Table 2. Study Characteristics for AChEI Trials

| **Medication** | **Author, year**  **USPSTF quality rating** | **Daily dosage** | **N randomized** | **Location** | **Longest f/u (m)** | **% followed up** | **Funding source** | **Inclusion criteria** | **Exclusion criteria** | **Diagnostic criteria** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Donepezil | Doody, 2009105,106  Fair | 5-10 mg | IG: 409  CG: 412 | US | 11 | 61 | Eisai; Pfizer | Healthy, ambulatory or ambulatory-aided amenstic subjects with MCI; 45 to 90 y old; expressed a memory complaint representing a change from previous functioning (corroborated by an informant and confirmed by neuropsychological testing scores); had an informant with daily contact; CT scan or MRI within 12 months of screening showing no clinical evidence of infection, infarction, other focal lesions or clinically significant comorbid pathologies. | Diagnosis of probably or possible VaD (NINCDS-ADRDA, DSM-IV criteria) or another form of dementia; a neurologic or psychiatric disorder, a sleep disorder that could affect cognitive performance; drug or alcohol abuse or dependence within the previous 5 y; uncontrolled hypertension regardless of antihypertensive medication; uncontrolled diabetes mellitus; any other medical condition deemed incompatible with participation; past treatment with AChEI or memantine for >1 month or within previous 3 months; taking concomitant anticholinergics, anticonvulsants, antiparkinson agents, stimulants, cholingeric agents, antipsychotics, antidepressants or anxiolytics with anticholinergic or procholinergic effects. | Memory component corroborated by informant and confirmed by neuropsychological scores (CDR 0.5 with Memory Box score 0.5 or 1.0, no box score >1.0; MMSE score 24-28; Logical Memory II Delayed Paragraph Recall subtest of Weschsler Memory Scale-Revised score ≤8 (16+ y education), ≤4 (8-15 y education), or ≤2 (<8 y education); Rosen modified Hachinski Ischemia scale score ≤4 |
| Mori, 2012107  Fair | 3-10 mg | IG1: 35  IG2: 33  IG3: 37  CG: 34 | Japan | 3 | 87.9 | Eisai | Outpatients who met probable DLB criteria (McKeith) aged 50 y or older with mild to moderate-severe dementia (MMSE 10-26; CDR ≥ 5) with behavioral symptoms (NPI+ ≥ 8); caregivers who routinely stayed with them at least 3 days a week and 4 hours per day provided informaiton to study, assisted in compliance and escorted patients to required visits | Parkinson disease diagnosed at least 1 year prior to onset of dementia; focal vascular lesions on MRI or CT that might cause cognitive impairment or other neurological or psychiatric diseases; clinically significant systemic disease; complications of history of sever GI ulcer, severe asthma, or obstructive pulmonary disease; systolic hypotension (<90 mm Hg); bradycardia (<50/m); sick sinus syndrome; atrial or atrioventricular conduction block; QT interval prolongation (450+ msec); hypersensitivity to donepezil or piperidine derivatives; severe parkinsonism (Hoehn  and Yahr score IV+); treatment with ChEI or any investigational drug within 3 months prior to screening | McKeith |
| Requena, 2004108,109 | 5-10 mg | IG: 30  CG: 18 | Spain | 24 | 96.5 | Pfizer | DSM-IIIR and NINCDS-ADRDA for AD | Severe dementia; loss of all capacity of speech; requiring assistance for all daily activities; loss of basic psychomotor abilities; lack of capacity to express emotions adequately; apparent failure of the brain to give orders to the body; appearance of generalized and cortical neurological signs and symptoms. | DSM-IIIR; NINDS-ADRDA |
| Galantamine | Auchus, 2007110  GAL-INT-26 Study  Fair | 16-24 mg | IG: 397  CG: 391 | Multi | 6 | 80.5 | NR | NINDS-AIREN diagnosis of VaD with MRI confirmation of clinical diagnosis; MMSE score 10-26; ADAS-cog score ≥12; onset of disease at age 40-90 y; availability of caregiver. | Diagnosis of AD, Parkinson's disease, Hungington disase, other neurodegenerative dementia; serious coexisting medical condition; CVD that  would limit trial participation; or already taking drugs to treat dementia. | NINDS-AIREN |
| Rockwood, 2006111-114  VISTA  Fair | 16-24 mg | IG: 64  CG: 66 | Canada | 4 | 84 | Janssen-Ortho Canada; Canadian Institute of Health Research | English-speaking individuals with probable AD (NINCDS-ADRDA); mild-to-moderate dementia (MMSE score 10-25; ADAS-cog score ≥18); had daily contact with a responsible caregiver. | Resided in nursing homes; disabling communication  difficulties (problems in language, speech, vision or hearing); other active medical issues or competing causes of dementia; took anti-dementia medications within 30 days before screening; hypersensitive to cholinomimetic agents or bromide; participated  in other galantamine trials. | NINDS-ADRDA |
| Rivastigmine | Ballard, 2008115  VantagE Study  Fair | 3-12 mg | IG: 365  CG: 345 | Multi | 6 | 80.6 | Novartis | Men or women aged 50-85 y with a diagnosis of VaD according to DSM-IV and a diagnosis of probable VaD according to NINDS-AIREN criteria; MMSE 10-24; contact with a responsible caregiver on at least 3 days per week; written informed consent. | Any primary neuro-degenerative disorder other than VaD or any other causes of dementia; a major depressive episode; active, uncontrolled seizure disorder; any disability or unstable disease that  may prevent the patient from completing all study requirements; current diagnosis of bradycardia (hr <50 bpm), sick sinus syndrome, or conduction effects; unstable or poorly controlled blood pressure over the past 3 months; current diagnosis of uncontrolled atrial fibrillation (hr>100 bpm); presence of any metal objects (e.g. pacemaker) within the patient that prevented him or her from undergoing an MRI scan. | DSM-IV; NINDS-AIREN |
| Feldman, 2007116  Study 304  Fair | 2-12 mg | IG1: 227  IG2: 229  CG: 222 | Multi | 6 | 82 | Novartis | Community dwelling patients at least 50 y old and met criteria for Alzheimer's disease (DSM-IV) and in accordance with criteria for probable AD of the NINDS-ADRDA); MMSE score 10-26. | Severe and unstable cardiac disease, severe obstructive pulmonary disease or other life threatening conditions. | DSM-IV; NINDS-ADRDA |
| Mok, 2007117  Fair | 6 mg | IG: 20  CG: 20 | China | 6 | 98 | Norvartis | Chinese patients with subcortical VaD, aged 40-90 y and MMSE score 3-24. | Other concurrent dementing diseases (e.g., B12 deficiency), unstable medical conditions, stroke within 3 months of study, concurrent use of cholinergic drugs, frequent changes in dose of centrally acting drugs (e.g., benzodiazepines)  3 months prior to study entry, severe dementia or language problems making participant in cognitive testing impossible, and no close caregivers (defined by <3 visits/week). | Standardized criteria to define subcortical vascular dementia and brain imaging criteria, both by Erkinjuntti |
| Winblad, 2007118-127 IDEAL Study  Fair | 9.5-17.4 mg/24 hours patch;  12 mg capsule | IG1: 293  IG2: 303  IG3: 297  CG: 302 | Multi | 6 | 81.2 | Norvartis | Women or men aged 50-85 y with a diagnosis of dementia of the Alzheimer's type (DSM-IV) and probable AD (NINDS-ADRDA); brain scan within one year prior to randomization; MMSE score 10-20; living with someone in the community or if living alone, in daily contact with a responsible caregiver. | Advanced, severe, progressive, or unstable disease of any type that would interfere with study assessment or put the patient at special risk;  any condition other than AD that could explain dementia; use of any investigational drugs,  new psychotropic or dopaminergic agents, cholinesterase inhibitors or anti-cholinergic agents in previous 4 weeks. | DSM-IV; NINDS-ADRDA |
| Memantine | Bakchine, 2008128  Good | 20 mg | IG: 318  CG: 152 | Multi | 6 | 87 | H. Lundbeck A/S | Probable Alzheimer's Disease (see dementia diagnosis) with a CT or MRI of the brain within the past 12 months with results consistent with such diagnosis; outpatient; >50 y old; MMSE score 11-23; reliable and knowledgeable caregiver who could accompany subject to all visits during the study. | VaD, dementia or clinically significant neurological disease  other than AD, major depressive disorder or a modified Haskinski Ischemic Rating Scale scale >4; clinically significant coexisting medical conditions or lab abnormalities; receiving anticonvulsants, antiparkinson agents, classical and depot antipsychotics, anxiolytics, hypnotics, non-SSRI antidepresants, cholinesterase inhibitors, or any other investigational products. | DSM-IV; NINDS-ADRDA |
| Ferris, 2007129  Fair | 20 mg | IG: 30  CG: 30 | US | 3 | 90 | Forest Research Institute | Men and women aged 50 to 79 y who complained that they have experienced memory loss over the course of adult life and performed at least one standard deviation below the mean for young adults on a standardized memory test. | MMSE score ≤26; showed other evidence of dementia; depression (GDS score of ≥ 11); showed evidence on history or examination or medical or neurologic problems that could account for memory loss over the course of decades; taking or were likely to require over the course of the study a wide range of drugs that can impair cognition. | Reported memory loss over the course of their adult life and performed at least one standard deviation below the mean for young adults on a standardized memory test |
| Porsteinsson, 2008130  MEM-MD-12 Study  Good | 20 mg | IG: 217  CG: 216 | US | 6 | 89 | Forest  Labs | Subjects with probable AD using NINCDS-ADRDA criteria; MMSE score 10-22; minimum age 50 y; CT or MRI within 12 months consistent with probably AD diagnosis; treatment with a cholinesterase inhibitor for 6 months or longer; stable dose regimine for 3 months or longer (donepezil 5 or 10 mg/day; rivastigmine 6, 9, 12 mg/day; galantamine 16 or 24 mg/day); knowledgeable and reliable caregiver to accompany and supervise participant; MADRS score <22; ability to ambulate; vision and hearing capabilities to permit compliance with assessments; and medically stable condition. At least 2 y post-menopausal or surgically sterile (females only). | Clinically significant and active pulmonary, GI, renal, hepatic, endocrine or CVD; vitamin B12 or folate deficiency; evidence of any psychiatric or neurologic disorder; dementia complicated by organic disease or AD with delusions or delirium; Hachinski Ischemi Score >4; oncology diagnosis and ongoing/recent (within 6 months); poorly controlled hypertension; substance abuse; depot neuroleptic use within 6 months; positive urine drug test; likely institutionalization during trial; previous memantine treatment; participation in an investigational drug treatment (including memantine) within last 30 days; and likely cessation of cholinesterase treatment during trial. | NINDS-ADRDA |
| Saxton, 2012131  MEM-MD-71  Good | 20 MG | IG: 136  CG: 129 | Multi | 3 | 94.7 | Forest Labs | Native English speakers with NINCDS-ADRDA diagnosis of probable AD, MMSE 10-19, CT or MRI results within the past 12 months consistent with diagnosis, stable dose ofChEI (if taking) for at least 3 months, pass physical exam, laboratory evaluation and ECG; ambulatroy or ambulatory-aided with vision and hearing capabilities sufficient for completion of the study; females must be surgically sterile or postmenopausal for at least 2 y; knowledgable and reliable caregive who spoke English and would accompany subject at visit | Clinically significant and active pulmonary, GI, renal, hepatic, endocrine, or CVD or cancer; evidence of psychiatric or neurologic disorders  other than probable AD; dementia complicated by other organic brain disease or predominant delusions; clinically significant vitamin B12 or folate defienciency; Hachinski Ischemic Score >4; hypertension (SBP >180 mm Hg; DBP >100 mm Hg); hypotension (SBP <90 mm Hg; DBP <50 mm Hg); history of alcoholism and drug abuse within the past 5 y; severe renal impairment or impaired kidney function, preivous memantine treatment, participation in memantine trial, hypersensitivity to amantadine or rimantidine, likely institutionalized during trial; any other condition that make patient or caregiver unsuitable for trial | NINCDS-ADRDA |
| Wilkinson, 2012132  Fair |  | IG: 134  CG: 144 | Multi | 12 | 78.1 | H. Lundbeck A/S; Merz Pharma-ceuticals GmbH | Outpatients aged ≥50 y with a diagnosis of probable AD (NINCDS-ADRDA) consistent with MRI scan; MMSE 12-20, healthy, ambulatory or ambulatory aided, relibale caregiver, fluent speaker of native language, women had to be at least 2 y post-menopausal or surgically sterile, with or without stable current AChEI treatment allowed | Clinically significant and active pulmonary, GI, renal, hepatic, endocrine, or CVD; severe renal impairment, high or low BP, hypersensitivity to memantine, amantadine, rimantidine, or lactose; any clinically significant neurodegenerative disease or other serious neurological diosrder other than AD; unable to tolerate MRI, further scans scheduled during study or contraindicated for MRI; modified Hachinski Ischemia score >4, foreseen to enter a nursing or residential home within the next 12 months; VaD (NINDS-AIREN) criteria from MRI scan | NINCDS-ADRDA |

**Abbreviations:** AChEI = acetyl cholinesterase inhibitor; AD = Alzheimer’s disease; ADAS-cog = Alzheimer’s Disease Assessment Scale-cognitive subscale; bpm = beats per minute; CDR = Clinical Dementia Rating; CG = control group; CT = computed tomography; CVD = cardiovascular disease; DBP = diastolic blood pressure; DLB = dementia with Lewy bodies; DSM = Diagnostic and Statistical Manual; ECG = electrocardiogram; f/u = followup; GDS = Geriatric Depression Scale; GI = gastrointestinal; hr = heart rate; IG = intervention group; MADRS = Montgomery-Asberg Depression Rating Scale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; m = months; MRI = magnetic resonance imaging; Multi = multi-country; N = number; NINDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association; NINDS-AIREN = National Institute of Neurological Disorders and Stroke and the Association Internationale pour las Recherche et l’Enseignment en Neurosciences; NPI = neuropsychiatric inventory; NR = not reported; RCT = randomized controlled trial; SBP = systolic blood pressure; SSRI = selective serotonin reuptake inhibitor; USPSTF = U.S. Preventive Services Task Force; VaD = vascular dementia.