Age and Ageing

Short Report

Title Page

Title: Systematic review investigating the reporting of comorbidities and medication in randomised controlled trials of people with dementia

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Abstract

Objectives: Dementia is a debilitating condition characterised by global loss of cognitive and intellectual functioning, which reduces social and occupational performance. This population frequently present with medical co-morbidities such as hypertension, cardiovascular disease and diabetes. The CONSORT statement outlines recommended guidance on reporting of participant characteristics in clinical trials. It is however unclear how much these are adhered to in trials assessing people with dementia. This paper assesses the reporting of medical co-morbidities and prescribed medications for people with dementia within randomised controlled trial (RCT) reports.

Design: A systematic review of the published literature from the databases AMED, CINAHL, MEDLINE, EMBASE and the Cochrane Clinical Trial Registry from 1st January 1997 to 9th January 2014, to identify RCTs detailing baseline medical co-morbidities and prescribed medications was undertaken. Eligible studies were appraised using the Critical Appraisal Skills Programme (CASP) RCT appraisal tool, and descriptive statistical analyses were calculated to determine point prevalence.

Results: Nine trials including 1474 people with dementia were identified presenting medical co-morbidity data. These indicated neurological disorders (prevalence 91%), vascular disorders (prevalence 91%), cardiac disorders (prevalence 74%) and ischaemic cerebrovascular disease (prevalence 53%) were most frequently seen.

Conclusions: Published RCTs poorly report medical co-morbidities and medications for people with dementia. Future trials should include report of these items to allow interpretation of whether the results are generalisable to frailer older older populations.

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Keywords: Cognitive impairment; dementia ; co-morbidity; elderly; systematic review

Key Points:

- Dementia is a growing health challenge for primary and secondary care providers worldwide.

- CONSORT statement recommends participant demographic information be provide to ease trial generalisability.
- Currently medical co-morbidities and medicine prescribing is poorly reported in randomised controlled trials in dementia.
- Future research must address this limitation to improve reporting of medical comorbidities and prescribed medications.

Introduction

Dementia is a debilitating condition characterised by global loss of cognitive and intellectual functioning, which gradually interferes with social and occupational performance. It is anticipated that the incidence of people with dementia will increase during the next 25 years due to the ageing population [1]. Since dementia is most frequently associated with older people, people with dementia most commonly present with additional co-existing medical conditions. Such co-morbidities may include diabetes, chronic obstructive pulmonary disorder, musculoskeletal disorders and chronic cardiac failure [2].

No studies have previously attempted to determine what the co-morbidities of this group of people are. This is important as it will highlight what the common care needs are, based on a diagnosis of dementia and other medical conditions, which this population share. Given documented difficulties in people with dementia accessing healthcare resources and communicating medical complaints [3], a greater awareness of all the physical and mental health needs of this group of people is important.

The CONSORT statement was developed to improve the reporting of randomised controlled trials (RCTs) published within the literature [4]. Item 15 of the 2010 CONSORT statement emphasises the importance of identifying key variables at baseline which may have prognostic strength of the variables measured. Therefore the reporting of comorbidities in RCTs, can be considered essential practice for people with dementia. Given this importance, the purpose of this paper was to: (1) identify the medical co-morbidities have been reported for people with dementia who have been recruited into trials; and (2) to assess the frequency of reporting for medical co-morbidities within the literature for this population.

Materials and Methods

Eligibility Criteria

A search of randomised controlled trials (RCTs) was undertaken to gain the necessary data to answer this question. All RCTs published from 1st January 1997 to 1st January 2014 which recruited people aged 65 years or over, diagnosed with dementia and presented data on their co-morbidities and/or detailed the medications these people were prescribed, were included. Dementia was defined as any form of dementia (i.e. vascular, multi-infarct, Alzheimers).

Search Strategy

An electronic search of the databases: AMED, CINAHL, MEDLINE, EMBASE and the Cochrane Clinical Trial Registry were conducted on 9th January 2014. The MEDLINE search strategy is presented in **Supplementary Table 1**. Two review authors reviewed the titles and/or full texts of all identified studies (TS/IM). An iterative search was adopted where initially databases from 2014 to 2007 were searched to identify co-morbidities. The search was extended to 1997, where, no more co-morbidities or medications were identified. It was considered that 'saturation' had been reached, therefore further searches were not required.

Extraction and Appraisal

Data were extracted independently by two review authors (JH/TM) using a pre-defined sheet. The quality of the included papers was determined using a modified version of the Critical Appraisal Skills Programme (CASP) RCT study tool [5]. This was undertaken by two reviewers (JH/TM). Any disagreements between the reviewers on data extraction or appraisal were adjudicated by a third reviewer (TS).

Data Analysis

Each co-morbidity was ranked as a physical or psychological co-morbidity based on the frequency of the condition reported within the literature. The frequency of presentation within the included studies was determined, and the prevalence estimated.

Results

Search Results

The search strategy results are presented in **Supplementary Figure 1**. A total of 1234 papers were identified from the search strategy. Following examination, nine papers were eligible and included. The principle reason for exclusion was the absence of data reporting on co-morbidities from study cohorts (94%).

Critical Appraisal

Supplementary Table 2 summarises the results of the critical appraisal exercise. The evidence was of largely moderate quality with only one study [6] assessed as low quality. Recurrent limitations within the evidence included not clearly documenting how co-morbidities were determined within the cohorts assessed (n=7), not documenting the characteristics of the cohort sufficiently clearly to determine generalizability to the wider population (n=8).

Characteristics of Included Studies

A summary of the study characteristics is presented in **Supplementary Table 3**. In total 1474 people with dementia were included; 560 males and 914 females. Mean age across the studies ranged from 65 years [7] to 84.4 years [6]. Studies were conducted in the Ukraine [7], Japan [6], Russia [8], Brazil [9], Italy [10], Germany [11], Sweden [12] and the USA [13]. One study was multi-national and was conducted across the Netherlands, Germany, UK and USA [14].

Dementia was diagnosed by a variety of methods. These included the Mini Mental State Examination (MMSE) [8,10-14], the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) [7,8,10,11,14], radiological investigations such as magnetic resonance imaging (MRI) and computed tomography [7,8,11,13,14], Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV) [6,8,13], Clinical Dementia Rating (CDR) [9] and the modified Haschinki Ischaemic Score [8]. Mean impairment scores, as assessed using the MMSE ranged from 6.9 [12] to 24 [14].

Clinical Findings

Thirteen co-morbidities were identified from the evidence-base (**Table 1**). The most prevalent of these was termed neurological disorders (prevalence 91%), vascular disorders (prevalence 91%), cardiac disorders (prevalence 73%) and depression (prevalence 59%). Sleep apnoea was reported in all 23 people in one study, but this study was specifically investigating this co-morbidity and therefore is not representative of the general population of people with dementia. The least prevalent co-morbidities were cancer (prevalence 11%), diabetes (prevalence 15%) and osteoporosis (prevalence 27%).

Twenty-one prescribed medications were identified. These were divided into four groups: cardiovascular, central nervous system, antithrombotic agents and others, and are presented in **Table 2**. The others category consisted of calcium supplements, analgesics, gastric ulcer medications, thyroid medications and vitamin K. Overall, there was generally a low prevalence of prescribed medications for this population (**Table 2**). The most frequently prescribed medications were hypertensive medications, specifically prescribed with a prevalence of 74%. Following this, analgesics (prevalence 30%), anxiolytic drugs (prevalence 37%) and renin-angiotensin drugs were prescribed within the reported cohorts.

Discussion

This paper has provided preliminary information on common co-morbidities which are seen in people with dementia. Cardiovascular pathologies appear to be the most prevalent, based on both the results of co-morbidities reported and prescribed medications from the reported cohorts with dementia. This reflects the findings in elderly populations in general, irrespective of a dementia diagnosis [15]. These findings can be used to better inform clinicians about which conditions they can expect to see exhibited in this population. This is of particular relevance for dementia which can significantly impair a person's capability to communicate and express their health status.

The results are based on RCT data, and consequently these findings are likely to be based on a self-selecting sample of the population with dementia through two means. Firstly, only people eligible to participate in the included trials would have been included in our analysis. Accordingly, people with an active infection, such as a urinary tract infection, those with unstable cardiovascular status, or those taking medications with contraindications for an experimental intervention would have been excluded. Therefore a number of important co-morbidities or medications may have been omitted from the review. Secondly, as the results are based on clinical trial populations, a proportion of participants and/or their carers may be disengaged from participating in a clinical trial due to social or environmental factors [16]. Accordingly, this population may have presented with different medical co-morbidities or prescribed medications.

The findings acknowledge the poor reporting of co-morbidities and prescribed medications. Whilst nine papers presented data on the overall medical status and co-morbidities exhibited by their study cohorts, fifteen otherwise eligible papers did not present this data. As well as limiting the possible dataset available for this review, this raises a major issue about potential study generalisability of previous clinical trials in dementia research. Not fully appreciating the medical status and co-morbidities of cohorts means that the reader is unable to fully generalise the findings of a specific trial to their own patient group. Furthermore, interventions such as medication or physical activity may be more or less effective for some specific participant groups dependent on their co-morbidities.

Therefore a major recommendation is that medical co-morbidities should be more widely reported within the description of cohort characteristics.

There was variable terminology in co-morbidities. For example, vascular, cardiac and neurological disorders were terms used in Ihl et al's [7] paper; these terms provide an indication of the general medical co-morbidity, but do not specifically describe exactly which medical conditions are associated with this pathology. Similarly medication usage was poorly reported with a lack of standardisation making it difficult to compare usage between the different studies. Some of the terminology used was imprecise with the potential for confusion. For example Doody et al [8] included the classification "psychoactive drugs" which, although not defined, appeared to include antidepressants, sedatives, hypnotic and antipsychotics. The same study included the classification anxiolytic however the difference between an anxiolytic and a psychoactive drug was not clearly stated. Both co-morbidities and medication usage should therefore be reported in a standardised fashion, for example using the WHO Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atc_ddd_index/) for medications.

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Declaration of Conflicts of Interest: none

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Tables and Figure Legends

Table 1: Results of identified comorbidities and prevalence values from included studies

Table 2: Prescribed medications people with dementia were documented as receiving in included studies

Supplementary Figure 1: PRISMA flow-chart presenting search results

Supplementary Table 1: MEDLINE search strategy

Supplementary Table 2: Summary of the CASP critical appraisal results

Supplementary Table 3: Characteristics of included studies

Table 1. Results of identified comorbidities and prevalence values from included studies.

Co-morbidity	Number of Studies	Total Number of People with/cohort size	Prevalence (%)
Ischaemic cerebrovascular disease	2	49/92	53
Hypertension	2	121/255	47
Cardiovascular	2	79/193	41
Diabetes Mellitus	2	29/193	15
Depression	2	113/193	59
Vascular Disorder	1	368/404	91
Hypercholesteremia	1	79/225	35
Osteoporosis	1	61/225	27
Neurological Disorder	1	368/404	91
Cardiac disorder	1	298/404	74
Cancer	1	7/62	11
Psychosis	1	41/132	31
Sleep apnoea	1	23/23	100

Table 2. Prescribed medications people with dementia were documented as receiving in included studies.

Cardiovascular Medicines

Medication	Number of Studies	Total Number of People with/cohort size	Prevalence (%)
Renin-Angiotensin Drugs	3	165/464	36
Ca-Antagonists	2	23/434	5
Beta-blockers	1	42/404	10
Termed "hypertensive medications"	1	73/98	74
Vasodilators	1	3/30	10

Central Nervous System Medicines

Medication	Number of Studies	Total Number of People with/cohort size	Prevalence (%)
Antidepressants	2	42/94	45
Anxiolytic drugs	1	36/98	37
Psychoactive medications	1	23/98	23
Antipsychotics	1	3/30	10
Sedatives	1	3/30	10

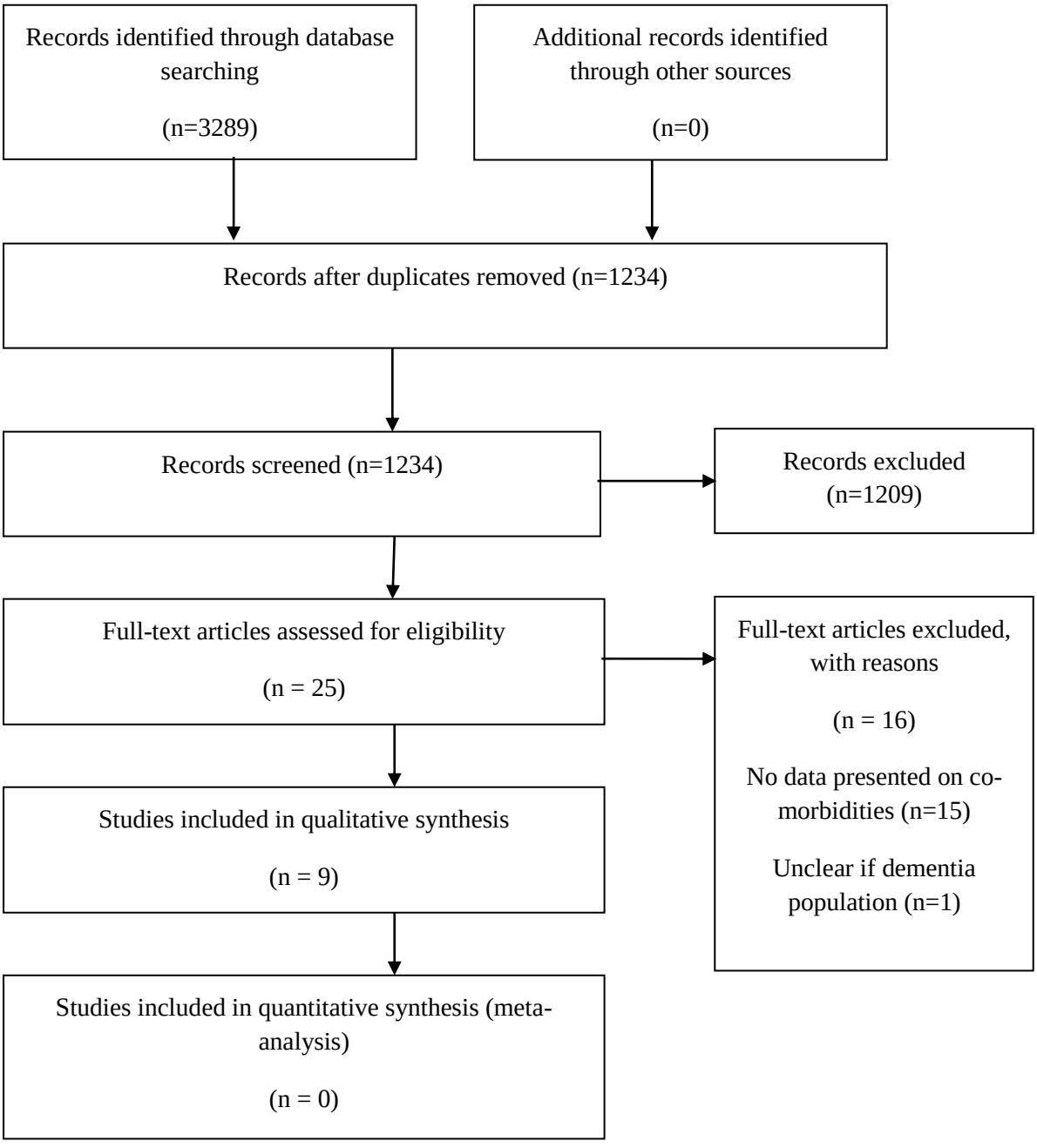
Antithrombotic agents

Medication	Number of Studies	Total Number of People with/cohort size	Prevalence (%)
Antithrombotic agents	2	34/434	8
Antiplatelet drugs	1	22/98	22

Others

Medication	Number of Studies	Total Number of People with/cohort size	Prevalence (%)
Calcium supplements	1	3/30	10
Analgesics	1	9/30	30
Peptic Ulcer Drugs	1	6/30	20
Vitamin K	1	3/30	10
Thyroid therapy	1	3/30	10
Benign prostatic hypertrophy drugs	1	3/30	10

Supplementary Figure 1: PRISMA flow-chart presenting search results



Supplementary Table 1: MEDLINE Search Strategy

1. dementia.ti,ab
2. dement*.ti,ab
3. alzheimer*.ti,ab
4. ((lewy* adj2 bod*)).ti,ab
5. 1 OR 2 OR 3 OR 4
6. (randomized AND controlled AND trial).ti,ab
7. (controlled AND clinical AND trial).ti,abrandomi?ed.ti,ab
8. randomly.ti,ab
9. ((RCT OR CCT)).ti,ab
10. 6 OR 7 OR 8 OR 9 OR 10
11. 5 AND 11

Supplementary Table 2: Summary of the CASP critical appraisal results

Criterion	del Ser [11]	Doody [8]	Ihl [7]	Iwasaki [6]	Moraes [9]	Scarpini [10]	Scheltens [14]	Stenvall [12]	Trzepacz [13]
Was the cohort recruited in an acceptable way?	✓	✓	✓	N/C	✓	✓	✓	✓	✓
Was the co-morbidity accurately measured to minimize bias?	X	X	X	✓	✓	X	X	X	X
Was the diagnosis of dementia clearly presented? [1]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the cohort typical (generalizable) of the dementia population?	X	X	✓	X	X	N/C	X	✓	✓
Do the results of this study fit with other available evidence?	✓	✓	✓	X	✓	✓	✓	✓	✓
Overall Methodological Quality	3	4	4	2	5	3	3	4	4

✓ - yes; x – no; N/C – Not Clear; Methodological Quality: 5/5 = high; 4-3/5 = moderate; 2-0/5 = low

Supplementary Table 3. Characteristics of included studies.

Study	**Sample Size**	**Gender (m/f)**	**Age in years (mean,range,both)**	**Diagnosis of Dementia**	**Impairment score (e.g. MMSE/** ADAS-Cog)	**Institutional Living (Frequency in cohort)**
del Ser [11]	n=30 Treatment group: n=20 Placebo group: n=10	F = 20/30 (67%) M = 10/30 (33%) Treatment group: F = 13/20 (65%) M= 7/20 (45%) Control group: F = 7/10 (70%) M = 3/10 (30%)	60-85yr Treatment group: 73.1yr (7.4) Placebo group: 72.6yr (5.4)	1. Dx Probable AD with NINCDS-ADRDA 2. MMSE = 16-26 3. MRI/CT scan consistent w dx	Treatment group: MMSE = 21.2 (3.5) ADAS-cog+ = 36.5 (14.3) Word fluency test=9.6 (3.9) Placebo group: MMSE = 21.7 (3.3) ADAS-cog+ = 35.3 (13.3) Word fluency test=9.8 (5.3)	N/A Inclusion criteria: Patients needed to reside at home with carer
Doody [8]	Treatment group: n = 89 Placebo group: n = 94	Treatment Group: 25:64 (M:F) Placebo Group: 36:58 (M:F)	Treatment Group: 68.1yr (9.3) Placebo Group: 68.4yr (8.7)	DSM – IV. Probable AD according to NINCDS-ADRDA MMSE = 20-24. Modified Haschinki Ischaemic Score = 4 or less. MRI/CT scan compatible with diagnosis in the last 12 months.	Treatment Group MMSE= 18.7 (3.3) Modified Haschinki Ischaemic Score = 1.6 (0.9) At Baseline; Placebo Group: MMSE= 18.3 (3.5) Modified Hachinki Ischaemic Score = 1.7 (1.0)	None

Ihl [7]	n=404 Treatment group: n=202 Placebo group: n=202	F=272/404 (67%) M=132/404 (33%) *(p=0.524)* Treatment group: F=139/202 (69%) M=63/202 (31%) Placebo group: F=133/202 (66%) M=69/202 (34%)	Treatment group: 65yr (10) Placebo group: 65yr (9)	1. Dx Probable AD with NINCDS-ARDA or Probable VaD with NINCDS-ARDA or Probable AD w/CVD with NINCDS-ARDA 2. CT/MRI consistent w dx 3. TE4D error score ≤35 4.SKT test = 9-23	Treatment group: TE4D = 26.2(5.3) SKT =16.7 (3.9) Placebo group: TE4D = 26.0 (5.0) SKT = 17.2 (3.7)	N/A Inclusion criteria: Outpatient status with carer
Iwasaki [6]	n=33	F = 26/33 (78.8%) M = 7/33 (21.2%) (p>0.5)	Mean=84.4yr (7.8) Treatment group: 85.6yr (6.4) Placebo group: 83.5yr (9.3)	1. Dx of Dementia according to DSM-III	At enrolment: MMSE 0-25 Treatment group: MMSE = 13.5 (8.5) Placebo group: MMSE = 16.8 (6.3)	All Institutional Living (Long Term Care Facility)
Moraes [9]	Treatment Group: n = 11 Placebo Group: n = 12	Treatment Group: 3:8 (M:F) Placebo Group: 5:7 (M:F)	Treatment Group: 76.8yr (6.2) Placebo Group: 72.6yr (11)	Probability criteria of the Alzheimer's disease and related disorders association. Brazilian version of CDR = 1 and 2.	Baseline Treatment Group; MMSE = 19 (3.6) ADAS-cog = 34.5 (15.8) Placebo group: MMSE =17.2 (7.8) ADAS-cog = 29.3 (17.3)	None

Scarpini [10]	Open label phase n=254 Double-blind phase Treatment group: n=76 Placebo group: n=63	Open label Phase: F=156/254 (61.4%) M=98/254(38.6%) Treatment group: F=49/76 (64.5%) M=27/76 (35.5%) Placebo group: F=34/63 (54.0%) M=29/63 (46.0%)	Open Label Phase mean = 74.2y Double Blind Phase Treatment group: 74.5y Placebo group: 74.4y	1. Dx Probable AD with NINCDS-ADRDA 2. MMSE 11-24	Open-Label Phase: MMSE, mean: 18.9 (3.6) ADAS-cog/11, mean: 24.7 (9.3)	N/A Inclusion criteria: Patients needed to have carer
Scheltens [14]	n=212 Treatment group: n=106 Placebo group: n=106	F:106/212 (50%) M: 106/212 (50%) Treatment: F=52(49%) M=54(51%) Control: F=54 (51%) M=52(49%)	52-92yo mean=73.7yo	1. Dx Probable AD with NINCDS 2. MMSE=20-26 3. MRI/CT scan compatible w AD	Treatment group: MMSE=23.8 (2.7) ADAS-cog=25.9(7.6) WMS-r delayed=1.0[01-16] WMS-r imm.=4.9[0-15] Placebo group: MMSE=24.0(2.5) ADAS-cog= 25.5(8.8) WMS-r delayed = 2.0[0-17] WMS-r imm. = 5.0 [0-19]	N/A Inclusion criteria: Outpt status with carer
Stenvall [12]	n=64 Treatment group: n=28 Control group: n=36	F:47/64 (73%) M: 17/64 (37%) Treatment: F=22(79%) M=6(21%) Control: F=25 (69%) M=11(31%)	Treatment group: 81.0y Placebo group: 83.2y	1. Dx Probable AD with NINCDS 2. MMSE	Treatment group: MMSE=8.6 (7.1) Placebo group: MMSE=6.9(5.0)	Treatment group: Institutional Living=22 (79%) Control group: Institutional Living=26 (72%)

Trzepacz [13]	n = 132 <u>Treatment group:</u> n=63 <u>Placebo group:</u> n=69	F = 67/132 (50.8%) M =65/132 (49.2%) <u>Treatment group:</u> F = 31/63 (49.2%) M = 32/63 (50.8%) <u>Placebo group:</u> F = 36/69 (52.2%) M = 33/69 (47.8%)	59-93yr 77.4yr (7.87) <u>Treatment group:</u> 59-93yr 77.2yo (8.2) <u>Placebo group:</u> 60-93yr 77.7yr (7.6)	1. Probable AD with NINCDS-ADRDA or DSM IV-TR 2. MMSE = 6-26 3. NPI-10 = ≥ 10 4. NPI-4-A/A = ≥4 5. CT/MRI consistent with dx	<u>Treatment group:</u> MMSE = 16.0 (6.1) ADAS-cog14 = 43.3 (20.4) NPI-10 = 31.9 (16.7) NPI-4-A/A = 18.8 (8.7) <u>Placebo group:</u> MMSE = 18.0 (5.3) ADAS-cog14 = 40.0 (18.1) NPI-10 = 29.7 (13.2) NPI-4-A/A = 18.1 (8.2)	N/A Inclusion criteria: Pt needs to be community dwelling with carer

AD**,** Alzheimer's Disease; NINCDS-ARDRDA, National Institute of Neurological and Communicative Disorders and the Alzheimer's Disease and Related Disorders Association; MMSE, Mini-Mental Status Examination; MRI, magnetic resonance imaging; CT, computed tomography; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; VaD, vascular dementia; TE4D, Test for Early Detection of Dementia with Discrimination from Depression; SKT, Short Cognitive Perfromance Test; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition; CDR, clinical dementia rating; ADAS-cog 11, Alzheimer's Disease Assessment Scale –Cognitive 11 Item Scale; Wechsler Memory Scale – revised; NPI-10, Neuropsychiatry Inventory; NPI-4-A/A, Neuropsychiatry Inventory – Agitation and Aggression; ADAS-cog 14, Alzheimer's Disease Assessment Scale – Cognitive 14 Item Scale;