTERACT Short/ BRS/BMD)	POSITIVE	- 7 VaD and 10 mixed dementia patients included. - benefit declined following end of intervention
Cott et al[33]	86 [ITT]	82	Tailored conversation while walking in pairs (walk-and-talk group), or conversation while sitting in pairs (talk-only group), or neither of the two	Long-term care facilities	16	Engagement, communication (FACS, LPRS)	No significant between-group differences.	AD dementia subjects
Schrijnemaekers et al[34]	151 (15 male)	85	Emotion-oriented care vs usual care	NH	48 (1 y)	Dutch behavior observation Scale for psychogeriatric Inpatients (GIP)	No significant changes observed	
Baker et al[35]	136 (65/71)	81 (MSS group) 83 (activity group)	MSS	Day hospital (UK), psycho-geriatric wards (the Netherlands, Sweden)	4	BRS/BMD/ Gedragsobservatieschaal voor de Intramurale Psychogeriatrie—GIP/INTERACT Short (BRS/BMD/ GIP/INTERACT Short)	NEGATIVE	- 3 country sites - data used here include data used in Baker et al[32]
Politis et al[36]	36 (18/18)	84.4 ("kit" group) 83.5 (1-on-1 group)	Kit-based activity intervention	Model care facility for patients with dementia	4	NPI (NPI)	POSITIVE	

(Continues)

TABLE 1 (Continued)

Trial	N (experimental/ control)	Mean age (y)	Intervention	Context	Treatment duration (weeks)	Apathy measure (primary measure)	Outcome[b]	Comments
Chapman et al[37]	54 (26/28)	76.38	Cognitive-communication stimulation (donepezil-plus) vs donepezil-only	At-home dementia patients and their caregivers	48	NPI (NPI)	NEGATIVE	- differences in change scores were at $P = 0.0773$ for the apathy severity index, $P = 0.0556$ for a group factor, $P = 0.0618$ for a group × time factor. - effect size was 0.45, in apathy severity index
Lai et al[38]	101 [ITT]	85.6	Specific reminiscence/ discussion of the patient's life history individually based on Hellen's (1998) "LSB" concepts, or discussion on other themes, or no intervention	NHs	6	Social engagement and well-being (SES, WIB)	No significant between-group differences.	DSM-IV dementia, moderate and severe.
	146	83.8 (treatment group) 83.6 (control group)	Integrated emotion-oriented and usual care or usual care alone	NHs	36	BIP (BIP, CSDD, C-MAI, GRGS, PGCMS)	Apathy worsened	Moderate and severe AD subjects
van Weert et al[39]	125	83.3	Individual 24-h snoezel program, based on family history Taking and stimulus preference screening	NHs	72 (1.5 y)	INTERACT program	Significant greater change was observed for what concerns apathetic behavior in the experimental group vs the control group (1.26, 95% CI for the adjusted means. $P < 0.05$) based on the certified nursing assistants' observations	- A quasi experimental pretest and posttest design was used. - 69 AD patients, 18 VD patients, 26 AD + VD patients, 18 suffering other dementias
Holmes et al[40]	32	84.9	Live interactive music	NHs	Immediately	DCM (DCM)	POSITIVE	Only immediate effects of a 30-min intervention are reported.
Staal et al[41]	24 (12/12)	80.33 (experimental group) 72 (control group)	Multisensory behavior therapy	Geriatric psychiatric unit	Immediately	Assessment of negative symptoms in Alzheimer's disease scale (assessment of negative symptoms in Alzheimer's disease scale)	POSITIVE	Effects after 6 sessions of a 25–30-min intervention are reported.
Tadaka and Kanagawa[42]	24 AD (12/12) and 36 VD (18/18)	83.29	Reminiscence	Geriatric health services facility in Japan	24	MOSES (MOSES)	POSITIVE	- vascular dementia patients included. - apathy non-specific outcome reported

(Continues)

TABLE 1 (Continued)

Trial	N (experimental/ control)	Mean age (y)	Intervention	Context	Treatment duration (weeks)	Apathy measure (primary measure)	Outcome[b]	Comments
Gitlin et al[43]	60 (30/30)	79	Tailored activity program or wait-list control	At-home dementia patients and their caregivers	16	Activity engagement measured using a 5-item, investigator-developed index of caregiver report of patient in the past 2 wk	POSITIVE	Apathy non-specific outcome reported
Raglio et al[44]	59	84.4(treatment group) 85.8 (control group)	Music therapy or educational/ entertainment activities	NH	16	NPI	Friedmann $\chi^2 = 8.1$ ($P < 0.05$) for the difference in apathy	- moderate and severe AD, VD, and mixed dementia cases. - effect sizes only for NPI global score changes
Tappen and William[45]	36 (3 men)	83.8 (treatment group) 90.26 (control group)	Therapeutic conversation or care as usual	NH	64	AD-RD Mood Scale	Significant decline in apathy ($F[2,27] = 4.21$, $P = 0.05$)	- moderate and severe AD dementia cases.
Hsieh et al[46]	61	77.56	Reminiscence group therapy	NH	12 on average	AES-C (AES-C, NPI, GDS)	Significant reduction in apathy cognition score ($Z = -1.95$) and apathy behavior score ($Z = -3.10$) in the experimental group ($P < 0.05$)	- not double-blind - greater baseline emotional apathy in the experimental group ($P = 0.04$) - DSM-IV criteria for dementia
Lam et al[47]	74 (37/37)	83.45	Individualized daily activities (functional enhancement program)	Social centers and old aged home for the elderly in Hong Kong	16	NPI (NPI)	POSITIVE	
Niu et al[48]	32 (16/16)	80.56 (experimental group) 79.13 (control group)	Cognitive stimulation	A military sanatorium in China	10	NPI (NPI)	POSITIVE	
Raglio et al[49]	60 (30/30)	85.4 (experimental group) 84.6(control group)	Music therapy	NHs	24	NPI (NPI)	POSITIVE	
Ferrero-Arias et al[50]	146 (73/71)	83.6	Music and art therapy and psychomotor activity or free activities in the day room	NHs or day care centers	8	NPI/DAIR (NPI/DAIR)	POSITIVE	Institutionalized or day care dementia patients
Hattori et al[51]	39 (20/19)	75.3 (experimental group) 73.3 (control group)	Art therapy	Outpatient clinic of a clinical centre	12	Apathy Scale (Apathy Scale)	POSITIVE	

(Continues)

TABLE 1 (Continued)

Trial	N (experimental/control)	Mean age (y)	Intervention	Context	Treatment duration (weeks)	Apathy measure (primary measure)	Outcome[b]	Comments
Kolanowski et al[52]	128	86	Activities tailored to functional level (FL), and personality style of interest (PSI) alone or in combination (FL + PSI).	NHs	3	Passivity and engagement (PDS, C-MAI, time on task, intensity of engagement, ARS, DMPT)	Positive outcome only for differences in engagement when in PSI activities.	- moderate and severe dementia - $MMSE_{PSI} > MMSE_{PSI+FL}$ at baseline - education years in PSI > Education years in FL, PSI + FL and control groups $_{FL}$ at baseline.
Maci et al[53]	14 (7/7)	75 (treatment group) 70.3 (control group)	Cognitive stimulation, physical activity, and socialization	Clinical dementia centre in Spain	12	AES (AES)	POSITIVE	
Leone et al[54]	230 (119/111)	88.325	Nursing home staff education program	Sixteen NHs	16	NPI/AI (NPI/AI)	POSITIVE	13 nursing homes
Leontjevas et al[55]	503	83.6 (dementia units) 76.9 (somatic units)	Structured multidisciplinary (activating strategies, psychotherapy, antidepressant medication) program (AiD)	Dementia special care units and somatic units	Roughly 16	AES-10 item (AES-10 item, CSDD)	Reduction of apathy in dementia units (overall effect across all time point, 2.3; 95% CI, −3.3–1.3; $P < 0.001$; Cohen's $d = -0.35$)[a]	- step-wedged cluster-randomized pseudo-RCT - positive effect mainly attributed to activating strategies
Moyle et al[56]	18	85.3	PARO vs interactive reading	Residential care facility	10	AES (QOL-AD, RAID, AES, GDS, Revised Algase Wandering Scale—NH version, OERS)	Negative for clinical significance (ie, RCI[c] < 1 SD). Cohen's $d = 0.2$	- crossover design - mid-stage to late-stage or DSM-IV-TR criteria for probable dementia
Telenius et al[57]	163 (82/81)	86.9 (experimental group) 86.4 (control group)	Individually fitted, average 18, 50 to 60-min sessions of high intensity physical exercise or control activity	18 NHs	12	NPI-Q-apathy independently (BBS, NPI-Q, BI, CSDD)	Slightly significant mean difference ($P = 0.048$) between groups, at $P < 0.05$. Cohen's $d = 0.3$.	Dementia diagnoses not specified (CDR score 1 or 2)
Treusch et al[58]	117 (67/50)	80.12	"biography-orientated mobilization"	18 NHs in Berlin	40	AES/NPI (AES/NPI)	POSITIVE	
Valentí Soler[79]	101 (at NH) to 110 (at day care center)	84.7	NAO, PARO (phase 1) vs PARO, real dog (phase 2) vs control	Parallel NH and day care center	24	APADEM-NH/AI (G.D.S., severe MMSE, MMSE, NPI, APADEM-NH, AI, QUALID)	Significant improvements in APADEM-NH for both robot groups and in APADEM-cognitive inertia, NPI-apathy/indifference for the NAO group found only in phase 1, in nursing homes (all $P < 0.05$, uncorrected) no significant differences found for the day care center.	- randomization carried out only in NHs – NAO followed by PARO was implemented in the day care center. - 84%–88% AD, 7%–11% mixed dementia, 1–2% DLB, 1%–3% PDD or FTD. - 88.5% (phase 1), and 90% (phase 2) were women.

(Continues)

TABLE 1 (Continued)

Trial	*N* (experimental/ control)	Mean age (y)	Intervention	Context	Treatment duration (weeks)	Apathy measure (primary measure)	Outcome[b]	Comments
Amieva et al[59]	653 (499/154) Cognitive training *N* = 170 Reminiscence therapy *N* = 172 Individualized cognitive rehabilitation program *N* = 157	78.7	Individual cognitive therapies cognitive training (group sessions), reminiscence therapy (group sessions), individualized cognitive rehabilitation program (individual sessions) vs controls	40 French clinical sites	104	NPI/apathy inventory (rate of survival at 2 y for patients without moderately severe to severe dementia)	Greater clinical improvement was seen with the individualized cognitive rehabilitation intervention (lower functional disability and delayed institutionalization).	Apathy secondary measure
Di Domenico et al[60]	32	70.46 (AD patients) 70.88 (control group)	Mixed design with a 2 (conditioned stimulus-CS: Non-word vs activity) within-subject × 2 (unconditioned stimulus-US: neutral vs positive) × 2 (group: AD patients vs healthy subjects) between-subjects manipulation	Outpatient clinics	12	AES (AES)	- significant effects of group ($F(1,48) = 54.07$, $P < 0.001$, $\eta_p^2 = 0.529$) CS ($F(1,48) = 58.91$, $P < 0.001$, $\eta_p^2 = 0.551$) and US ($F(1,48) = 11.58$, $P < 0.01$, $\eta_p^2 = 0.194$) to "yes" responses to engage in activity. - apathy motivation reached healthy controls' baseline motivation	- probable AD (NINCDS-ADRDA criteria) - AES > 45, GDS < 20 included - AD with apathy vs healthy older subjects
Ikemata et al[61]	37	86.89 (treatment group) 86.74 (control group)	Progressive muscle relaxation by 7 group of muscles: forearm and upper arm; lower leg and front thigh; lower leg and rear thigh; chest; shoulder; forehead; periorbital and lower law	NH	13	NPI-NH (NPI-NH, NM scale)	- apathy: Baseline, 1.17 ± 3.00; 30 d PI, 0.94 ± 2.92; 90 d PI, 0.44 ± 1.42. - interest, volition, social relationship: Baseline, 6.06 ± 2.29; 30 d PI, 6.22 ± 2.37; 90 d PI, 7.22 ± 1.90. (values are mean ± SD. Differences are considered significant at $P < 0.05$)[a]	- lack a diagnosis based on clinical criteria. - clinical type of dementia not specified in 27 subjects.
Manera et al[62]	57	75 (MCI patients) 76.3 (AD patients)	Attentional task (written condition vs virtual reality condition)	Memory center and research unit	N/A	AI	No significant between-group differences.	- mild to moderate dementia (ICD-10 criteria) and MCI (NIA-AA criteria) subjects were compared - exploratory study

(Continues)

TABLE 1 (Continued)

Trial	*N* (experimental/control)	Mean age (y)	Intervention	Context	Treatment duration (weeks)	Apathy measure (primary measure)	Outcome[b]	Comments
Rajkumar et al[63]	273	85.7 (with apathy 84.7)	Evidence-based person-centered care (control) or additional NICE/Alzheimer's Society/Department of Health-Guided antipsychotic review (AR) alone, or in combination with either 1 h/w exercise (EX) or 1 h/w social interaction (SI) (or 20% increase if existing at baseline)	Nursing home (NH)	36	NPI-NH (antipsychotic reduction rate. NPI-NH)	- Cohen's d = 0.49, for AR + SI vs AR alone[a] - Cohen's d = 0.2, for AR + EX vs AR alone[a]	- strong design - clinical diagnostic criteria for type of dementia not stated - apathy at baseline associated with study withdrawal (χ^2 = 8.04; df = 1; P = 0.005) - approximately 30% less completed the study
Sanchez et al[64]	32 (11/10) N = 11 for 1-to-1 activity session	85.4	Multisensory stimulation environment vs 1-to-1 activity session vs control group	Specialized dementia elderly center	16 and 8-week follow-up	NPI (NPI)	MSSE may have better effects on neuropsychiatric symptoms and dementia severity in comparison with 1-to-1 activity sessions	Improvements found during the intervention were lost in the follow-up period

[a]Corrected for multiple comparisons.

[b]Outcomes considered as positive or negative are for statistical significant results (P < 0.05) favoring the specific treatment for apathy.

[c]RCI: Reliability Change Index (difference in pre-intervention and post-intervention apathy score divided by the standard error of the difference to establish a cut-off change score for clinical significance at 95% confidence [ie, 1.96 SD]).

Abbreviations: AARS, Philadelphia Geriatric Center Apparent Affect Rating Scale; AES, Apathy Evaluation Scale; AD, Alzheimer's disease; AD-RD Mood Scale, Alzheimer's disease and Related Disorders Mood Scale; AES-C, Apathy Evaluation Scale, Clinician-administered; AI, Apathy Inventory; AiD, Act in case of Depression; APADEM-NH, Apathy Scale for Institutionalized Patients with Dementia-Nursing Home version; ARS(PARS), Philadelphia Geriatric Center Affect Rating Scale; AS, Apathy Scale; BBS, Berg Balance Scale; BI, Barthel index; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease scale; BIP, Behavior observation scale for Psychogeriatric in-patients; CMAI, Cohen-Mansfield Agitation Inventory; CSDD, Cornell Scale for Depression in Dementia; DMPT, Dementia Mood Picture Test; FACS, Functional Assessment of Communication Skills for Adults; GDS, Geriatric Depression Scale; GDS, Global Deterioration Scale; GRGS, Geriatric Resident Goal Scale; ICD-10, International Classification of Diseases—10th revision; INTERACT, Interventions to Reduce Acute Care Transfers; ITT, Intention-to treat; LPRS, London Psychogeriatric Rating Scale; MCI, Mild Cognitive Impairment; MOSES, Multidimensional Observational Scale for Elderly Subjects; MSS: Multi-sensory stimulation; NAO, Humanoid social robot; NIA-AA, National Institute on Ageing and Alzheimer's Association; NICE, National Institute for Health and Care Excellence; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NM scale, Nishimura Mental State scale for the elderly; NPI, Neuropsychiatric Inventory; NPI-NH, Neuropsychiatric Inventory—Nursing Home; NPI-Q, NPI brief version; N/A, Not available; OERS, Observed Emotion Rating Scale; PARO, animal-shaped social robot; PDS, Passivity in dementia scale; PGCMS, Philadelphia Geriatric Center Morale Scale; QOL-AD, Quality of Life in Alzheimer's Disease Scale; QUALID, Quality of Life in Late-stage Dementia; RAID, Rating Anxiety in Dementia Scale; SD, Standard deviation; SES, Social Engagement Scale; SOAPD, Scale for the Observation of Agitation in Persons with Dementia; VAS, Visual Analog Scale; VD, Vascular Dementia; WIB, Well-being/Ill-being Scale.

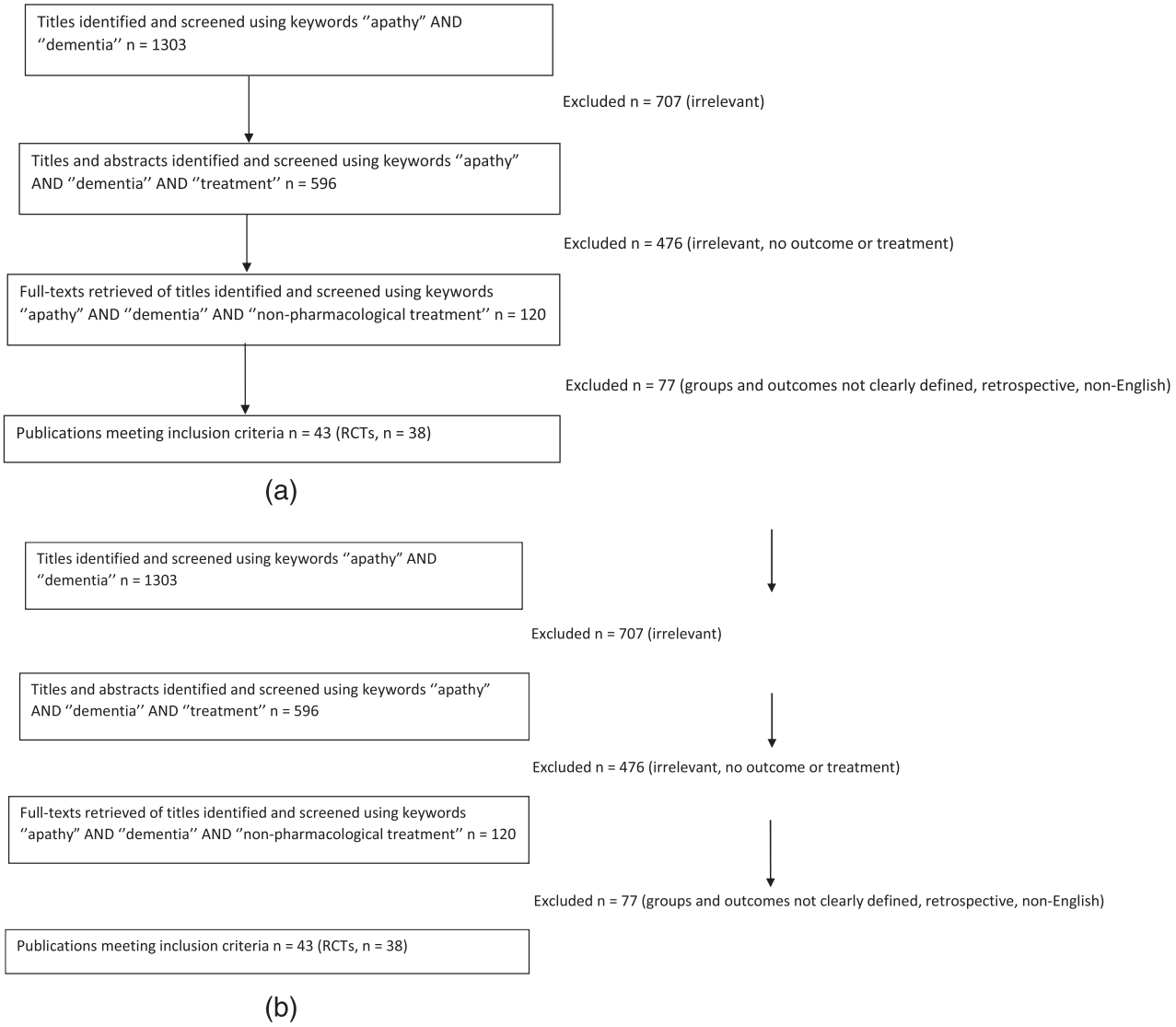

FIGURE 1 Flow chart of study selection process

activity programming, family support) versus usual care was assessed in AD patients over 12 months. A significant increase for activities and time use in experimental group was found vs control group. Fifty-four home residents with AD took part in the study by Camberg et al[31] in order to evaluate the efficacy of Simulated Presence, a personalized audiotapes approach. Staff reported Simulated Presence improved withdrawn behavior 69% of the time. Simulated Presence increased the level of interest more than placebo and usual care. Baker et al[32] conducted a RCT to compare MSS with a credible control of 1-to-1 activities in 33 patients. Significant interaction effect on "attentiveness to the environment" (assessed by Interact Short) was observed. In the study by Cott, Dawson, Sidani, and Wells,[33] the effects of a walking/talking program on residents' communication, ambulation, and level of function were investigated. There were no statistically significant results. In the study by Schrijnemaekers et al,[34] 151 residents with cognitive impairment and behavioral problems were randomly allocated to an intervention (emotion-oriented care) or control group. There were not any significant results in favor of the intervention group based on the short version of the GIP. Baker et al[35] compared MSS vs a control activity. Both groups related better to others and were less bored/inactive after sessions. The severely cognitively impaired in the MSS group were significantly less apathetic on the BRS apathy subscale after sessions vs baseline scores.

One RCT study by Politis et al[36] evaluated the efficacy of a kit-based activity intervention vs 1-on-1 meetings with an activity therapist, in reducing apathy in 36 patients. Apathy improved substantially in both treatment groups. It was suggested that regular 1-on-1 personal patient contact with staff members may improve apathy symptoms. Chapman, Weiner, Rackley, Hynan, and Zientz[37] in a RCT evaluated the efficacy of the combined effect of a cognitive-communication program plus donepezil vs donepezil alone in 54 patients. A Group × Time interaction was found for the donepezil-plus-stimulation group in apathy vs donepezil-only group.

In a single-blinded, parallel-groups (1 intervention, 1 comparison, 1 no-intervention group), RCT was adopted to investigate whether a specific reminiscence program leads to improved psychosocial well-being in demented nursing home residents.[38] There was a significant improvement in psychosocial well-being only for the intervention group. Finnema et al[39] in a multi-site RCT with matched groups

TABLE 2 Study quality assessments using the PEDro scale (rated items only are displayed) and Oxford Center of Evidence-Based Medicine (OCEBM)

Author	PEDro Random group allocation	PEDro Allocation concealed	PEDro Baseline group similarity	PEDro Blinding of all subjects	PEDro Blinding of all therapists	PEDro Blinding of all assessors of at least 1 key outcome	PEDro Less than 15% dropouts	PEDro Intention to treat analysis of at least 1 key outcome	PEDro Between-group statistical comparisons reported for at least 1 key outcome	PEDro Point measurements and measurements of variability provided for at least 1 key outcome	PEDro Total yes	PEDro Quality	OCEBM
Lawton et al[30]	N	N	Y	N	N	N	N	N	Y	Y	3	Poor	C
Camberg et al[31]	N	Y	N	N	Y	Y	Y	Y	Y	Y	7	High	B
Baker et al[32]	Y	N	N	N	N	N	Y	Y	Y	Y	5	Moderate	B
Cott et al[33]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	High	B
Schrijnemaekers et al[34]	Y	N	Y	N	N	N	Y	Y	Y	Y	6	Moderate	B
Baker et al[35]	Y	N	N	N	N	N	Y	Y	Y	Y	6	Moderate	B
Politis et al[36]	Y	N	N	N	N	Y	Y	Y	Y	Y	6	Moderate	B
Chapman et al[37]	Y	Y	N	N	N	Y	N	Y	Y	Y	6	Moderate	B
Lai et al[38]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	9	High	B
Finemma et al[39]	Y	N	Y	N	Y	Y	N	N	N	Y	5	Moderate	B
van Weert et al[40]	Y	N	Y	N	N	Y	Y	N	Y	Y	6	Moderate	B
Holmes et al[41]	Y	N	N	Y	Y	Y	Y	N	N	N	5	Moderate	B
Staal et al[42]	Y	N	Y	N	N	Y	Y	N	Y	Y	6	Moderate	B
Tadaka et al[43]	Y	Y	N	N	Y	Y	N	Y	N	N	5	Moderate	B
Gitlin et al[44]	Y	Y	Y	N	Y	Y	Y	Y	N	N	7	High	B
Raglio et al[45]	Y	N	Y	N	N	Y	Y	N	Y	Y	6	Moderate	B
Tappen et al[46]	Y	N	N	N	N	Y	N	N	Y	Y	4	Poor	C
Hsieh et al[47]	Y	N	Y	N	N	N	Y	N	N	Y	4	Poor	C
Lam et al[48]	Y	N	Y	Y	Y	Y	N	Y	Y	Y	8	High	B
Niu et al[49]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7	High	B
Raglio et al[50]	N	N	Y	N	N	Y	Y	N	Y	Y	5	Moderate	B
Ferrero-Arias et al[51]	Y	Y	Y	N	N	Y	N	Y	Y	Y	7	High	B
Hattori et al[52]	Y	N	Y	N	N	N	Y	N	Y	Y	5	Moderate	B
Kolanowski et al[53]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	High	B
Maci et al[54]	Y	N	N	N	N	Y	N	N	Y	Y	4	Poor	C
Leone et al[55]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7	High	B
Leontjevas et al[56]	N	Y	N	Y	N	Y	N	Y	Y	Y	6	Moderate	B
Moyle et al[57]	Y	N	Y	N	N	Y	N	N	Y	Y	5	Moderate	B
Telenius et al[58]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	High	B

(Continues)

TABLE 2 (Continued)

Author	PEDro Random group allocation	PEDro Allocation concealed	PEDro Baseline group similarity	PEDro Blinding of all subjects	PEDro Blinding of all therapists	PEDro Blinding of all assessors of at least 1 key outcome	PEDro Less than 15% dropouts	PEDro Intention to treat analysis of at least 1 key outcome	PEDro Between-group statistical comparisons reported for at least 1 key outcome	PEDro Point measurements and measurements of variability provided for at least 1 key outcome	PEDro Total yes	PEDro Quality	OCEBM
Treusch et al[59]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7	High	B
Valenti Soler et al[60]	Y	N	Y	N	Y	Y	Y	N	Y	Y	7	High	B
Amieva et al[61]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	High	B
Di Domenico et al[60]	Y	N	N	Y	N	N	N	N	Y	Y	4	Poor	C
Ikemata et al[63]	Y	N	Y	N	N	N	Y	N	Y	Y	5	Moderate	B
Manera et al[64]	Y	N	N	N	N	N	N	Y	Y	Y	4	Poor	C
Rajkumar et al[65]	Y	Y	Y	N	Y	Y	N	N	Y	Y	7	High	B
Sanchez et al[66]	Y	N	Y	N	N	N	Y	N	N	N	3	Poor	C

Abbreviations: OCEBM, Levels of Evidence and Grades of Recommendation with Oxford Centre for Evidence-Based Medicine System; PEDro: PEDro Rating Scale; Y, yes; N, no.

compared emotion-oriented care to usual care. A total of 146 elderly residents with dementia and 99 nursing assistants took part in the study. No significant differences (assessed with BIP apathy score) were found between groups. In a study by Kolanowski et al,[25] the efficacy of recreational activities, derived from the Need-driven Dementia-compromised Behavior (NDB) model, was assessed in 30 patients. Significantly less passivity was found under NDB-derived and matched to interest only treatments vs the matched to skill level only treatment or baseline. In the study by van Weert, van Dulmen, Spreeuwenberg, Ribbe and Bensing[40] residents receiving snoezel care demonstrated a significant treatment effect with respect to their level of apathetic behavior vs control group that received usual nursing home care (assessed with the Dutch Behavior Observation Scale for Psychogeriatric In-patients [BIP]). Holmes, Knights, Dean, Hodkinson, and Hopkins[41] in a RCT evaluated the effect of live interactive music on apathy vs silence and pre-recorded music in 32 patients. Live interactive music had positive engagement effects in subjects. Staal et al[42] conducted a RCT to compare MSBT vs a structured activity session in 24 participants. Utilizing MSBT with inpatient care may reduce apathy more than standard care alone.

In the RCT study by Tadaka and Kanagawa,[43] 24 patients were randomized to a reminiscence group or control group. The intervention group exhibited significant improvement of withdrawal vs control group. Tondi et al,[27] in a case-control study in 50 patients, found that apathy improved in subjects who underwent the validation therapy vs control group. Gitlin et al[44] randomized 60 patients to tailored activity program (TAP) or wait-list control. Caregivers reported greater activity engagement and ability to keep busy in treatment groups vs control groups.

In the study by Raglio et al[45] in 59 patients with dementia, music therapy improved significantly NPI apathy scores in the experimental group vs control group. In the study by Tappen and Williams,[46] therapeutic counseling approach was found to be efficacious in improving apathy scores (assessed with AD and Related Disorders Mood Scale) in nursing home AD patients. In the study by Hsieh et al,[47] a reminiscence group therapy intervention improved symptoms of apathy (assessed with AES-C). Lam et al[48] randomized 2 groups of patients to individualized (FEP) or general occupational therapy. At 1 month post-FEP, there was a significant improvement in NPI-apathy scores in the intervention group, while from 1 to 4-month post-FEP, rebound of apathy occurred. The authors suggested a potential benefit for individualized occupational therapy. In the 10-week RCT study by Niu, Tan, Guan, Zhang, and Wang[49] in 32 patients, cognitive stimulation therapy had significant efficacy in lowering apathy vs control treatment. Raglio et al[50] undertook a RCT in 60 patients and found that NPI apathy scores significantly improved in the music therapy group, vs control group. In the RCT by Ferrero-Arias et al,[51] 146 patients were randomized to initial intervention (music, art therapy, psychomotor activity) or initial control (free activities in day room). A significant difference between intervention and control periods was found with DAIR scale, especially in patients with moderate apathy. Hattori, Hattori, Hokao, Mizushima, and Mase[52] evaluated with a RCT the usefulness of art therapy vs calculation training in 39 patients. Significant improvement was reported in the Apathy Scale of the art therapy

group. In a RCT by Kolanowski, Litaker, Buettner, Moeller, and Costa,[53] activities tailored to functional level and personality style of interest were found to improve passive behavior (assessed with Passivity in Dementia Scale [PDS]) in demented patients. Fischer-Terworth and Probst[29] randomized 2 groups of patients to a multi-component psychological intervention or standard occupational therapy. After 6 months, the experimental group exhibited improvement in apathy NPI scores. Maci et al[54] in a RCT assessed the effect of a 3-month program of cognitive stimulation, physical activity and socialization vs usual home activities in 14 patients. In the active treatment group, significant improvement in the apathy AES scores was found. Johnson et al,[24] in a non-RCT, compared standard of care for dementia-related neuropsychiatric crisis (hospitalized) vs a pilot coordinated care intervention project in 129 patients. Significant improvements were observed, for the coordinated care intervention group, in the apathy scores of the NPI-Q patient symptom scale and the caregiver distress scale. Leone et al,[55] in a RCT, assessed the effect of a nursing home staff education program in 230 patients. In the intervention group, a significant decrease in the emotional blunting score dimension was found in the Apathy Inventory and the Group Observation Scale.

In a cluster RCT, Leontjevas et al[56] showed that depression management program reduces apathy (assessed with the 10-item AES) in dementia units. Moyle et al[57] in a pilot cross-over RCT found that the use of a companion robot did not result in improvement in apathy scores (assessed with AES) in 18 demented patients. In the pilot study by Manera et al,[26] the efficacy of a serious game "Kitchen and cooking" was assessed with the Apathy Inventory in 9 MCI and 12 AD patients. Apathetic participants were reported to be as interested, motivated, and satisfied by the game experience as non-apathetic participants. Telenius et al[58] conducted a single-blinded RCT in 170 persons with dementia living in nursing homes. The intervention consisted of intensive strengthening and balance exercises in small groups twice a week for 12 weeks. The level of apathy was lower in the exercise group after the intervention vs control group. Treusch et al[59] conducted a 10-month RCT in 117 patients and found that increase in apathy AES scores was significantly reduced in a "biography-orientated mobilization" group vs control group. In a study by Valenti Soler et al,[60] patients with dementia who came in contact with social robots exhibited an improvement in NPI apathy scores. In the multicenter RCT by Amieva et al[61] that compared receiving standardized programs of cognitive training (group sessions), with reminiscence therapy (group sessions), individualized cognitive rehabilitation program (individual sessions), and usual care, 653 AD outpatients were recruited. The individualized cognitive rehabilitation intervention was the only one to provide clinically significant results.

Di Domenico, Palumbo, Fairfield, and Mammarella[62] in a study involving 26 AD patients and 26 healthy controls demonstrated that a brief emotional shaping intervention, developed to reduce apathy (assessed with AES) and increase willingness-to-do in AD patients, was effective in increasing patients' immediate motivation. In a study by Ikemata and Momose,[63] 44 demented patients were randomly assigned to receive a progressive muscle relaxation treatment or activities as usual. The intervention group showed significantly lower NPI-NH Apathy scores and significant improvement in the Interest, Volition, and Social relationships scores on the Mental State Scale, with improvement in the activities of daily living total. In the study by Manera et al,[64] participants reported a preference for the virtual reality (VR) condition vs the paper condition, even if the task was more difficult. In a cluster RCT by Rajkumar et al,[65] antipsychotic review in combination with either social interaction or exercise significantly reduced NPI-NH apathy scores in demented patients living in nursing homes. In the pilot RCT by Sanchez et al,[66] a positive effect was observed on neuropsychiatric symptoms and dementia severity in the MSS environment (MSSE) treatment vs the activity group. Finally, in a retrospective cohort study (C) by Tokuchi et al,[28] the effects of a galantamine therapy vs a combination therapy of galantamine plus ambulatory cognitive rehabilitation were investigated in AD patients. The Apathy Scale score showed significant improvements in the combination therapy group vs the galantamine group at 3 months ($P = 0.04$) and 6 months of treatment ($P = 0.03$)

4 | DISCUSSION

4.1 | Principal findings

We attempted to systematically review non-pharmacological treatments for apathy in aging neurodegenerative dementia including combined treatments. Although, a real effect is not quantified and limitations in study design are inherently applied, the strength of evidence, in terms of level and quality of the aggregated studies, suggests that apathy improvements may occur in this group of patients with a variety of non-pharmacological interventions.

4.2 | Strengths and weaknesses

4.2.1 | Appraisal of methodological quality of the review

While a certain amount of studies showed at least some benefit of various interventions for apathetic symptoms, they often have not primarily focused on apathy or the tools to measure apathy were not validated or appropriate. Using a real world situation-targeted design for our review to explore effectiveness adds to the existing study heterogeneity. We were only able to review the studies by combining them in a synthesis, although the studies were not similar enough. We did not perform a sensitivity analysis. To evaluate the reported evidence, we used 2 published semi-quantitative methods. Several limitations apply to this review. First, any conclusions drawn are relying on the quality of the included studies. Inherent limitations (eg, blinding of all the study members involved) limit proper conduct of trials; however, there are ways to adjust and improve in this regard. Second, while not so prone to publication bias, as apathy was secondary outcome in more than half of the cases, selective reporting cannot be excluded. Third, publication bias was not appraised, while in most of the studies, allocation concealment, as well as concealment before randomization, was not stated explicitly. It is worth noting that a study dropout higher than 15% was identified in 14 of the 37 trials assessed for quality.

4.2.2 | Relation to other reviews, in particular considering any differences

There are only few reviews that specifically have focused on apathy outcomes in dementia following non-pharmacological

interventions.[67-69] Moreover, a variable amount of studies with combined treatments might have been excluded by the review design in older reviews. Our intention was to capture treatment benefits for apathy throughout non-pharmacological treatments and settings wishing to pragmatically highlight diagnostic and therapeutic issues. We demonstrated that a number of non-pharmacological interventions alone or as combined multidisciplinary programs might offer more choices for treatment for the demented patient with apathy.

Other reviews[66-68] have yielded similar results to our findings. Verkaik et al[68] proposed that MSBT—Snoezelen might be effective for apathy. Lane-Brown and Tate[67] found that music therapy and cognitive rehabilitation appear to be effective. Politis et al[36] proposed that an activity therapist who is creative and well versed in the patient's interests might be beneficial for the apathetic AD patient. Furthermore, Treusch et al[58] suggested that the use of physical activation and biography-orientated mobilization could motivate demented patients. Moreover, Brodaty and Burns[65] propose that individually provided therapeutic activities may have the best available evidence for effectiveness in dementia. Additionally, education is necessary to assist families in understanding apathy, as apathetic patients are often characterized lazy or oppositional.[18]

The diversity of the outcome measures employed may pose a limitation to the study design. In the systematic review by Radakovic, Harley, Abrahams, and Starr,[69] among the highest quality apathy scales in AD were the Dementia Apathy Interview and Rating (DAIR) and the Apathy Evaluation Scale-Clinical version (AES-C)—each appeared once in the present review. While in the review by Clarke et al,[70] the most psychometrically robust apathy measures in dementia appeared to be the Apathy Evaluation Scale (AES) and the apathy subscale of NPI, while for AD patients, the DAIR was found to be the best measure.

5 | IMPLICATIONS

The review updates the existing literature on the effectiveness of non-pharmacological treatments covering also combined treatments trials. Regarding the non-pharmacological type of treatment that could help in different kinds of apathy, it is worth noting the following: the stimulation retreat model of care increased external engagement (improved lack of interest and lack of initiative),[30] the simulated presence (a personalized audiotapes approach) improved withdrawn behavior and increased the level of interest[31]; MSS improved lack of interest and lack of initiative,[32,35] a kit-based activity intervention improved lack of interest and lack of initiative[36]; recreational activities, derived from the Need-driven Dementia-compromised Behavior (NDB) model, improved emotional blunting,[25] live interactive music had positive engagement effects and improved lack of interest and lack of initiative,[40] while Snoezelen (MSBT) improved lack of interest[41]; a reminiscence group treatment improved lack of interest and emotional blunting,[42] while in a different study,[46] a reminiscence group therapy intervention improved behavior, cognition subscales of AES. Gitlin et al,[43] using a TAP, improved lack of interest and lack of initiative; Ferrero-Arias et al[50] using music and art therapy and psychomotor activity improved engagement, while Kolanowski et al[52] using activities tailored to functional level and personality style of interest improved passive behavior and engagement. An individualized cognitive rehabilitation intervention resulted in lowered functional disability and delayed institutionalization,[60] while brief emotional shaping intervention improved lack of interest and lack of initiative[61]; finally, progressive muscle relaxation treatment improved significantly interest, volition, and social relationships.[62]

The results could inform future studies in terms of study design and treatment selection. It appears that combined treatments[37,49] might be of greater benefit vs monotherapies. Apathy seems to respond to a series of non-pharmacological interventions that when are appropriately applied could be effective. However, inherently, the design (eg, single-blinding) of studies assessing non-pharmacological interventions is not robust. Moreover, it is often not reported if these patients were taking any medication.[43,50] A meta-analysis to compute the effect sizes and assess the heterogeneity of the studies in context is needed and is our future scope.

5.1 | Implications for practice

Non-pharmacological treatments for apathy are quite safe and well accepted. Specifically, more individualized treatments that take into account the patient's past preferences and environmental factors could improve apathy treatment outcomes. Cohen-Mansfield et al[72] proposed that person attributes, environmental factors, and stimulus characteristics all contribute to the level and nature of engagement. Consequently, caregivers may increase the daily functioning of apathetic patients by directly prompting them to initiate activities, using visual cues to behaviours and setting up routines for daily activities.[18,71]

5.1.1 | Implications for research

Apathy is still understudied. Studies should set up their design so that they facilitate symptom expression and engagement (individualized therapies, environmental and cultural considerations, psychoeducation). Issues concerning the design (eg, randomization, blinding) but also the implementation, such as the natural variation of the interventionists (environmental considerations and contextual issues [NHs, day care centers]) are relevant in how the design is implemented and affect outcomes. Problematic allocation concealment and non-double-blind design may positively bias an effect by 41% and 17%, respectively.[74] Further, the current lack of standard and widely accepted tools concerning apathy measurement differentially adds to studies' heterogeneity and influences outcomes and their appraisal. Because most of the studies aimed at effectiveness of the intervention, it is critical to incorporate more efficacy studies criteria, in order to add internal validity to generalizability (eg CONsolidated Standards of Reporting Trials [CONSORT] statement). Consequently, recommendations[75] on the design of clinical trials on apathy have recently been published. Clinical trials implementing combination strategies are of interest. It would be also interesting to investigate health outcomes and individual implications by interventions administered for longer periods against the cost.

6 | CONCLUSIONS

We believe that apathetic patients with dementia could benefit from individualized treatment that would stem from a combination of specific evidence-based pharmacologic and non-pharmacologic interventions.[76-78] This combination should be evaluated, and treatment effects both on apathy and its consequences in quality of life, physical conditioning, and caregiver state should be investigated. Consequently, Kales et al[77,79] proposed that the Describe, Investigate, Create, Evaluate (DICE) approach may enable clinicians to choose optimal treatment plans for the management of neuropsychiatric symptoms by considering conjointly the role of specific non-pharmacological, medical, and pharmacological treatment. Finally, the incorporation of targeted lifestyle modifications and context interventions, including exercise, leisure activities, cognitive stimulation, and social activities, might be effective for prevention of apathy and MCI progression.[80]

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

ORCID

Christos Theleritis http://orcid.org/0000-0002-7313-6908
Kostas Siarkos http://orcid.org/0000-0002-3366-2989
Antonios Politis http://orcid.org/0000-0003-0261-7517

REFERENCES

1. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology*. 1996;46(1):130-135. https://doi.org/10.1212/WNL.46.1.130
2. Benoit M, Dygai I, Migneco O, et al. Behavioral and psychological symptoms in Alzheimer's disease. Relation between apathy and regional cerebral perfusion. *Dement Geriatr Cogn Disord*. 1999;10(6):511-517. https://doi.org/10.1159/000017198
3. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology*. 1997;48(suppl 6):s10-s16. https://doi.org/10.1212/WNL.48.5_Suppl_6.10S
4. 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. *Am J Psychiatry*. 2000;157(5):708-714. https://doi.org/10.1176/appi.ajp.157.5.708
5. 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*. 2002;288(12):1475-1483. https://doi.org/10.1001/jama.288.12.1475
6. Lyketsos CG, Carrillo MC, Ryan JM, et al. Neuropsychiatric symptoms in Alzheimer' disease. *Alzheimers Dement*. 2011;7(5):532-539. https://doi.org/10.1016/j.jalz.2011.05.2410
7. Cummings JL, Diaz C, Levy M, Binetti G, Litvan II. Behavioral syndromes in neurodegenerative diseases: Frequency and significance. *Semin Clin Neuropsychiatry*. 1996;1:241-247. https://doi.org/10.1053/SCNP00100241
8. Marin RS. Differential diagnosis and classification of apathy. *Am J Psychiatry*. 1990;147(1):22-30. https://doi.org/10.1176/ajp.147.1.22
9. Starkstein SE, Petracca G, Chemerinski E, Kremer J. Syndromic validity of apathy in Alzheimer's disease. *Am J Psychiatry*. 2001;158(6):872-877. https://doi.org/10.1176/appi.ajp.158.6.872
10. Robert P, Onyike CU, Leentjens AFG, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry*. 2009;24(2):98-104. https://doi.org/10.1016/j.eurpsy.2008.09.001
11. Mulin E, Leone E, Dujardin K, et al. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry*. 2011;26(2):158-165. https://doi.org/10.1002/gps.2508
12. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex*. 2006;16(7):916-928. https://doi.org/10.1093/cercor/bhj043
13. Lyketsos CG, Rosenblatt A, Rabins P. Forgotten frontal lobe syndrome or "executive dysfunction syndrome". *Psychosomatics*. 2004;45(3):247-255. https://doi.org/10.1176/appi.psy.45.3.247
14. Theleritis C, Politis A, Siarkos K, Lyketsos CG. A review of neuroimaging findings of apathy in Alzheimer's disease. *Int Psychogeriatr*. 2014;26(2):195-207. https://doi.org/10.1017/S1041610213001725
15. Drijgers RL, Verhey FR, Leentjens AF, Köhler S, Aalten P. Neuropsychological correlates of apathy in mild cognitive impairment and Alzheimer's disease: the role of executive functioning. *Int Psychogeriatr*. 2011;23(8):1327-1333. https://doi.org/10.1017/S1041610211001037
16. Clarke DE, Ko JY, Lyketsos C, Rebok GW, Eaton WW. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *Int Psychogeriatr*. 2010;22(5):819-829. https://doi.org/10.1017/1041610209991402
17. Onyike CU, Sheppard JME, Tschanz JT, et al. Epidemiology of apathy in older adults: the Cache County Study. *Am J Geriatr Psychiatry*. 2007;15(5):365-375. https://doi.org/10.1097/01.JGP.0000235689.42910.0d
18. Landes AM, Sperry SD, Strauss ME, Geldmacher DS. Apathy in Alzheimer's disease. *J Am Geriatr Soc*. 2001;49(12):1700-1707. https://doi.org/10.1046/j.1532-5415.2001.49282.x
19. Politis AM, Mayer LS, Passa M, Maillis A, Lyketsos CG. Validity and reliability of the newly translated Hellenic Neuropsychiatric Inventory (H-NPI) applied to Greek outpatients with Alzheimer's disease: a study of disturbing behaviors among referrals to a memory clinic. *Int J Geriatr Psychiatry*. 2004;19(3):203-208. https://doi.org/10.1002/gps.1045
20. Theleritis C, Siarkos K, Katirtzoglou E, Politis A. Pharmacological and nonpharmacological treatment for apathy in Alzheimer Disease: a systematic review across modalities. *J Geriatr Psychiatry Neurol*. 2017;30(1):26-49. https://doi.org/10.1177/0891988716678684
21. Oxford Centre for Evidence-Based Medicine. Medicine OCfE-b: levels of evidence and grades of recommendation. University of Oxford; 2009. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed March 1, 2017.
22. Maher C, Sherrington C, Herbert R, Moseley A, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther*. 2003;83(8):713-721. https://doi.org/10.1093/ptj/83.8.713
23. Harvey L, Herbert R, Crosbie J. Does stretch induce lasting increases in joint ROM? A systematic review. *Physiother Res Int*. 2002;7(1):1-13. https://doi.org/10.1002/pri.236
24. Johnson DK, Niedens M, Wilson JR, Swartzendruber L, Yeager A, Jones K. Treatment outcomes of a crisis intervention program for dementia with severe psychiatric complications: the Kansas bridge project. *Gerontologist*. 2013;53(1):102-112. https://doi.org/10.1093/geront/gns104
25. Kolanowski AM, Litaker M, Buettner L. 2005. Efficacy of theory based activities for behavioral symptoms of dementia. *Nurs Res* 54(4):219–228. https://ovidsp.uk.ovid.com/sp3.24.0a/ovidweb.cgi?&S=AMLFPDLHNCHFMEHCFNHKIDBGMBMDAA00&Link+Set=S.sh.22%7c27%7csl_10 Accessed February 27, 2017.
26. Manera V, Petit PD, Derreumaux A. 'Kitchen and cooking', a serious game for mild cognitive impairment and Alzheimer's disease: a pilot study. *Front Aging Neurosci*. 2015;7:24. https://doi.org/10.3389/fnagi.2015.00024.eCollection
27. Tondi L, Ribani L, Bottazzi M, Viscomi G, Vulkano V. Validation therapy (VT) in nursing home: a case-control study. *Arch Gerontol Geriatr*. 2007;44(suppl 1):407-411. https://doi.org/10.1016/j.archger.2007.01.057

28. Tokuchi R, Hishikawa N, Matsuzono K, et al. Cognitive and affective benefits of combination therapy with galantamine plus cognitive rehabilitation for Alzheimer's disease. *Geriatr Gerontol Int*. 2016;16(4):440-445. https://doi.org/10.1111/ggi.12488

29. Fischer-Terworth C, Probst P. Effects of a psychological group intervention on neuropsychiatric symptoms and communication in Alzheimer's dementia. *Z Gerontol Geriatr*. 2012;45(5):392-397. https://doi.org/10.1007/s00391-012-0296-4

30. Lawton MP, Van Haitsma K, Klapper J, et al. A stimulation-retreat special care unit for elders with dementing illness. *Int Psychogeriatr*. 1998;10(4):379-395. https://doi.org/10.1017/S104161029800547X

31. Camberg L, Woods P, Ooi WL, et al. Evaluation of simulated presence: a personalized approach to enhance well-being in persons with Alzheimer's disease. *J Am Geriatr Soc*. 1999;47(4):446-452. https://doi.org/10.1111/j.1532-5415.1999.tb07237.x

32. Baker R, Bell S, Baker E, et al. A randomized controlled trial of the effects of multi-sensory stimulation (MSS) for people with dementia. *Br J Clin Psychol*. 2001;40(pt 1):81-96. https://doi.org/10.1348/014466501163508

33. Cott CA, Dawson P, Sidani S, Wells D. The effects of a walking/talking program on communication, ambulation, and functional status in residents with Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2002;16(2):81-87. https://doi.org/10.1097/01.WAD.0000015569.76518.F1

34. Schrijnemaekers V, van Rossum E, Candel M, et al. Effects of emotion-oriented care on elderly people with cognitive impairment and behavioral problems. *Int J Geriatr Psychiatry*. 2002;17(10):926-937. https://doi.org/10.1002/gps.681

35. Baker R, Holloway J, Holtkamp CC, et al. Effects of multisensory stimulation for people with dementia. *J Adv Nurs*. 2003;43(5):465-477. https://doi.org/10.1046/j.1365-2648.2003.02744.x

36. Politis AM, Vozzella S, Mayer LS, Onyike CU, Baker AS, Lyketsos CG. A randomized, controlled, clinical trial of activity therapy for apathy in patients with dementia residing in long term care. *Int J Geriatr Psychiatry*. 2004;19(11):1087-1094. https://doi.org/10.1002/gps.1215

37. Chapman SB, Weiner MF, Rackley A, Hynan LS, Zientz J. Effects of cognitive-communication stimulation for Alzheimer's disease patients treated with donepezil. *J Speech Lang Hear Res*. 2004;47(5):1149-1163. https://doi.org/10.1044/1092-4388(2004/085)

38. Lai CKY, Chi I, Kayser-Jones J. A randomized controlled trial of a specific reminiscence approach to promote the well-being of nursing home residents with dementia. *Int Psychogeriatr*. 2004;16:33-49. https://doi.org/10.1017/S1041610204000055

39. Finnema E, Dröes R-M, Ettema T, et al. The effect of integrated emotion-oriented care versus usual care on elderly persons with dementia in the nursing home and on nursing assistants: a randomized clinical trial. *Int J Geriatr Psychiatry*. 2005;20(4):330-343. https://doi.org/10.1002/gps.1286

40. van Weert JC, van Dulmen AM, Spreeuwenberg PM, Ribbe MW, Bensing JM. Behavioral and mood effects of snoezelen integrated into 24-hour dementia care. *J Am Geriatr Soc*. 2005;53(1):24-33. https://doi.org/10.1111/j.1532-5415.2005.53006.x

41. Holmes C, Knights A, Dean C, Hodkinson S, Hopkins V. Keep music live: Music and the alleviation of apathy in dementia subjects. *Int Psychogeriatr*. 2006;18(4):623-630. https://doi.org/10.1017/S1041610206003887

42. Staal JA, Sacks A, Matheis R, et al. The effects of Snoezelen (multi-sensory behavior therapy) and psychiatric care on agitation, apathy, and activities of daily living in dementia patients on a short term geriatric psychiatric inpatient unit. *Int J Psychiatry Med*. 2007;37(4):357-370. https://doi.org/10.2190/PM.37.4.a

43. Tadaka E, Kanagawa K. Effects of reminiscence group in elderly people with Alzheimer disease and vascular dementia in a community setting. *Geriatr Gerontol Int*. 2007;7(2):167-173. https://doi.org/10.1111/j.1447-0594.2007.00381.x

44. Gitlin LN, Winter L, Burke J, Chernett N, Dennis MP, Hauck WW. Tailored activities to manage neuropsychiatric behaviors in persons with dementia and reduce caregiver burden: a randomized pilot study. *Am J Geriatr Psychiatry*. 2008;16(3):229-239. https://doi.org/10.1097/JGP.0b013e318160da72

45. Raglio A, Bellelli G, Traficante D, et al. Efficacy of music therapy in the treatment of behavioral and psychiatric symptoms of dementia. *Alzheimer Dis Assoc Disord*. 2008;22(2):158-162. https://doi.org/10.1097/WAD.0b013e3181630b6f.

46. Tappen RM, Williams CL. Therapeutic conversation to improve mood in nursing home residents with Alzheimer's disease. *Res Gerontol Nurs*. 2009;2(4):267-275. https://doi.org/10.3928/19404921-20090428-02

47. Hsieh C-J, Chang C, Su S-F, et al. Reminiscence group therapy on depression and apathy in nursing home residents with mild-to-moderate dementia. *J Exp Clin. Med*. 2010;2(2):72-78. https://doi.org/10.1016/S1878-3317(10)60012-5

48. Lam LC, Lui VW, Luk DN, et al. Effectiveness of an individualized functional training program on affective disturbances and functional skills in mild and moderate dementia—a randomized control trial. *Int J Geriatr Psychiatry*. 2010;25(2):133-141. https://doi.org/10.1002/gps.2309

49. Niu YX, Tan JP, Guan JQ, Zhang ZQ, Wang LN. Cognitive stimulation therapy in the treatment of neuropsychiatric symptoms in Alzheimer's disease: a randomized controlled trial. *Clin Rehabil*. 2010;24(12):1102-1111. https://doi.org/10.1177/0269215510376004

50. Raglio A, Bellelli G, Traficante D, et al. Efficacy of music therapy treatment based on cycles of sessions: a randomized controlled trial. *Aging Ment Health*. 2010;14(8):900-904. https://doi.org/10.1080/13607861003713158

51. Ferrero-Arias J, Goni-Imızcoz M, Gonzalez-Bernal J, Lara-Ortega F, da Silva-Gonzalez A, Dıez-Lopez M. The efficacy of non pharmacological treatment for dementia-related apathy. *Alzheimer Dis Assoc Disord*. 2011;25(3):213-219. https://doi.org/10.1097/WAD.0b013e3182087dbc

52. Hattori H, Hattori C, Hokao C, Mizushima K, Mase T. Controlled study on the cognitive and psychological effect of coloring and drawing in mild Alzheimer's disease patients. *Geriatr Gerontol Int*. 2011;11(4):431-437. https://doi.org/10.1111/j.1447-0594.2011.00698.x

53. Kolanowski A, Litaker M, Buettner L, Moeller J, Costa PT Jr. A randomized clinical trial of theory-based activities for the behavioral symptoms of dementia in nursing home residents. *J Am Geriatr Soc*. 2011;59(6):1032-1041. https://doi.org/10.1111/j.1532-5415.2011.03449.x

54. Maci T, Pira FL, Quattrocchi G, Di Nuovo S, Perciavalle V, Zappia M. Physical and cognitive stimulation in Alzheimer disease. The GAIA project: A pilot study. *Am J Alzheimers Dis Other Demen*. 2012;27(2):107-113. https://doi.org/10.1177/1533317512440493

55. Leone E, Deudon A, Bauchet M, et al. Management of apathy in nursing homes using a teaching program for care staff: the STIM-EHPAD study. *Int J Geriatr Psychiatry*. 2013;28(4):383-392. https://doi.org/10.1002/gps.3836

56. Leontjevas R, Teerenstra S, Smalbrugge M, et al. More insight into the concept of apathy: a multidisciplinary depression management program has different effects on depressive symptoms and apathy in nursing homes. *Int Psychogeriatr*. 2013;25(12):1941-1952. https://doi.org/10.1017/S1041610213001440

57. Moyle W, Cooke M, Beattie E, et al. Exploring the effect of companion robots on emotional expression in older adults with dementia: a pilot randomized controlled trial. *J Gerontol Nurs*. 2013;39(5):46-53. https://doi.org/10.3928/00989134-20130313-03

58. Telenius EW, Engedal K, Bergland A. Effect of a high intensity exercise program on physical function and mental health in nursing home residents with dementia: an assessor blinded randomized controlled trial. *PLoS One*. 2015;10(5):e0126102. https://doi.org/10.1371/journal.pone.0126102

59. Treusch Y, Majic T, Page J, Gutzmann H, Heinz A, Rapp MA. Apathy in nursing home residents with dementia: results from a cluster-randomized controlled trial. *Eur Psychiatry*. 2015;30(2):251-257. https://doi.org/10.1016/j.eurpsy.2014.02.004

60. Valentí Soler M, Agüera-Ortiz L, Olazarán Rodríguez J, et al. Social robots in advanced dementia. *Frontiers in Aging Neuroscience*. 2015;7:133. https://doi.org/10.3389/fnagi.2015.00133

61. Amieva H, Robert PH, Grandoulier AS, et al. Group and individual cognitive therapies in Alzheimer's disease: the ETNA3 randomized trial. *Int Psychogeriatr*. 2016;28(5):707-717. https://doi.org/10.1017/S1041610215001830

62. Di Domenico A, Palumbo R, Fairfield B, Mammarella N. Fighting apathy in Alzheimer's dementia: a brief emotional-based intervention. *Psychiatry Res*. 2016;242:331-335. https://doi.org/10.1016/j.psychres.2016.06.009

63. Ikemata S, Momose Y. Effects of a progressive muscle relaxation intervention on dementia symptoms, activities of daily living, and immune function in group home residents with dementia in Japan. *Jpn J Nurs Sci*. 2016; [Epub ahead of print Oct 3 2016]. DOI: https://doi.org/10.1111/jjns.12147

64. Manera V, Chapoulie E, Bourgeois J, et al. Feasibility study with image-based rendered virtual reality in patients with mild cognitive impairment and dementia. *PLoS One*. 2016;11(3):e0151487. https://doi.org/10.1371/journal.pone.0151487

65. Rajkumar AP, Ballard C, Fossey J, et al. Apathy and its response to antipsychotic review and nonpharmacological interventions in people with dementia living in nursing homes: WHELD, a factorial cluster randomized controlled trial. *J Am Med Dir Assoc*. 2016;17(8):741-747. https://doi.org/10.1016/j.jamda.2016.04.006

66. Sanchez A, Marante-Moar MP, Sarabia C, et al. Multisensory stimulation as an intervention strategy for elderly patients with severe dementia: a pilot randomized controlled trial. *Am J Alzheimers Dis Other Demen*. 2016;31(4):341-350. https://doi.org/10.1177/1533317515618801

67. Brodaty H, Burns K. Nonpharmacological management of apathy in dementia: a systematic review. *Am J Geriatr Psychiatry*. 2012;20(7):549-564. https://doi.org/10.1097/JGP.0b013e31822be242

68. Lane-Brown AT, Tate RL. Apathy after acquired brain impairment: a systematic review of non-pharmacological interventions. *Neuropsychol Rehabil*. 2009;19(4):481-516. https://doi.org/10.1080/09602010902949207

69. Verkaik R, van Weert JC, Francke AL. The effects of psychosocial methods on depressed, aggressive and apathetic behaviors of people with dementia: a systematic review. *Int J Geriatr Psychiatry*. 2005;20(4):301-314. https://doi.org/10.1002/gps.1279

70. Radakovic R, Harley C, Abrahams S, Starr JM. A systematic review of the validity and reliability of apathy scales in neurodegenerative conditions. *Int Psychogeriatr*. 2015;27(6):903-923. https://doi.org/10.1017/S1041610214002221

71. Clarke DE, Ko JY, Kuhl EA, van Reekum R, Salvador R, Marin RS. Are the available apathy measures reliable and valid? A review of the psychometric evidence. *J Psychosom Res*. 2011;70(1):73-97. https://doi.org/10.1016/j.jpsychores.2010.01.012

72. Cohen-Mansfield J, Marx MS, Freedman LS, et al. The comprehensive process model of engagement. *Am J Geriatr Psychiatry*. 2011;19(10):859-870. https://doi.org/10.1097/JGP.0b013e318202bf5b

73. Gitlin LN, Piersol CV, Hodgson N, et al. Reducing neuropsychiatric symptoms in persons with dementia and associated burden in family caregivers using tailored activities: design and methods of a randomized clinical trial. *Contemp Clin Trials*. 2016;49:92-102. https://doi.org/10.1016/j.cct.2016.06.006

74. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273(5):408-412. https://doi.org/10.1001/jama.1995.03520290060030

75. Cummings J, Friedman JH, Garibaldi G, et al. Apathy in neurodegenerative diseases: Recommendations on the design of clinical trials. *J Geriatr Psychiatry Neurol*. 2015;28(3):159-173. https://doi.org/10.1177/0891988715573534

76. Fraker J, Kales HC, Blazek M, Kavanagh J, Gitlin LN. The role of the occupational therapist in the management of neuropsychiatric symptoms of dementia in clinical settings. *Occup Ther Health Care*. 2014;28(1):4-20. https://doi.org/10.3109/07380577.2013.867468

77. Kales HC, Gitlin LN, Lyketsos CG, Detroit Expert Panel on Assessment and Management of Neuropsychiatric Symptoms of Dementia. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc*. 2014;62(4):762-769. https://doi.org/10.1111/jgs.12730

78. Lyketsos CG. Apathy and agitation: challenges and future directions. *American Journal of Geriatric Psychiatry*. 2007;15(5):361-364. https://doi.org/10.1097/JGP.0b013e31803d15c1

79. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350:h369. https://doi.org/10.1136/bmj.h369

80. Rosenberg PB, Lyketsos CG. Mild cognitive impairment: searching for the prodrome of Alzheimer's disease. *World Psychiatry*. 2008;7(2):72-78. https://doi.org/10.1002/j.2051-5545.2008.tb00159.x

How to cite this article: Theleritis C, Siarkos K, Politis AA, Katirtzoglou E, Politis A. A systematic review of non-pharmacological treatments for apathy in dementia. *Int J Geriatr Psychiatry*. 2018;33:e177–e192. https://doi.org/10.1002/gps.4783