Physical exercise and dementia

Bossers, Willem

CHAPTER

2

Recommended measures for the assessment of cognitive and physical performance in older patients with dementia: a systematic review.[1]

Willem Bossers, Lucas van der Woude, Froukje Boersma,
Erik Scherder, Marieke van Heuvelen

[1] See also: Dementia and Geriatric Cognitive Disorders EXTRA 2012 Jan;2(1):589-609 doi: 10.1159/000345038

ABSTRACT

Aim
Recommend a set of neuropsychological and physical exercise tests for researchers to assess cognitive and motor function in clinical trials with older patients with dementia; to create consensus, decrease heterogeneity, and improve research quality.

Methods
A literature search (2005 – 2011) yielded 89 randomized controlled trials (RCTs). To provide information for test recommendations, the frequency of test use, effect size of the test outcome, study quality, and clinimetric properties of tests were analyzed.

Results
Fifty-nine neuropsychological tests (cognitive function domains: global cognition, executive functioning, memory, and attention) and ten physical exercise tests (motor function domains: endurance capacity, muscle strength, balance, and mobility) were found.

Conclusion/recommendations
To measure global cognition, the Mini Mental State Examination, Alzheimer Disease Assessment Scale-cognitive subscale, and the Severe Impairment Battery were recommended. To measure executive functioning, the Verbal Fluency Test Category/Letters, Clock Drawing Test, and Trail Making Test-B were recommended. No specific memory test could be recommended. The Digit Span Forward, Digit Span Backward, and Trail Making Test-A were recommended to measure attention. The Timed Up and Go test and Six Meter Walk test for mobility, the Six Minute Walk Distance for endurance capacity, and the Tinetti Balance Scale for balance were recommended as physical exercise tests.

INTRODUCTION

With the worldwide trend of an aging population, the number of patients with dementia will increase dramatically in the coming decades.[1] Dementia is characterized by a loss of neurons and atrophy of brain tissue.[2-5] Eventually, this leads to limitations in cognitive performance, including a decline in executive functioning, memory, and attention.[6, 7] The neurodegenerative processes in the brain go hand in hand with a decline in motor function, including a loss of endurance capacity, muscle strength, balance, and mobility.[6, 8] Eventually, decline in cognitive and motor function result in problems in activities of daily living, leading to institutionalization and a decreased quality of life.[3, 9, 10] Therefore, prevention of decline, and preferably an improvement in both cognitive and motor performance, in patients with dementia is of utmost importance.

With the growing impact of dementia on today's society, new treatments need to be developed that effectively reduce the limitations that are caused by a decline of cognitive and motor performance.[11] Meta-analysis and systematic reviews reported that pharmacological (e.g., medication) and non-pharmacological (e.g., exercise) interventions in patients with dementia may have a positive effect on cognitive and/or motor function.[12-18] However, the individual studies in these reviews showed ambiguous results and the tests that measured cognitive and motor function appeared to show large heterogeneity. Consequently, the comparability of the outcomes of clinical trials is hampered.[19] Therefore, future intervention studies that aim to improve cognitive and/or motor function should strive to use a limited number of generally accepted, feasible, reliable, and valid tests that adequately cover the domains of cognitive and motor function in patients with dementia.

Recommendations on cognitive tests for the purpose of diagnosing dementia were recently provided.[20, 21] However, information regarding which cognitive tests to use in measuring treatment effects are not available yet. To the author's knowledge, recommendations regarding the use of physical exercise tests for evaluating motor function are fully lacking.

The aim of this systematic review was to give up-to-date recommendations of neuropsychological and physical exercise tests to investigate treatment effects on cognitive and motor function in older patients with dementia. The current search was based on recent randomized controlled trials (RCTs) to give a comprehensive overview of neuropsychological and physical exercise tests. Frequently used neuropsychological and physical exercise tests were evaluated in relation with the study quality of the RCTs in which the tests were used, the nature of the interventions, the type of dementia of the included participants, and the sensitivity to change of the tests. Furthermore, the clinimetric properties (i.e., reliability and validity) of frequently used tests were reviewed.

METHODS

Data sources

Between August 2010 and August 2011, computer databases Pubmed, EMBASE, Biological abstracts, Web of Science (ISI), PsycINFO, CINAHL, and Cochrane Library were searched for relevant studies published between 2005 and 2011. Limits for the searches in the computer databases were set on: clinical trial, humans, and age: 65+ years. Keywords in the search included terms from Medical Subject Headings (MESH) and Embase thesaurus (EMTREE). The following terms were used in the MESH database and EMTREE thesaurus: dementia, Alzheimer Disease, Vascular Dementia, Frontotemporal Dementia, Lewy Body Disease, neuropsychological tests, and exercise tests. Keywords for dementia (Dementia OR Alzheimer Disease OR Vascular Dementia OR Frontotemporal Dementia OR Lewy Body Disease) were combined (with 'AND') with terms that expressed the use of neuropsychological or exercise tests (neuropsychological tests OR exercise tests). In addition, reference lists of reviews regarding the subject were hand searched for additional studies.

Inclusion criteria

Studies were included if they met the following criteria: RCT design, participants were diagnosed with dementia, participants were on average older than 65 years, neuropsychological tests and/or exercise tests were used to measure intervention effects, and the study was written in English, German, French, or Dutch.

Selection process

After the literature search, a first selection of studies was made on title, followed by a selection after reading the abstracts. Two reviewers (WB and MvH) independently performed both steps to identify those studies that met the inclusion criteria (agreement 94%, disagreement 6%). Disagreement was solved with full text screening. Full text analysis, to check the inclusion criteria, was performed for the studies that were identified in the preceding steps. Subsequently, reviews were hand searched for clinical trials that were not already found in the literature search. Finally, full text analysis and data extraction was performed from the selected studies.

Data extraction

From the selected RCTs the following data were extracted: neuropsychological tests, physical exercise tests, type of dementia, sample size, and data regarding the intervention description (e.g., pharmacological, exercise). For each neuropsychological or physical exercise test the overall means and standard deviations were calculated from all RCTs that used a given test. Based on the selected RCTs the overall means and standard deviations were calculated for age, baseline scores, and posttest scores.

Effect size

In order to express the sensitivity to change for each neuropsychological or physical exercise test, Cohen's d effect sizes per test were calculated over the selected RCTs.[22, 23] If the mean and standard deviation of pretest and posttest were presented in the RCT, the following formula was used[24]: d = [($post_{exp}$ – pre_{exp}) – ($post_{cont}$ – pre_{cont})] / *Sqrt* [([s^2 pre_{exp} (n_{exp}) + s^2 pre_{cont} (n_{cont})] / [n_{exp} + n_{cont}]) + ([s^2 $post_{exp}$ (n_{exp}) + s^2 $post_{cont}$ (n_{cont})] / [n_{exp} + n_{cont}]) / 2]. If the means and standard deviations were not presented in the RCT, the F statistic was used with the following formula[24]: d = *Sqrt* [F ([(n_{exp} + n_{cont}) / (n_{exp} · n_{cont})] · [(n_{exp} + n_{cont}) / (n_{exp} + n_{cont} –2)])]. The overall effect size d was calculated as the mean of individual effect sizes weighted for the sample size. Cohen's d benchmarks were used to indicate small (d = 0.20), medium (d = 0.50), and large (d = 0.80) effect sizes.[22]

Study quality

Study quality of each RCT that used a given test was assessed with the Physiotherapy Evidence Database (PEDro).[25] According to the PEDro scoring system a score of 9 – 10 was considered as excellent, a score of 6 – 8 as good, a score of 4 – 5 as moderate, and a score of 0 – 3 as poor.[25] Further clinimetric analysis of neuropsychological and physical exercise tests was done when the study quality of at least five RCTs were good or excellent.

Reliability and validity of frequently used tests

After identifying the tests that were used in five or more good or excellent quality RCTs, a second search in Pubmed was conducted in September 2011 to select the studies aimed at reporting the reliability and validity of these tests as evidenced in a population with dementia. Searches were performed by combining the terms 'reliability' OR 'validity' OR 'reproducibility of results' in combination with (with AND) keywords for dementia and the selected neuropsychological and physical exercise tests. By means of references, additional reliability and validity studies were searched.

RESULTS

Study characteristics

The literature search for RCTs yielded a total of 840 publications. Eventually, 178 publications were full text screened, of which 89 were included for further analysis. A flowchart of the process is presented in Figure 2.1. The results are described in two separate sections: *neuropsychological tests* and *exercise tests*. These sections describe the test use in RCTs (no. of RCTs), test use related to intervention type, test use related to dementia type, effect sizes, and study quality of RCTs. Table 2.1 describes 59 neuropsychological tests that covered the cognitive domains global cognition, executive functioning, memory, and attention. Thereafter, Table 2.2 describes the clinimetric data of the neuropsychological tests that were most often used. Finally, ten exercise tests that covered the motor function domains endurance capacity, muscle strength, balance, and mobility are presented in Table 2.3.

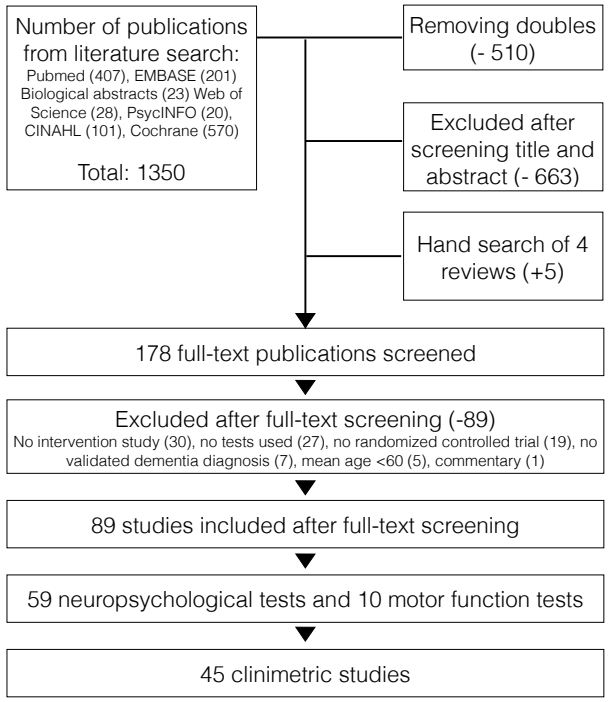

Figure 2.1. *Flowchart of literature search and study selection.*

Neuropsychological tests

Frequency of test use

As shown in table 2.1, global cognitive functioning was measured most often with the Mini Mental State Examination (MMSE) (54 times), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) (43 times), and the Severe Impairment Battery (SIB) (8 times). Tests for global cognition were used more than neuropsychological tests that covered a specific cognitive area.

Thirty-two domain specific neuropsychological tests were used in 63 RCTs, of which 7 tests were used in 5 or more RCTs. Executive functioning was measured with the Verbal Fluency Test Category (12 times), Clock Drawing Test (6 times), Verbal Fluency Test Letters (6 times), and the Trail Making Test-B (5 times). Attention was measured with the Digit Span Forward (8 times), Digit Span Backward (7 times), and Trail Making Test-A (6 times).

In sum, global cognitive tests were used more often than neuropsychological tests that covered a specific cognitive area. Frequently used neuropsychological tests that were used in five or more RCTs covered the cognitive domains executive functioning and attention. Memory tests that were used in more than five RCTs were not found.

Table 2.1. Descriptive data of 63 randomized clinical trials that used 59 different neuropsychological tests.

Neuropsychological test	No. of studies	N	Intervention type (No. of RCTs)	Age [a] Mean (SD)	Gender (% ♀)	Dementia type (%)	Baseline [a] Mean (SD)	ES [a]	PEDro
Mini Mental State Examination[26-79]	54	7,606	Pharm.(39) Cognitive(9) Exerc.(5) Acupuncture(1)	75.8 (6.7)	58%	AD(80) VD(18) LB(2)	8.0 (4.0)	small	E(6) G(45) Mo(3) P(0)
Alzheimer's Disease Assessment Scale – cognitive subscale[26-28, 31, 32, 35, 39, 41, 43, 47, 48, 51, 54, 55, 58, 61, 63, 64, 67, 68, 70-72, 75, 77, 80-97]	43	10,133	Pharm.(37) Cognitive(5) Exerc.(1)	74.4 (6.7)	59%	AD(81) VD(17) LB(2)	24.4 (11.0)	small	E(12) G(28) Mo(3) P(0)
Verbal Fluency Test Category[31, 36, 46, 47, 56, 98-104]	12	726	Pharm.(5) Cognitive(2) Exerc.(2) Airway(1) CES(1) Nerve stimuli(1)	74.2 (7.1)	56%	AD(47) VD(29) n.r.(24)	10.9 (9.2)	med.	E(4) G(6) Mo(1) P(1)
Severe Impairment Battery[30, 37, 66, 73, 74, 105-107]	8	2,134	Pharm.(8)	76.6 (7.7)	67%	AD(100)	69.3 (19.2)	small	E(3) G(5) Mo(0) P(0)
Digit Span Forward[31, 33, 49, 99, 101-104]	8	342	Pharm.(1) Cognitive(2) Exerc.(2) Airway(1) CES(1) Nerve stimuli(1)	82.6 (6.7)	55%	AD(76) n.r.(24)	5.4 (2.3)	small	E(3) G(4) Mo(0) P(1)
Digit Span Backward[31, 49, 99, 101-104]	7	280	Cognitive(2) Exerc.(2) Airway (1) CES(1) Nerve stimuli(1)	82.2 (6.5)	50%	AD(44) n.r.(56)	3.9 (1.5)	small	E(3) G(3) Mo(0) P(1)
Clock Drawing Test[42, 50, 56, 95, 100, 108]	6	1,674	Pharm.(5) Exerc.(1)	72.1 (7.7)	68%	AD(82) VD(18)	4.5 (3.2)	small	E(3) G(2) M(0) P(1)
Trail Making Test-A[31, 42, 83, 101-103]	6	1,502	Pharm.(3) Cognitive(1) Airway(1) CES(1)	73.8 (8.0)	67%	AD(98) FTD(2)	161 (82.5)	small	E(1) G(4) Mo(0) P(1)
Verbal Fluency Test Letters[36, 56, 99, 101-103]	6	319	Pharm.(1) Cognitive(1) Exerc.(1) Airway(1) CES(1) Nerve stimuli(1)	78.9 (5.6)	44%	AD(56) Pick's(44)	16.3 (4.6)	small	E(2) G(3) Mo(0) P(1)
Trail Making Test-B[27, 31, 47, 98, 101]	5	214	Pharm.(3) Cognitive(1) Airway(1)	73.9 (6.2)	58%	AD(100)	242.8(91.3)	small	E(2) G(3) Mo(0) P(0)
Logical Memory Test - immediate recall[28, 49, 69, 70]	4	277	Pharm.(2) Cognitive(2)	75.6 (6.8)	69%	AD(100)	11.5 (4.7)	small	E(2) G(2) Mo(0) P(0)
Logical Memory Test - delayed recognition[28, 49, 69,70]	4	277	Pharm(2) Cognitive(2)	75.6 (6.8)	69%	AD(100)	2.8 (2.9)	small	E(2) G(2) Mo(0) P(0)
Logical Memory Test - delayed recall[28, 49, 69, 70]	4	277	Pharm.(2) Cognitive(2)	75.6 (6.8)	69%	AD(100)	0.9 (1.6)	small	E(2) G(2) Mo(0) P(0)
Eight Word Test - immediate recall[99, 102-104]	4	196	Exerc.(2) CES(1) Nerve stimuli(1)	84.7 (6.1)	62%	AD(38) n.r.(62)	17.6 (8.1)	small	E(2) G(1) Mo(0) P(1)
Eight Word Test - delayed recall[99, 102-104]	4	196	Exerc.(2) CES(1) Nerve stimuli(1)	84.7 (6.1)	62%	AD(38) n.r.(62)	0.35 (0.94)	small	E(2) G(1) Mo(0) P(1)
Eight Word Test - delayed recognition[99, 102-104]	4	196	Exerc.(2) CES(1) Nerve stimuli(1)	84.7 (6.1)	62%	AD(38) n.r.(62)	10.7 (3.9)	small	E(2) G(1) Mo(0) P(1)
RBMT – face recognition[99, 102-104]	4	196	Exerc.(2) CES(1) Nerve stimuli(1)	84.6 (6.1)	59%	AD(54) n.r.(46)	6.6 (3.5)	small	E(2) G(1) Mo(0) P(1)
RBMT - picture recognition[99, 102-104]	4	196	Exerc.(2) CES(1) Nerve stimuli(1)	84.6 (6.1)	59%	AD(54) n.r.(46)	12.2 (6.3)	small	E(2) G(1) Mo(0) P(1)
Mattis Dementia Rating Scale[46, 50, 101]	3	105	Pharm.(2) Airway(1)	77.1 (7.3)	67%	AD(78) LB(22)	108.8(15.7)	small	E(1) G(2) Mo(0) P(0)
Modified Boson Naming Test[31, 49, 69]	3	62	Pharm.(1) Cognitive(2)	77.4 (7.8)	76%	AD(100)	10.4 (4.6)	small	E(1) G(2) Mo(0) P(0)
Syndrome Kurtz Test[52, 100]	2	290	Pharm.(2)	65.2 (7.5)	64%	AD(38) VD(62)	16.0 (3.7)	large	E(2) G(0) Mo(0) P(0)
Digit Symbol Test[42, 101]	2	273	Pharm.(1) Airway(1)	73.8 (8.0)	72%	AD(100)	11.7 (5.8)	small	E(1) G(1) Mo(0) P(0)
STROOP interference[98, 101]	2	67	Pharm.(1) Airway(1)	77.7 (6.6)	54%	AD(100)	65.5 (41.2)	small	E(1) G(1) Mo(0) P(0)
Cambridge Neuropsychological Test Battery[78,109]	2	50	Pharm.(1) Exerc.(1)	71.2 (8.1)	56%	AD(65) FTD(35)	-	-	E(0) G(1) Mo(1) P(0)
Visual Memory Span[102, 103]	2	38	CES(1) Nerve stimuli(1)	84.4 (6.3)	59%	AD(100)	9.0 (3.8)	small	E(0) G(1) Mo(0) P(1)
Selective Reminding Test[28, 49]	2	35	Cognitive(2)	72.9 (7.1)	89%	AD(100)	13.3 (12.4)	small	E(2) G(0) Mo(0) P(0)
Block Design Test[84, 98]	2	31	Pharm.(2)	72.8 (6.8)	0%	AD(100)	45.5 (14.9)	small	E(2) G(0) Mo(0) P(0)
The Executive Interview[81]	1	363	Pharm.(1)	72.3 (9.0)	38%	VD(100)	18.3 (7.0)	small	E(0) G(1) Mo(0) P(0)
Cambridge Cognitive Examination[38]	1	179	Pharm.(1)	87.4 (6.0)	57%	AD(100)	69.0 (13.0)	small	E(0) G(1) Mo(0) P(0)
Age-adjusted Concentration Task[65]	1	65	Pharm.(1)	77.8 (5.6)	58%	AD(66) VD(11)	-	small	E(0) G(1) Mo(0) P(0)
Auditory Verbal Learning Test[33]	1	62	Pharm.(1)	83.9 (7.6)	80%	AD(100)	2.6 (1.5)	small	E(0) G(0) Mo(1) P(0)
Stop Signal Reaction Time[104]	1	61	Hand movement(1)	84.7 (5.1)	58%	n.r.	-	-	E(0) G(0) Mo(1) P(0)
Attention Network Task[104]	1	61	Hand movement(1)	84.7 (5.1)	58%	n.r.	-	-	E(0) G(0) Mo(1) P(0)
Hasegawa's Evaluation of Cognition[76]	1	60	Acupuncture(1)	66.7 (10.5)	34%	VD(100)	11.3 (4.5)	small	E(0) G(0) Mo(1) P(0)
Cognitive Abilities Screen Instrument[40]	1	60	Cognitive(1)	82.3 (5.9)	67%	VD(100)	54.6 (15.3)	small	E(1) G(0) Mo(0) P(0)
Digit Cancellation Task[101]	1	52	Airway(1)	78.2 (7.2)	69%	AD(100)	-	-	E(0) G(0) Mo(1) P(0)
Hopkins Verbal Learning Test[101]	1	52	Airway(1)	78.2 (7.2)	69%	AD(100)	3.3 (1.5)	small	E(0) G(1) Mo(0) P(0)
Wisconsin Card Sorting Test[101]	1	52	Airway(1)	78.2 (7.2)	69%	AD(100)	-	-	E(0) G(1) Mo(0) P(0)
The Executive Clock Drawing - 1[110]	1	51	Pharm.(1)	77.9 (7.0)	55%	AD(100)	6.2 (3.7)	small	E(0) G(1) Mo(0) P(0)
The Executive Clock Drawing - 2[110]	1	51	Pharm.(1)	77.9 (7.0)	55%	AD(100)	10.7 (3.0)	small	E(0) G(1) Mo(0) P(0)
Rey-Osterrieth Figure Test - Copy[36]	1	32	Cognitive(1)	73.0 (7.2)	62%	AD(100)	16.5 (14.6)	small	E(0) G(1) Mo(0) P(0)
Rey-Osterrieth Figure Test - Recall[36]	1	32	Cognitive(1)	73.0 (7.2)	62%	AD(100)	1.2 (2.0)	small	E(0) G(1) Mo(0) P(0)
3-D Constructional Praxis[69]	1	32	Cognitive(1)	73.0 (7.2)	62%	AD(100)	11.9 (0.48)	-	E(0) G(1) Mo(0) P(0)
Extended RBMT - profile[36]	1	32	Cognitive(1)	73.0 (7.2)	62%	AD(100)	1.2 (1.3)	small	E(0) G(1) Mo(0) P(0)
Attention Matrices Test[36]	1	32	Cognitive(1)	73.0 (7.2)	62%	AD(100)	32.4 (11.7)	small	E(0) G(1) Mo(0) P(0)
Visual Reproduction Test-1[28]	1	16	Cognitive(1)	73.8 (4.8)	82%	AD(100)	13.8 (3.6)	large	E(1) G(0) Mo(0) P(0)
Rapid Evaluation of Cognition Test[111]	1	31	Exerc.(1)	81.8 (5.3)	74%	AD(100)	27.6 (6.8)	large	E(0) G(1) Mo(0) P(0)
Developmental Test Visual Motor Integration[84]	1	16	Pharm.(1)	69.8 (8.6)	0%	AD(100)	18.1 (2.7)	small	E(1) G(0) Mo(0) P(0)
Visual Reproduction -2[28]	1	16	Cognitive(1)	73.8 (4.8)	82%	AD(100)	1.3 (2.8)	small	E(1) G(0) Mo(0) P(0)
Judgment of Line Orientation[84]	1	16	Pharm.(1)	69.8 (8.6)	0%	AD(100)	18.2 (8.9)	small	E(1) G(0) Mo(0) P(0)
California Verbal learning Test - delayed recall[84]	1	16	Pharm.(1)	69.8 (8.6)	0%	AD(100)	1.6 (1.9)	small	E(1) G(0) Mo(0) P(0)
Recognition Memory Test - faces[28]	1	16	Cognitive(1)	73.8 (4.8)	82%	AD(100)	28.0 (5.9)	small	E(1) G(0) Mo(0) P(0)
Benton Visual Retention Test[49]	1	19	Cognitive(1)	72.1 (8.5)	95%	AD(100)	1.9 (1.8)	small	E(1) G(0) Mo(0) P(0)
Recognition Memory Test - words[28]	1	16	Cognitive(1)	73.8 (4.8)	82%	AD(100)	32.7 (8.9)	small	E(1) G(0) Mo(0) P(0)
Milan Overall Dementia Assessment[59]	1	16	Cognitive(1)	68.0 (6.5)	48%	AD(100)	-	small	E(0) G(0) Mo(1) P(0)
Proactive Interference Test[98]	1	15	Pharm.(1)	76.0 (4.0)	0%	AD(100)	7.7 (4.2)	small	E(1) G(0) Mo(0) P(0)
Route Test[98]	1	15	Pharm.(1)	76.0 (4.0)	0%	AD(100)	15.1 (9.6)	small	E(1) G(0) Mo(0) P(0)
Story Recall Test[98]	1	15	Pharm.(1)	76.0 (4.0)	0%	AD(100)	12.0 (13.2)	small	E(1) G(0) Mo(0) P(0)
Fuld Object and Memory Evaluation[31]	1	13	Cognitive(1)	73.3 (6.4)	69%	AD(100)	24.7 (11.1)	small	E(0) G(1) Mo(0) P(0)

Note: ES, effect size; PEDro, Physiotherapy Evidence Database; Pharm., Pharmacological; Exerc. = Exercise; E, excellent (9-10); G, Good (6-8); Mo, Moderate (4-5); P, Poor (0-3); CES, Cranial Electro Stimulation; AD, Alzheimer's Disease; VD, Vascular Dementia; LB, Lewy Body Disease; Pick's, Pick's Disease; FTD, Frontotemporal Dementia; RBMT, Rivermead Behavioral memory Test; n.r., not reported.; [a], Pooled and weighted data as a function of the number of participants.

Dementia type

Table 2.1 shows that a majority of the participants were diagnosed with Alzheimer's disease (AD) (84%) or vascular dementia (VaD) (7%). Neuropsychological tests that were used only in RCTs with AD patients were the SIB (global cognitive functioning), Verbal Fluency Test Letters (executive functioning), Trail Making Test-A, Digit Span Forward, and Digit Span Backward (attention). Tests used in RCTs with AD or VaD patients were the MMSE and ADAS-cog (global cognitive functioning), Verbal Fluency Test Category, Clock Drawing Test, and Trail Making Test-B (executive functioning). Tests that were used in RCTs with only VaD, Lewy Body Disease, Pick's Disease, and frontotemporal dementia patients were not found.

Effect size

Pooled effect sizes ranged from small (*d* = -0.16) to large (*d* = 1.58). The global cognitive test Rapid Evaluation of Cognitive Functioning measured a large effect size (*d* = 1.12). The global cognitive tests SIB (*d* = 0.34), ADAS-cog (*d* = 0.19) and MMSE (*d* = 0.09) showed small effect sizes. Overall effect sizes were small for both pharmacological and non-pharmacological RCTs. Furthermore, two neuropsychological tests that measured memory revealed large pooled effect sizes with the Visual Reproduction Test (*d* = 1.58) and the Syndrome Kurtz Test (*d* = 0.82). The Verbal Fluency Test Category that measures executive functioning measured a medium effect size (*d* = 0.61).

Study quality

According to the PEDro scale, the study quality of RCTs that used neuropsychological tests ranged from 2 (*poor*) to 10 (*excellent*). Three RCTs with poor study quality used the Verbal Fluency Test Category, Digit Span Forward, Digit Span Backward, Clock Drawing Test, Trail Making Test-A, and Verbal Fluency Test Letters. Because these tests were also found in RCTs with excellent and good study quality, this had no effect on the selection process of these neuropsychological tests.

Reliability and validity

Table 2.2 presents clinimetric data (i.e., reliability and validity) of ten neuropsychological tests that were used in five or more RCTs of good or excellent study quality, according to PEDro. The global cognitive tests MMSE, ADAS-cog and SIB were found to be reliable and valid tools for dementia patients. The Clock Drawing Test was reliable but showed an unsatisfactory concurrent validity with other tests that measured executive functioning.[149] No reliability or validity studies with dementia patients were found for the Verbal Fluency Test Category, Verbal Fluency Test Letters, Trail Making Test-B, Digit Span Forward, Digit Span Backward, and Trail Making Test-A.

Table 2.2. Clinimetric data of ten selected neuropsychological tests that were used in five or more good-high quality randomized controlled trials.

Neuropsychological test	Reliability	Validity	Summary
Mini Mental State Examination	Test-retest reliability (ICC): .85 – .90[112]; .89[113]; .92[114], .69 [115]; .89[116]; .80[117]; .86[118] Inter-rater reliability: ICC = .69 – .78[115]; Kappa = .63[114]; ICC = .69[115] Internal consistency (α): .54 – .96[119]; .78[120]; .77[121]; .68[122]; .96[123]; .90[124]; .81[125]	Concurrent validity with Wechsler Adult Intelligence Scale Verbal IQ (r = .78) and performance IQ (r = .66)[113]	Reliable and valid test in dementia patients. There is a floor effect in severe dementia patients.[119] Sensitivity to change over time is questionable because small changes could be due to measurement errors.[125]
Alzheimer's Disease Assessment Scale – cognitive subscale	Test-retest reliability (ICC): .91 – .95[126]; .65 – .92[127]; .90[128]; .93[129]; .96[130]; .86 – .96[131]; .90[132] Inter-rater reliability: ICC = .65 – .95[131]; Kappa = .99[130]; ICC = .98 – .99[126]; ICC = .97 – .99[127]; Kappa = .99[133] Internal consistency (α): .65 – .91[131]; .87[130]; .52 – .87[126]; .96[128]; .15 – .93[134]; .81[129]; .84[135]	Concurrent validity with Mini Mental State Examination (r = -.63)[135]	Reliable and valid test in patients with mild to moderate dementia.
Verbal Fluency Test Category	-	-	No data available about reliability and validity for dementia patients.
Severe Impairment Battery	Test-retest reliability (ICC): .79[136]; .97[137]; .87[138]; .90[139]; .93[135] Inter-rater reliability: Spearmans Rho: .85[140]; Spearmans Rho: .97[137]; ICC = .99[138] Internal consistency (α): .97[136]; .97[140]; .98[137]	Concurrent validity with Mini Mental State Examination (r = .85)[140]	Reliable and valid test in dementia patients.[140] This test is sensitive to changes in patients with moderate to severe dementia (MMSE 0-12)[140] Promising test for follow-up in therapeutic trials.[138]
Digit Span Forward	-	-	No data available about reliability and validity for dementia patients. Digit Span Test as a sub-test in the Severe Impairment Battery was sensitive to change in dementia patients.[141]
Verbal Fluency Test Letters	-	-	No data available about reliability and validity for dementia patients.
Digit Span Backward	-	-	No data available about reliability and validity for dementia patients. Digit Span Test as a sub-test in the Severe Impairment Battery was sensitive to change in dementia patients.[141]
Clock Drawing Test	Test-retest reliability (ICC): .70 – .78[142] Inter-rater reliability: ICC = .82[143]; ICC = .92[144]; ICC = .88[145]; Kappa: .82 – .94[146];Kappa: .94[147]; Kappa = .63 – 1.0[148] Internal consistency (α): .75[142]	Concurrent validity with Mini Mental State Examination (r=.13)[142]	Reliable test in dementia patients.
Trail Making Test-A	-	-	No data available about reliability and validity for dementia patients.
Trail Making Test-B	-	-	No data available about reliability and validity for dementia patients.

Note: ICC, Intra Class Correlation; MMSE, mini mental state examination

Exercise tests

Frequency of test use

Ten different exercise tests were used in 13 RCTs (Table 2.3). These tests measured the motor function domains endurance capacity with the Six Minute Walk Distance and Two Minute Step Test; muscle strength with the Five Times Sit To Stand and 30 Second Chair Stand; balance with the Tinetti Balance Scale, Abnormal One-Leg Balance, and Berg Balance Scale; mobility with the Timed Up and Go and Six Meter Walk; and flexibility with the Functional Reach Test. All physical exercise tests were used in non-pharmacological RCTs, except for the Tinetti Balance Scale, which was also used in one pharmacological RCT.

Dementia type

A majority of the participants was diagnosed with AD (84% or VaD (6%). Six exercise tests were used only in AD patients, and covered the motor function domains endurance capacity (Two Minute Step Test), muscle strength (30 Second Chair Stand), balance (Tinetti Balance Scale, Abnormal One-Leg Balance), and mobility (Timed Up and Go, Six Meter Walk). In RCTs that included both AD and VaD, three physical exercise tests measured the motor function domains endurance capacity (Six Minute Walk Distance), flexibility (Functional Reach Test), and balance (Berg Balance Scale).

Study quality

The study quality of RCTs ranged from 5 (moderate) to 9 (excellent). Only the Tinetti Balance Scale was used in a RCT with excellent study quality (PEDro [9]).

Effect size

Pooled effect sizes of RCTs ranged from small (d = 0.02) to large (d = 0.87). A large effect was found with the Tinetti Balance Scale (d = 0.87). Medium effect sizes were found with the Six Meter Walk test (d = 0.58) and the Six Minute Walk Distance test (d = 0.51).

Reliability and validity

The Timed Up and Go test (Intra Class Correlation (ICC) = .985 – .988), Six Minute Walk Distance (ICC = .982 – .987), and Six Meter Walk test (ICC = .973 – .977) showed excellent test retest values in patients with dementia.[153] No further clinimetric data were available in patients with dementia for the remaining physical exercise tests that were presented in Table 2.3.

Table 2.3. Descriptive data of 13 randomized clinical trials that used 10 different motor function tests.

Physical exercise test	No. of studies	N	Intervention type (No. of RCTs)	Age [a] Mean (SD)	Gender (% ♀)	Dementia type (%)	Baseline [a] Mean (SD)	ES [a]	PEDro
Timed Up & Go[45, 150, 151]	3	179	Exerc(3)	81.9 (7.3)	71%	AD(100)	17.1 (7.5)	small	E(0) G(2) Mo(1) P(0)
Six Minute Walk Test[45, 77]	2	105	Exerc(2)	77.6 (6.6)	65%	AD(39) VaD(16) LB (16) n.r.(29)	221.0 (82.6)	medium	E(0) G(2) Mo(0) P(0)
Functional Reach Test[77,150]	2	94	Exerc(2)	76.6 (6.6)	52%	AD(82) VaD(18)	20.4 (8.1)	small	E(0) G(2) Mo(0) P(0)
Six Meter Walk Test[151]	1	134	Exerc(1)	83.0 (7.4)	75%	AD(100)	0.4 (0.2)	medium	E(0) G(1) Mo(0) P(0)
One-leg Balance Test[151]	1	134	Exerc(1)	83.0 (7.4)	75%	AD(100)	-	-	E(0) G(1) Mo(0) P(0)
Tinetti Balance Scale[56]	1	116	Pharm(1)	73.4 (2.5)	62%	AD(100)	8.5 (1.2)	large	E(1) G(0) Mo(0) P(0)
Five Times Sit to Stand[150]	1	29	Exerc(1)	76.9 (6.7)	51%	AD(72) LB(28)	18.9 (7.2)	small	E(0) G(1) Mo(0) P(0)
Berg Balance Scale[77]	1	85	Exerc(1)	76.6 (6.5)	52%	AD(61) VaD(20) LB (19)	47.5 (16.9)	small	E(0) G(1) Mo(0) P(0)
30 Second Chair Stand[152]	1	16	Exerc(1)	74.5 (-)	37%	AD(100)	-	-	E(0) G(0) Mo(1) P(0)
Two Minute Step Test[152]	1	16	Exerc(1)	74.5 (-)	37%	AD(100)	-	-	E(0) G(0) Mo(1) P(0)

Note: [a], Weighted data as a function of the number of participants; ES, effect size; PEDro, Physiotherapy Evidence Database; E, excellent (9-10); G, Good (6-8); Mo, Moderate (4-5); P, Poor (0-3); Pharm., Pharmacological; Exerc., Exercise; AD, Alzheimer's Disease; VaD, Vascular Dementia; LB, Lewy Body Disease; n.r., not reported.

DISCUSSION

To improve the study quality and increase comparability of clinical trials and observational studies, researchers should strive to use a limited number of generally accepted, feasible, reliable, and valid tests that cover the domains of cognitive and motor function. Following previous studies that recommended neuropsychological tests for the diagnoses of dementia[20, 21] and studies that stated the importance of physical exercise to attenuate cognitive impairment in older patients with dementia[154], the aim of the current review was to give up-to-date recommendations of both neuropsychological and physical exercise tests for high quality experimental research in older patients with dementia.

Neuropsychological tests

This study revealed 59 different neuropsychological tests that were used in 63 RCTs. This confirms the assumption that there is a large heterogeneity in neuropsychological test use in RCTs with older patients with dementia. The results showed that global cognitive tests were used more often in comparison with neuropsychological tests that measured one specific cognitive domain.

In particular, the global cognitive tests MMSE, ADAS-cog and the SIB were standing out from other global cognitive tests because of their excellent clinimetric properties (Table 2.2). Furthermore, these tests were frequently used in high quality RCTs (i.e., respectively 54, 43, and 8 times), which suggest that they are feasible to use in patients with dementia. However, for all three tests the sensitivity to change was low. The low sensitivity to change of the MMSE and ADAS-cog was previously challenged in other studies because changes in test scores may be caused by small measurement errors.[125, 140] For the SIB however, previous research suggest that this test may be sensitive to change in patients with severe dementia.[140] Based on the above, we recommend to use the SIB in RCTs to measure global cognitive treatment effects. However, when comparing effects with previous studies in patients with dementia, the MMSE and ADAS-cog are suggested.

Memory tests could not be selected in this review due to the large heterogeneity in memory test use. Earlier work on memory tests for diagnosing dementia showed that verbal memory and visual memory can be assessed with several neuropsychological tests.[20] Most of these proposed neuropsychological tests were only used once in RCTs between 2005 and 2011. Moreover, the proposed 'Word List' of the *Consortium to Establish a Registry for Alzheimer's* disease was not used at all in RCTs over that period. Additionally, because these tests were specifically recommended for diagnosis of dementia, we suggest that they are not suitable to measure intervention effects over time. Furthermore, studies that investigated the clinimetric properties

of these memory tests in patients with dementia are lacking.

To measure executive function, we recommend using the Verbal Fluency Test Category, Clock Drawing Test, Verbal Fluency Test Letters, and the Trail Making Test-B because these tests were frequently used in high quality RCTs. However, we only found that the Verbal Fluency Test Category was able to detect change and only the Clock Drawing Test was found reliable in older dementia patients. Since information and clinimetric quality is in many cases still insufficient, the recommended selection should be used with care and further evaluation of these tests is needed.

For the cognitive domain attention, we recommend the Digit Span Forward, Digit Span Backward, and Trail making Test-A because of their frequent use in high quality studies. However, no studies were found that investigated the clinimetric properties of these tests in patients with dementia. Furthermore, the results showed that the sensitivity to change was small.

Table 2.4. Recommended neuropsychological tests ordered on the basis of frequency of test use, overall effect size, study quality, reliability, and validity for the cognitive domains global cognitive functioning, executive functioning, memory, and attention.

Global cognitive functioning	Executive functioning	Memory	Attention
Severe Impairment Battery [a, b, c, d]	Verbal Fluency Test Category [a, b, c]	Visual Reproduction Test* [b, c]	Digit Span Forward [a, c]
Mini Mental State Examination [a, c, d]	Clock Drawing Test [a, c, d]	Eight Word Test* [c]	Digit Span Backward [a, c]
Alzheimer's Disease Assessment Scale – cognitive subscale [a, c, d]	Verbal Fluency Test Letters [a, c]	Logical Memory Test* [c]	Trail Making Test-A [a, c]
Rapid Evaluation of Cognitive Functioning* [b, c, d]	Trail Making Test-B [a, c]		

Note: [a], Frequently used in RCTs (feasibility); [b], Able to measure an effect (sensitivity to change); [c], Test was used in excellent / good quality RCTs (PEDro); [d], Reliable / valid in dementia patients; *, more research is needed.

Based on the current results, Table 2.4 sums up the currently best available tests used in international intervention studies with older patients with dementia. Although widely applied, it was shown that the recommended neuropsychological tests lack clinimetric data. Therefore, future research into the clinimetric quality for these tests is essential. The recommended selection of currently optimal cognitive tests should be used with care. Researchers are advised to select those recommended tests that most closely fit into their study objectives.

Physical exercise tests

The current review presented ten different exercise tests, which covered the motor function domains endurance capacity, muscle strength, balance, and mobility. However, a large heterogeneity in tests used was found, and none of the tests were used frequently enough in RCTs to recommend them. Preliminary recommendations based on the results of this review may be a first step for the selection of exercise tests in future studies.

The results showed that the Six Minute Walk Distance test, a test for endurance capacity, is reliable and sensitive to change.[153] Muscle strength was measured with the Five Times Sit to Stand test and the 30 Second Chair Stand test. However, no data was available on the feasibility and clinimetric properties of these tests. For the domain balance, results showed that the Tinetti Balance Scale was sensitive to measure change but again, no data was available on feasibility and clinimetric properties in patients with dementia. Mobility was measured with the Six Meter Walk test and the Timed Up and Go test, of which both were reliable in patients with dementia.[153] According to the present data, only the Six Meter Walk test was sensitive to measure change. Based on the limited information at hand, the best exercise tests yet available are summed up in Table 2.5.

Table 2.5. Domain specific physical exercise tests ordered on the basis of frequency of tests use, effect size, study quality, reliability, and validity for the motor function domains endurance capacity, muscle strength, balance, and mobility.

Endurance capacity	Muscle strength*	Balance	Mobility
Six Minute Walk Distance* [a, b, c]	Five Times Sit to Stand*	Tinetti Balance Scale* [a, b]	Timed Up and Go* [b, c]
	30 Second Chair Stand*		Six Meter Walk* [a, b, c]

Note: [a], Able to measure an effect (sensitivity to change); [b], Test was used in excellent / good quality RCTs (PEDro); [c], Reliable / valid in dementia patients; *, more research is needed.

Because of the importance of motor function in the disease process of dementia, it is essential that future research is done towards the feasibility, sensitivity to change, reliability, and validity of physical exercise tests that were found in this review.[154] Since this information is in many cases still insufficient, the recommendation of optimal physical exercise tests should be used with care.

CONCLUSION

This review mapped the large heterogeneity in cognitive and physical function tests, which were used in international intervention studies with older patients with dementia. The provided neuropsychological (Table 2.4) and exercise (Table 2.5) test recommendations may lead to a more evidence-based choice of tests that better fit the research question of future studies. Because information on clinimetric quality is in many cases still insufficient, the recommended selection of currently optimal cognitive and physical exercise tests should be used with care. Researchers are advised to select those recommended tests that most closely fit into their study objectives.

REFERENCES

1. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M. Alzheimer's Disease International: Global prevalence of dementia: a Delphi consensus study. Lancet 2005;366:2112-2117.

2. Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT, Delon MR. Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain. Science 1982;215:1237-1239.

3. Thomas VS, Hageman PA. Can neuromuscular strength and function in people with dementia be rehabilitated using resistance-exercise training? Results from a preliminary intervention study. J Gerontol A Biol Sci Med Sci 2003;58:746-751.

4. Clark CM, Forman MS. Frontotemporal lobar degeneration with motor neuron disease: A clinical and pathological spectrum. Arch Neurol 2006;63:489-490.

5. Bird TD. Genetic aspects of alzheimer disease. Genet Med 2008;10:231-239.

6. Barberger-Gateau P, Fabrigoule C, Amieva H, Helmer C, Dartigues JF. The disablement process: A conceptual framework for dementia-associated disability. Dement Geriatr Cogn Disord 2002;13:60-66.

7. Gershon RC, Cella D, Fox NA, Havlik RJ, Hendrie HC, Wagster MV. Assessment of neurological and behavioural function: The NIH toolbox. Lancet Neurol 2010;9:138-139.

8. Bruce B, Fries JF, Ambrosini D, Lingala B, Gandek B, Rose M, Ware JE,Jr. Better assessment of physical function: Item improvement is neglected but essential. Arthritis Res Ther 2009;11:R191.

9. Sauvaget C, Yamada M, Fujiwara S, Sasaki H, Mimori Y. Dementia as a predictor of functional disability: A four-year follow-up study. Gerontology 2002;48:226-233.

10. Traykov L, Rigaud AS, Cesaro P, Boller F. Neuropsychological impairment in the early alzheimer's disease. Encephale 2007;33:310-316.

11. Haan MN, Wallace R. Can dementia be prevented? Brain aging in a population-based context. Annu Rev Public Health 2004;25:1-24.

12. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. Arch Phys Med Rehabil 2004;85:1694-1704.

13. Eggermont L, Swaab D, Luiten P, Scherder E. Exercise, cognition and Alzheimer's disease: More is not necessarily better. Neurosci Biobehav Rev 2006;30:562-575.

14. Yu F, Kolanowski AM, Strumpf NE, Eslinger PJ. Improving cognition and function through exercise intervention in Alzheimer's disease. J Nurs Scholarsh 2006;38:358-365.

15. Netz Y, Axelrad S, Argov E. Group physical activity for demented older adults feasibility and effectiveness. Clin Rehabil 2007;21:977-986.

16. Forbes D, Forbes S, Morgan DG, Markle-Reid M, Wood J, Culum I. Physical activity programs for persons with dementia. Cochrane Database Syst Rev 2008;(3):CD006489.

17. Liu-Ambrose T, Donaldson MG. Exercise and cognition in older adults: Is there a role for resistance training programmes? Br J Sports Med 2009;43:25-27.

18. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: Clinical trials and drug development. Lancet Neurol 2010;9:702-716.

19. Maruta C, Guerreiro M, de Mendonca A, Hort J, Scheltens P. The use of neuropsychological tests across Europe: The need for a consensus in the use of assessment tools for dementia. Eur J Neurol 2011;18:279-285.

20. Chaves MLF, Godinho C, Porto CS, Masur L, Carthery-Goulart MT, Yassuda MS, Beato R. Cognitive, functional and behavioural assessment Alzheimer's disease. Dement Neuropsychol 2011;5:153-166.

21. Young J, Meagher D, Maclullich A. Cognitive assessment of older people. BMJ 2011;343:d5042.

22. Cohen J. Statistical power analysis for the behavioural sciences, ed 2. Hillsdale, Erlbaum, 1988.

23. Blankevoort CG, van Heuvelen MJ, Boersma F, Luning H, de Jong J, Scherder EJ. Review of effects of physical activity on strength, balance, mobility and ADL performance in elderly subjects with dementia. Dement Geriatr Cogn Disord 2010;30:392-402.

24. Thalheimer W, Cook S. How to calculate effect sizes from published research articles: a simplified methodology. 2002 http://worl-learning.com/effect_sizes.htm.

25. De Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: A demographic study. Aust J Physiother 2009;55:129-133.

26. Aisen PS, Saumier D, Briand R, Laurin J, Gervais F, Tremblay P, Garceau D. A phase II study targeting amyloid-beta with 3APS in mild-to-moderate Alzheimer disease. Neurology 2006;67:1757-1763.

27. Alvarez XA, Cacabelos R, Laredo M, Couceiro V, Sampedro C, Varela M, Corzo L, Fernandez-Novoa L, Vargas M, Aleixandre M, Linares C, Granizo E, Muresanu D, Moessler H. A 24-week, double-blind, placebo-controlled study of three dosages of cerebrolysin in patients with mild to moderate Alzheimer's disease. Eur J Neurol 2006;13:43-54.

28. Avila R, Carvalho IA, Bottino CM, Miotto EC. Neuropsychological rehabilitation in mild and moderate Alzheimer's disease patients. Behav Neurol 2007;18:225-233.

29. Bentham P, Gray R, Sellwood E, Hills R, Crome P, Raftery J. Aspirin in Alzheimer's disease (AD2000): A randomised open-label trial. Lancet Neurol 2008;7:41-49.

30. Black SE, Doody R, Li H, McRae T, Jambor KM, Xu Y, Sun Y, Perdomo CA, Richardson S. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. Neurology 2007;69:459-469.

31. Bottino CMC, Carvalho IAM, Alvarez AMMA, Avila R, Zukauskas PR, Bustamante SEZ, Andrade FC, Hototian SR, Saffi F, Camargo CHP. Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: A pilot study. Clin Rehabil 2005;19:861-869.

32. Boxer AL, Lipton AM, Womack K, Merrilees J, Neuhaus J, Pavlic D, Gandhi A, Red D, Martin-Cook K, Svetlik D, Miller BL. An open-label study of memantine treatment in 3 subtypes of frontotemporal lobar degeneration. Alzheimer Dis Assoc Disord 2009;23:211-217.

33. Cheng ST, Chan AC, Yu EC. An exploratory study of the effect of mahjong on the cognitive functioning of persons with dementia. Int J Geriatr Psychiatry 2006;21:611-617.

34. Choi AN, Lee MS, Cheong KJ, Lee JS. Effects of group music intervention on behavioral and psychological symptoms in patients with dementia: A pilot-controlled trial. Int J Neurosci 2009;119:471-481.

35. Cummings JL, Koumaras B, Chen M, Mirski D. Effects of rivastigmine treatment on the neuropsychiatric and behavioral disturbances of nursing home residents with moderate to severe probable Alzheimer's disease: A 26-week, multicenter, open-label study. Am J Geriatr Pharmacother 2005;3:137-148.

36. Farina E, Mantovani F, Fioravanti R, Pignatti R, Chiavari L, Imbornone E, Olivotto F, Alberoni M, Mariani C, Nemni R. Evaluating two group programmes of cognitive training in mild-to-moderate AD: Is there any difference between a 'global' stimulation and a 'cognitive-specific' one? Aging Ment Health 2006;10:211-218.

37. Feldman H, Gauthier S, Hecker J, Vellas B, Xu Y, Ieni JR, Schwam EM. Efficacy and safety of donepezil in patients with more severe Alzheimer's disease: A subgroup analysis from a randomized, placebo-controlled trial. Int J Geriatr Psychiatry 2005;20:559-569.

38. Frankfort SV, Appels BA, de BA, Tulner LR, van Campen JP, Koks CH, Beijnen JH, Schmand BA. Identification of responders and reactive domains to rivastigmine in Alzheimer's disease. Pharmacoepidemiol Drug Saf 2007;16:545-551.

39. Hampel H, Ewers M, Burger K, Annas P, Mortberg A, Bogstedt A, Frolich L, Schroder J, Schonknecht P, Riepe MW, Kraft I, Gasser T, Leyhe T, Moller HJ, Kurz A, Basun H. Lithium trial in Alzheimer's disease: A randomized, single-blind, placebo-controlled, multicenter 10-week study. J Clin Psychiatry 2009;70:922-931.

40. Ito T, Meguro K, Akanuma K, Ishii H, Mori E. A randomized controlled trial of the group reminiscence approach in patients with vascular dementia. Dement Geriatr Cogn Disord 2007;24:48-54.

41. Johannsen P, Salmon E, Hampel H, Xu Y, Richardson S, Qvitzau S, Schindler R. Assessing therapeutic efficacy in a progressive disease: A study of donepezil in Alzheimer's disease. CNS Drugs 2006;20:311-325.

42. Kadir A, Andreasen N, Almkvist O, Wall A, Forsberg A, Engler H, Hagman G, Larksater M, Winblad B, Zetterberg H, Blennow K, Langstrom B, Nordberg A. Effect of phenserine treatment on brain functional activity and amyloid in alzheimer's disease. Ann Neurol 2008;63:621-631.

43. Kennedy J, Deberdt W, Siegal A, Micca J, Degenhardt E, Ahl J, Meyers A, Kaiser C, Baker RW. Olanzapine does not enhance cognition in non-agitated and non-psychotic patients with mild to moderate Alzheimer's dementia. Int J Geriatr Psychiatry 2005;20:1020-1027.

44. Kurlan R, Cummings J, Raman R, Thal L. Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. Neurology 2007;68:1356-1363.

45. Kwak YS, Um SY, Son TG, Kim DJ. Effect of regular exercise on senile dementia patients. Int J Sports Med 2008;29:471-474.

46. Kwok T, Lee J, Lam L, Woo J. Vitamin B(12) supplementation did not improve cognition but reduced delirium in demented patients with vitamin B(12) deficiency. Arch Gerontol Geriatr 2008;46:273-282.

47. Lannfelt L, Blennow K, Zetterberg H, Batsman S, Ames D, Harrison J, Masters CL, Targum S, Bush AI, Murdoch R, Wilson J, Ritchie CW. Safety, efficacy, and biomarker findings of PBT2 in targeting A(beta) as a modifying therapy for Alzheimer's disease: A phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol 2008;7:779-786.

48. Lee ST, Chu K, Sim JY, Heo JH, Kim M. Panax ginseng enhances cognitive performance in Alzheimer disease. Alzheimer Dis Assoc Disord 2008;22:222-226.

49. Lee SB, Park CS, Jeong JW, Choe JY, Hwang YJ, Park CA, Park JH, Lee DY, Jhoo JH, Kim KW. Effects of spaced retrieval training (SRT) on cognitive function in Alzheimer's disease (AD) patients. Arch Gerontol Geriatr 2009;49:289-293.

50. Levin OS, Batukaeva LA, Smolentseva IG, Amosova NA. Efficacy and safety of memantine in dementia with lewy bodies. J Neurol Neurosurg Psychiatry 2008;108:39-46.

51. Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, Wetterholm AL, Haglund A, Zhang R, Schindler R. 3-year study of donepezil therapy in Alzheimer's disease: Effects of early and continuous therapy. Dement Geriatr Cogn Disord 2006;21:353-363.

52. Mazza M, Capuano A, Bria P, Mazza S. Ginkgo biloba and donepezil: A comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. Eur J Neurol 2006;13:981-985.

53. Mizukami K, Asada T, Kinoshita T, Tanaka K, Sonohara K, Nakai R, Yamaguchi K, Hanyu H, Kanaya K, Takao T, Okada M, Kudo S, Kotoku H, Iwakiri M, Kurita H, Miyamura T, Kawasaki Y, Omori K, Shiozaki K, Odawara T, Suzuki T, Yamada S, Nakamura Y, Toba K. A randomized cross-over study of a traditional japanese medicine (kampo), yokukansan, in the treatment of the behavioral and psychological symptoms of dementia. Int J Neuropsychopharmacol 2009;12:191-199.

54. Modrego PJ, Pina MA, Fayed N, Diaz M. Changes in metabolite ratios after treatment with rivastigmine in Alzheimer's disease: A nonrandomised controlled trial with magnetic resonance spectroscopy. CNS Drugs 2006;20:867-877.

55. Mohs RC, Shiovitz TM, Tariot PN, Porsteinsson AP, Baker KD, Feldman PD. Atomoxetine augmentation of cholinesterase inhibitor therapy in patients with Alzheimer disease: 6-month, randomized, double-blind, placebo-controlled, parallel-trial study. Am J Geriatr Psychiatry 2009;17:752-759.

56. Moretti R, Torre P, Antonello RM, Cazzato G, Pizzolato G. Different responses to rivastigmine in subcortical vascular dementia and multi-infarct dementia. Am J Alzheimers Dis Other Demen 2008;23:167-176.

57. Mowla A, Pani A. Comparison of topiramate and risperidone for the treatment of behavioral disturbances of patients with Alzheimer disease: A double-blind, randomized clinical trial. J Clin Psychopharmacol 2010;30:40-43.

58. Onder G, Zanetti O, Giacobini E, Frisoni GB, Bartorelli L, Carbone G, Lambertucci P, Silveri MC, Bernabei R. Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: Randomised controlled trial. Br J Psychiatry 2005;187:450-455.

59. Onor ML, Trevisiol M, Negro C, Signorini A, Saina M, Aguglia E. Impact of a multimodal rehabilitative intervention on demented patients and their caregivers. Am J Alzheimers Dis Other Demen 2007;22:261-272.

60. Ootani M, Nara I, Kaneko F, Okamura H. Construction of a speed feedback therapy system to improve cognitive impairment in elderly people with dementia: A preliminary report. Dement Geriatr Cogn Disord 2005;20:105-111.

61. Penner J, Rupsingh R, Smith M, Wells JL, Borrie MJ, Bartha R. Increased glutamate in the hippocampus after galantamine treatment for Alzheimer disease. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:104-110.

62. Plastino M, Fava A, Pirritano D, Cotronei P, Sacco N, Sperli T, Spano A, Gallo D, Mungari P, Consoli D, Bosco D. Effects of insulinic therapy on cognitive impairment in patients with Alzheimer disease and diabetes mellitus type-2. J Neurol Sci 2010;288:112-116.

63. Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: A randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res 2008;5:83-89.

64. Potkin SG, Alva G, Gunay I, Koumaras B, Chen M, Marski D. A pilot study evaluating the efficacy and safety of rivastigmine in patients with mixed dementia. Drugs Aging 2006;23:241-249.

65. Rainer M, Haushofer M, Pfolz H, Struhal C, Wick W. Quetiapine versus risperidone in elderly patients with behavioral and psychological symptoms of dementia: Efficacy, safety and cognitive function. Eur Psychiatry 2007;22:395-403.

66. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ. A 24-week open-label extension study of memantine in moderate to severe Alzheimer disease. Arch Neurol 2006;63:49-54.

67. Requena C, Maestu F, Campo P, Fernandez A, Ortiz T. Effects of cholinergic drugs and cognitive training on dementia: 2-year follow-up. Dement Geriatr Cogn Disord 2006;22:339-345.

68. Roman GC, Wilkinson DG, Doody RS, Black SE, Salloway SP, Schindler RJ. Donepezil in vascular dementia: Combined analysis of two large-scale clinical trials. Dement Geriatr Cogn Disord 2005;20:338-344.

69. Savaskan E, Schnitzler C, Schroder C, Cajochen C, Muller-Spahn F, Wirz-Justice A. Treatment of behavioral, cognitive and circadian rest-activity cycle disturbances in Alzheimer's disease: Haloperidol vs. quetiapine. Int J Neuropsychopharmacol 2006;9:507-516.

70. Scheltens P, Kamphuis PJ, Verhey FR, Olde Rikkert MG, Wurtman RJ, Wilkinson D, Twisk JW, Kurz A. Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial. Alzheimers Dement 2010;6:1-10.

71. Soininen H, West C, Robbins J, Niculescu L. Long-term efficacy and safety of celecoxib in Alzheimer's disease. Dement Geriatr Cogn Disord 2007;23:8-21.

72. Sparks DL, Connor DJ, Sabbagh MN, Petersen RB, Lopez J, Browne P. Circulating cholesterol levels, Apo lipoprotein E genotype and dementia severity influence the benefit of atorvastatin treatment in Alzheimer's disease: Results of the Alzheimer's disease cholesterol-lowering treatment (ADCLT) trial. Acta Neurol Scand , Suppl 2006;185:3-7.

73. Bullock R, Bergman H, Touchon J, Gambina G, He Y, Nagel J, Lane R. Effect of age on response to rivastigmine or donepezil in patients with alzheimer's disease. Curr Med Res Opin 2006;22:483-494.

74. Winblad B, Kilander L, Eriksson S, Minthon L, Batsman S, Wetterholm AL, Jansson-Blixt C, Haglund A, Severe Alzheimer's Disease Study Group. Donepezil in patients with severe Alzheimer's disease: Double-blind, parallel-group, placebo-controlled study. Lancet 2006;367:1057-1065.

75. Winstein CJ, Bentzen KR, Boyd L, Schneider LS. Does the cholinesterase inhibitor, donepezil, benefit both declarative and non-declarative processes in mild to moderate alzheimer's disease? Curr Alzheimer Res 2007;4:273-276.

76. Yu J, Zhang X, Liu C, Meng Y, Han J. Effect of acupuncture treatment on vascular dementia. Neurol Res 2006;28:97-103.

77. Miu DKY, Szeto SL, Mak YF. A randomized controlled trial on the effect of exercise on physical, cognitive and affective function in dementia subjects. Asian J Gerontol Geriatr 2008;3:8-16.

78. Yaguez L, Shaw KN, Morris R, Matthews D. The effects on cognitive functions of a movement-based intervention in patients with Alzheimer's type dementia: A pilot study. Int J Geriatr Psychiatry 2011;26:173-181.

79. Venturelli M, Scarsini R, Schena F. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. Am J Alzheimers Dis Other Demen 2011;26:381-8.

80. Aronson S, Van Baelen B, Kavanagh S, Schwalen S. Optimal dosing of galantamine in patients with mild or moderate Alzheimer's disease: Post hoc analysis of a randomized, double-blind, placebo-controlled trial. Drugs Aging 2009;26:231-239.

81. Auchus AP, Brashear HR, Salloway S, Korczyn AD, De Deyn PP, Gassmann-Mayer C. Galantamine treatment of vascular dementia: A randomized trial. Neurology 2007;69:448-458.

82. Bakchine S, Loft H. Memantine treatment in patients with mild to moderate alzheimer's disease: Results of a randomised, double-blind, placebo-controlled 6-month study. J Alzheimers Dis 2007;11:471-479.

83. Chappell AS, Gonzales C, Williams J, Witte MM, Mohs RC, Sperling R. AMPA potentiator treatment of cognitive deficits in Alzheimer disease. Neurology 2007;68:1008-1012.

84. Lu PH, Masterman DA, Mulnard R, Cotman C, Miller B, Yaffe K, Reback E, Porter V, Swerdloff R, Cummings JL. Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. Arch Neurol 2006;63:177-185.

85. Modrego PJ, Fayed N, Errea JM, Rios C, Pina MA, Sarasa M. Memantine versus donepezil in mild to moderate alzheimer's disease: A randomized trial with magnetic resonance spectroscopy. Eur J Neurol 2010;17:405-412.

86. Mori S, Mori E, Iseki E, Kosaka K. Efficacy and safety of donepezil in patients with dementia with lewy bodies: Preliminary findings from an open-label study. Psychiatry Clin Neurosci 2006;60:190-195.

87. Muresanu DF, Alvarez XA, Moessler H, Buia M, Stan A, Pintea D, Moldovan F, Popescu BO. A pilot study to evaluate the effects of cerebrolysin on cognition and qEEG in vascular dementia: Cognitive improvement correlates with qEEG acceleration. J Neurol Sci 2008;267:112-119.

88. Paleacu D, Barak Y, Mirecky I, Mazeh D. Quetiapine treatment for behavioral and psychological symptoms of dementia in Alzheimer's disease patients: A 6-week, double-blind, placebo-controlled study. Int J Geriatr Psychiatry 2008;23:393-400.

89. Peskind ER, Potkin SG, Pomara N, Ott BR, Graham SM, Olin JT, McDonald S. Memantine treatment in mild to moderate Alzheimer disease: A 24-week randomized, controlled trial. Am J Geriatr Psychiatry 2006;14:704-715.

90. Pomara N, Ott BR, Peskind E, Resnick EM. Memantine treatment of cognitive symptoms in mild to moderate alzheimer disease: Secondary analyses from a placebo-controlled randomized trial. Alzheimer Dis Assoc Disord 2007;21:60-64.

91. Raggi A, Iannaccone S, Marcone A, Ginex V, Ortelli P, Nonis A, Giusti MC, Cappa SF. The effects of a comprehensive rehabilitation program of Alzheimer's disease in a hospital setting. Behav Neurol 2007;18:1-6.

92. Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, Sabbagh M, Honig LS, Doody R, van Dyck CH, Mulnard R, Barakos J, Gregg KM, Liu E, Lieberburg I, Schenk D, Black R, Grundman M. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology 2009;73:2061-2070.

93. Suh GH, Jung HY, Lee CU, Oh BH, Lee SK, Lee N, Kim J, Kee BS, Ko D, Kim YH, Ju YS, Hong I, Choi S. Effect of the apolipoprotein E epsilon4 allele on the efficacy and tolerability of galantamine in the treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 2006;21:33-39.

94. Wilkinson D, Schindler R, Schwam E, Waldemar G, Jones RW, Gauthier S, Lopez OL, Cummings J, Xu Y, Feldman HH. Effectiveness of donepezil in reducing clinical worsening in patients with mild-to-moderate Alzheimer's disease. Dement Geriatr Cogn Disord 2009;28:244-251.

95. Winblad B, Grossberg G, Frolich L, Farlow M, Zechner S, Nagel J, Lane R. IDEAL: A 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. Neurology 2007;69:S14-S22.

96. McCarney R, Fisher P, Iliffe S, van Haselen R, Griffin M, van der Meulen J, Warner J. Ginkgo biloba for mild to moderate dementia in a community setting: A pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial. Int J Geriatr Psychiatry 2008;23:1222-1230.

97. Frolich L, Ashwood T, Nilsson J, Eckerwall G, Sirocco Investigators. Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: A phase IIb dose-finding study. J Alzheimers Dis 2011;24:363-374.

98. Cherrier MM, Matsumoto AM, Amory JK, Asthana S, Bremner W, Peskind ER, Raskind MA, Craft S. Testosterone improves spatial memory in men with alzheimer disease and mild cognitive impairment. Neurology 2005;64:2063-2068.

99. Eggermont L, Swaab D, Hol E, Scherder E. Walking the line: A randomised trial on the effects of a short term walking programme on cognition in dementia. J Neurol Neurosurg Psychiatry 2009;80:802-804.

100. Napryeyenko O, Sonnik G, Tartakovsky I. Efficacy and tolerability of ginkgo biloba extract EGb 761 by type of dementia: Analyses of a randomised controlled trial. J Neurol Sci 2009;283:224-229.

101. Ancoli-Israel S, Palmer BW, Cooke JR, Corey-Bloom J, Fiorentino L, Natarajan L, Liu L, Ayalon L, He F, Loredo JS. Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: A randomized controlled study. J Am Geriatr Soc 2008;56:2076-2081.

102. Scherder EJ, van Tol MJ, Swaab DF. High-frequency cranial electrostimulation (CES) in patients with probable Alzheimer's disease. Am J Phys Med Rehabil 2006;85:614-618.

103. Scherder EJ, Vuijk PJ, Swaab DF, Van Someren EJ. Estimating the effects of right median nerve stimulation on memory in Alzheimer's disease: A randomized controlled pilot study. Exp Aging Res 2007;33:177-186.

104. Eggermont LH, Knol DL, Hol EM, Swaab DF, Scherder EJ. Hand motor activity, cognition, mood, and the rest-activity rhythm in dementia A clustered RCT. Behav Brain Res 2009;196:271-278.

105. Homma A, Imai Y, Tago H, Asada T, Shigeta M, Iwamoto T, Takita M, Arimoto I, Koma H, Ohbayashi T. Donepezil treatment of patients with severe alzheimer's disease in a japanese population: Results from a 24-week, double-blind, placebo-controlled, randomized trial. Dement Geriatr Cogn Disord 2008;25:399-407.

106. Schmitt FA, van Dyck CH, Wichems CH, Olin JT. Cognitive response to memantine in moderate to severe alzheimer disease patients already receiving donepezil: An exploratory reanalysis. Alzheimer Dis Assoc Disord 2006;20:255-262.

107. van Dyck CH, Schmitt FA, Olin JT. A responder analysis of memantine treatment in patients with Alzheimer disease maintained on donepezil. Am J Geriatr Psychiatry 2006;14:428-437.

108. Stevens J, Killeen M. A randomised controlled trial testing the impact of exercise on cognitive symptoms and disability of residents with dementia. Contemp Nurse 2006;21:32-40.

109. Rahman S, Robbins TW, Hodges JR, Mehta MA, Nestor PJ, Clark L, Sahakian BJ. Methylphenidate ('ritalin') can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. Neuropsychopharmacology 2006;31:651-658.

110. Paskavitz JF, Gunstad JJ, Samuel JE. Clock drawing and frontal lobe behavioral effects of memantine in Alzheimer's disease: A rater-blinded study. Am J Alzheimers Dis Other Demen 2006;21:454-459.

111. Kemoun G, Thibaud M, Roumagne N, Carette P, Albinet C, Toussaint L, Paccalin M, Dugue B. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dement Geriatr Cogn Disord 2010;29:109-114.

112. Anthony JC, LeResche L, Niaz U, von Korff MR, Folstein MF. Limits of the 'mini-mental state' as a screening test for dementia and delirium among hospital patients. Psychol Med 1982;12:397-408.

113. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.

114. Dick JP, Guiloff RJ, Stewart A, Blackstock J, Bielawska C, Paul EA, Marsden CD. Mini-mental state examination in neurological patients. J Neurol Neurosurg Psychiatry 1984;47:496-499.

115. Molloy DW, Alemayehu E, Roberts R. Reliability of a standardized mini-mental state examination compared with the traditional mini-mental state examination. Am J Psychiatry 1991;148:102-105.

116. Fillenbaum GG, Heyman A, Wilkinson WE, Haynes CS. Comparison of two screening tests in alzheimer's disease. The correlation and reliability of the mini-mental state examination and the modified blessed test. Arch Neurol 1987;44:924-927.

117. Thal LJ, Grundman M, Golden R. Alzheimer's disease: A correlational analysis of the blessed information-memory-concentration test and the mini-mental state exam. Neurology 1986;36:262-264.

118. Uhlmann RF, Larson EB, Buchner DM. Correlations of mini-mental state and modified dementia rating scale to measures of transitional health status in dementia. J Gerontol 1987;42:33-36.

119. Tombaugh TN, McIntyre NJ. The mini-mental state examination: A comprehensive review. J Am Geriatr Soc 1992;40:922-935.

120. McDowell I, Kristjansson B, Hill GB, Hebert R. Community screening for dementia: The mini mental state exam (MMSE) and modified mini-mental state exam (3MS) compared. J Clin Epidemiol 1997;50:377-383.

121. Holzer CE, Tischler GL, Leaf P.J., Myers JK. An epidemiologic assessment of cognitive impairment in a community population. Res Com Health 1984;4:3-32.

122. Kay DW, Henderson AS, Scott R, Wilson J, Rickwood D, Grayson DA. Dementia and depression among the elderly living in the hobart community: The effect of the diagnostic criteria on the prevalence rates. Psychol Med 1985;15:771-788.

123. Foreman MD. Reliability and validity of mental status questionnaires in elderly hospitalized patients. Nurs Res 1987;36:216-220.

124. Albert M, Cohen C. The test for severe impairment: An instrument for the assessment of patients with severe cognitive dysfunction. J Am Geriatr Soc 1992;40:449-453.

125. Tombaugh TN, McDowell I, Kristjansson B, Hubley AM. Mini-mental state examination (MMSE) and the modified MMSE (3MS): A psychometric comparison and normative data. Arch Clin Neuropsychol 1996;8:48-59.

126. Mavioglu H, Gedizlioglu M, Akyel S, Aslaner T, Eser E. The validity and reliability of the turkish version of alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) in patients with mild and moderate alzheimer's disease and normal subjects. Int J Geriatr Psychiatry 2006;21:259-265.

127. Rosen WG, Mohs RC, Davis KL. A new rating scale for alzheimer's disease. Am J Psychiatry 1984;141:1356-1364.

128. Pena-Casanova J. Alzheimer's disease assessment scale--cognitive in clinical practice. Int Psychogeriatr 1997;9 Suppl 1:105-114.

129. Weyer G, Erzigkeit H, Kanowski S, Ihl R, Hadler D. Alzheimer's disease assessment scale: Reliability and validity in a multicenter clinical trial. Int Psychogeriatr 1997;9:123-138.

130. Liu HC, Teng EL, Chuang YY, Lin KN, Fuh JL, Wang PN. The alzheimer's disease assessment scale: Findings from a low-education population. Dement Geriatr Cogn Disord 2002;13:21-26.

131. Chu LW, Chiu KC, Hui SL, Yu GK, Tsui WJ, Lee PW. The reliability and validity of the alzheimer's disease assessment scale cognitive subscale (ADAS-cog) among the elderly Chinese in Hong Kong. Ann Acad Med Singapore 2000;29:474-485.

132. Kim YS, Nibbelink DW, Overall JE. Factor structure and reliability of the Alzheimer's disease assessment scale in a multicenter trial with linopirdine. J Geriatr Psychiatry Neurol 1994;7:74-83.

133. Mohs RC. The alzheimer's disease assessment scale. Int Psychogeriatr 1996;8:195-203.

134. Tsolaki M, Fountoulakis K, Nakopoulou E, Kazis A, Mohs RC. Alzheimer's disease assessment scale: The validation of the scale in Greece in elderly demented patients and normal subjects. Dement Geriatr Cogn Disord 1997;8:273-280.

135. Cano SJ, Posner HB, Moline ML, Hurt SW, Swartz J, Hsu T, Hobart JC. The ADAS-cog in Alzheimer's disease clinical trials: Psychometric evaluation of the sum and its parts. J Neurol Neurosurg Psychiatry 2010;81:1363-1368.

136. Ahn IS, Kim JH, Ku HM, Saxton J, Kim DK. Reliability and validity of the severe impairment battery (SIB) in Korean dementia patients. J Korean Med Sci 2006;21:506-517.

137. Suh GH, Kang CJ. Validation of the severe impairment battery for patients with Alzheimer's disease in Korea. Int J Geriatr Psychiatry 2006;21:626-632.

138. Panisset M, Roudier M, Saxton J, Boller F. Severe impairment battery. A neuropsychological test for severely demented patients. Arch Neurol 1994;51:41-45.

139. Schmitt FA, Ashford W, Ernesto C, Saxton J, Schneider LS, Clark CM, Ferris SH, Mackell JA, Schafer K, Thal LJ. The severe impairment battery: Concurrent validity and the assessment of longitudinal change in Alzheimer's disease. the Alzheimer's disease cooperative study. Alzheimer Dis Assoc Disord 1997;11 Suppl 2:S51-6.

140. Bergh S, Selbaek G, Engedal K. Reliability and validity of the Norwegian version of the severe impairment battery (SIB). Int J Geriatr Psychiatry 2008;23:896-902.

141. Schmitt FA, Saxton JA, Xu Y, McRae T, Sun Y, Richardson S, Li H. A brief instrument to assess treatment response in the patient with advanced Alzheimer disease. Alzheimer Dis Assoc Disord 2009;23:377-383.

142. Kim H, Chey J. Effects of education, literacy, and dementia on the clock drawing test performance. J Int Neuropsychol Soc 2010;16:1138-1146.

143. Shulman KI, Pushkar Gold D, Cohen CA, Zucchero CA. Clock-drawing and dementia in the community: A longitudinal study. Int J Geriatr Psychiatry 1993;8:487-496.

144. Sunderland T, Hill JL, Mellow AM, Lawlor BA, Gundersheimer J, Newhouse PA, Grafman JH. Clock drawing in Alzheimer's disease. A novel measure of dementia severity. J Am Geriatr Soc 1989;37:725-729.

145. Wolf-Klein GP, Silverstone FA, Levy AP, Brod MS. Screening for Alzheimer's disease by clock drawing. J Am Geriatr Soc 1989;37:730-734.

146. Schramm U, Berger G, Muller R, Kratzsch T, Peters J, Frolich L. Psychometric properties of clock drawing test and MMSE or short performance test (SKT) in dementia screening in a memory clinic population. Int J Geriatr Psychiatry 2002;17:254-260.

147. Manos PJ. The utility of the ten-point clock test as a screen for cognitive impairment in general hospital patients. Gen Hosp Psychiatry 1997;19:439-444.

148. Chiu YC, Li CL, Lin KN, Chiu YF, Liu HC. Sensitivity and specificity of the clock drawing test, incorporating rouleau scoring system, as a screening instrument for questionable and mild dementia: Scale development. Int J Nurs Stud 2008;45:75-84.

149. Seigerschmidt E, Mosch E, Siemen M, Forstl H, Bickel H. The clock drawing test and questionable dementia: Reliability and validity. Int J Geriatr Psychiatry 2002;17:1048-1054.

150. Netz Y, Axelrad S, Argov E. Group physical activity for demented older adults -feasibility and effectiveness. Clin Rehabil 2007;21:977-986.

151. Rolland Y, Pillard F, Klapouszczak A, Reynish E, Thomas D, Andrieu S, Riviere D, Vellas B. Exercise program for nursing home residents with Alzheimer's disease: A 1-year randomized, controlled trial. J Am Geriatr Soc 2007;55:158-165.

152. Santana-Sosa E, Barriopedro MI, Lopez-Mojares LM, Perez M, Lucia A. Exercise training is beneficial for Alzheimer's patients. Int J Sports Med 2008;29:845-850.

153. Ries JD, Echternach JL, Nof L, Gagnon Blodgett M. Test-retest reliability and minimal detectable change scores for the timed "up & go" test, the six-minute walk test, and gait speed in people with Alzheimer disease. Phys Ther 2009;89:569-579.

154. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clin Proc 2011;86:876-884.