Supplemental Table 1. Overview of published articles meeting search criteria (N=18)

Single study reports		
Reference	**Ballard et al. 2015** (13)	
Study details	**Design**	Multicenter, randomized, double-blind, double-dummy, parallel-group
	Comparator	Antipsychotic
	Patient no.	199
	Inclusion criteria	Diagnosis of probable or possible AD per NINCDS/ADRDA; residing in care facilities; prescribed antipsychotic >3 months earlier
	Exclusion criteria	Selected medications excluded; high/low BP; thyroid symptoms; aggression ≥8 per NPI; axis 1 disorder; other neurodegenerative disorder; seizures; delirium; renal or hepatic impairment
	Statistical measures	Mixed-effects regression model
Treatments	**Treatment type**	Memantine
	Treatment duration	24 weeks
	Concomitant	Cholinesterase inhibitors, carbamazepine, sodium valproate, antidepressants, benzodiazepines,

	medication	chlormethiazole
Patients	**Age, years**	Range 57-99
	AD diagnostic criteria	NINCDS/ADRDA
	AD severity measure	FAST, MMSE
	Agitation as primary or secondary end point	Primary
	Agitation measure	CMAI
Reference	**Cummings et al. 2015** (14)	
Study details	**Design**	Phase 2, multicenter, randomized, double-blind, SPCD
	Comparator	Placebo
	Patient no.	220
	Inclusion criteria	Diagnosis of probable AD per NIA-A/A; significant agitation; CGIS ≥4; MMSE 8-28; stable treatment

	Exclusion criteria	Non-AD dementia; non-AD agitation; hospitalization; MDD; psychotic disorder; significant or unstable medical conditions; cardiac symptoms; substance abuse; specified medications excluded
	Statistical measures	LOCF, mixed-effects model
Treatments	**Treatment type**	Dextromethorphan-quinidine
	Treatment duration	2 × 5 weeks
	Concomitant medication	Memantine, acetylcholinesterase inhibitors, specified antidepressants, antipsychotics, hypnotics (including benzodiazepines)
Patients	**Age, years**	Range 50-90
	AD diagnostic criteria	NIA-AA 2011
	AD severity measure	CGI-S, MMSE
	Agitation as primary or secondary end point	Primary
	Agitation measure	NPI-A/A

Reference	**van den Elsen et al. 2015** (15)	
Study details	**Design**	Phase 2, multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	50
	Inclusion criteria	AD or vascular dementia per NINCDS/ADRDA; NPI ≥10; ≥1 month of agitation or aggression; caregiver ≥2 times weekly who agrees to participation
	Exclusion criteria	Major psychiatric disorder; severe or unstable medical condition; cardiac symptoms; falling because of hypotension; substance abuse; antidepressants
	Statistical measures	Linear mixed model
Treatments	**Treatment type**	THC
	Treatment duration	3 weeks
	Concomitant medication	Psychotropic drugs at stable doses
Patients	**Age, years**	Mean (SD): 78 (7)

	AD diagnostic criteria	NINCDS/ADRDA, NINDS/AIREN
	AD severity measure	NPI
	Agitation as primary or secondary end point	Secondary
	Agitation measure	CMAI
Reference	**Porsteinsson et al. 2014** (16)	
Study details	**Design**	Phase 3, multicenter, randomized, double-blind, parallel group
	Comparator	Placebo
	Patient no.	186
	Inclusion criteria	Diagnosis of probable AD per NINCDS/ADRDA; MMSE 5-28; clinically significant agitation per NPI
	Exclusion criteria	MDD; psychosis; availability of caregiver who agrees to participate; psychotropic medications; cardiac symptoms
	Statistical measures	Mixed-effects regression model

Treatments	**Treatment type**	Citalopram
	Treatment duration	9 weeks
	Concomitant medication	Cholinesterase inhibitors, memantine
Patients	**Age, years**	Mean (SD): 78 (8)
	AD diagnostic criteria	NINCDS/ADRDA
	AD severity measure	MMSE
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	NBRS-A, mADCS-CGIC, CMAI
Reference	**Herrmann et al. 2013** (17)	
Study details	**Design**	Phase 3, multicenter, randomized, double-blind, parallel-group, fixed-dose
	Comparator	Placebo

	Patient no.	369
	Inclusion criteria	Diagnosis of probable AD per NINCDS/ADRDA; MMSE 8-18 (protocol amendment >5 to <15); stable medications; reliable caregiver; residence in the community; NPI total score ≥15 and A/A score ≥1
	Exclusion criteria	Unstable medical condition; other psychiatric or neurologic disorder; non-AD dementia; vascular dementia; MHIS >4
	Statistical measures	LOCF, ANCOVA
Treatments	**Treatment type**	Memantine
	Treatment duration	24 weeks
	Concomitant medication	Antidepressants, antihypertensives, anti-inflammatories, antipsychotics, anticoagulants, laxatives, diuretics, hypnotics
Patients	**Age, years**	Mean (SD): 75 (7-8)
	AD diagnostic criteria	NINCDS/ADRDA
	AD severity measure	MMSE
	Agitation as primary	Secondary

	or secondary end point	
	Agitation measure	NPI-A/A, CMAI
Reference	**Trzepacz et al. 2013** (18)	
Study details	**Design**	Phase 2, multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	132
	Inclusion criteria	Diagnosis of probable AD per NINCDS/ADRDA; significant agitation ≥4 weeks before baseline; community dwelling; reliable caregiver; MMSE 6-26; NPI total ≥10; NPI-4-A/A ≥4; brain imaging; MHIS ≤4
	Exclusion criteria	Delirium; psychotropic medication; other major neurologic or psychiatric disorder; CYP450 3A/4 inhibitors
	Statistical measures	Mixed-effects model, repeated-measures analysis, LOCF
Treatments	**Treatment type**	Mibampator
	Treatment duration	12 weeks

	Concomitant medication	Sertraline, citalopram, escitalopram, fluoxetine, acetylcholinesterase inhibitors, memantine
Patients	**Age, years**	Range: 60-93
	AD diagnostic criteria	NINCDS/ADRDA, *DSM-IV*-TR
	AD severity measure	MMSE, NPI-10
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	NPI-4-A/A, CMAI, CGIS
Reference	**Fox et al. 2012** (19)	
Study details	**Design**	Phase 4, multicenter, randomized, blinded
	Comparator	Placebo
	Patient no.	153

	Inclusion criteria	Inpatient or resident in care home; diagnosis of probable AD; MMSE score ≤19; MHIS ≤4; ≥2 weeks of significant agitation; CMAI ≥45
	Exclusion criteria	Current use of memantine or other selected medication; renal impairment; seizures; NMDA antagonists; cardiac symptoms; severe or unstable medical condition or inability to participate
	Statistical measures	Linear mixed-effects modeling
Treatments	**Treatment type**	Memantine
	Treatment duration	12 weeks
	Concomitant medication	Antipsychotics, antidepressants, benzodiazepines, hypnotics, lithium
Patients	**Age, years**	Mean (SD)*: 84-85 (7)
	AD diagnostic criteria	Not stated
	AD severity measure	MMSE, FAST
	Agitation as primary or secondary end	Primary and secondary

	point	
	Agitation measure	CMAI, NPI, CGI
Reference	**Devanand et al. 2012** (29)	
Study details	**Design**	Phase 4, multicenter, Phase A: open-label; Phase B: randomized, double-blind
	Comparator	Placebo
	Patient no.	Phase A, 180; Phase B, 110
	Inclusion criteria	Outpatient or care home resident; probable dementia per *DSM-IV*; probable AD per NINCDS/ADRDA; NPI psychosis or A/A score ≥4; MMSE 5-26 for outpatients or 2-26 for care home residents
	Exclusion criteria	Cerebrovascular or cardiac symptoms
	Statistical measures	Stratified log-rank
Treatments	**Treatment type**	Risperidone
	Treatment duration	Phase A, 16 weeks; Phase B, 32 weeks
	Concomitant	SSRIs, trazodone, sedative/hypnotics, cholinesterase inhibitors, and memantine at stable doses

	medication	
Patients	**Age, years**	Mean (SD)*: Phase A, 79.6 (7.6) Phase B, 79.1-80.7 (7.7-8.0)
	AD diagnostic criteria	*DSM-IV* and NINCDS/ADRDA
	AD severity measure	MMSE
	Agitation as primary or secondary end point	Primary
	Agitation measure	NPI core scores†
Reference	**Barak et al. 2011** (20)	
Study details	**Design**	Single-center, randomized, double-blind
	Comparator	Risperidone
	Patient no.	40
	Inclusion criteria	Diagnosis of AD-type dementia per *DSM-IV*; MMSE 5-24; hospitalization owing to psychosis or agitation; symptoms must have occurred almost daily during the week before enrollment

	Exclusion criteria	Primary psychotic disorder; non-AD agitation; substance abuse; previous treatment with study drugs
	Statistical measures	ANCOVA, LOCF
Treatments	**Treatment type**	Escitalopram
	Treatment duration	6 weeks
	Concomitant medication	Cholinesterase inhibitors, memantine
Patients	**Age, years**	Mean (SD)*: 77-80 (6-9)
	AD diagnostic criteria	*DSM-IV*
	AD severity measure	MMSE
	Agitation as primary or secondary end point	Secondary
	Agitation measure	NPI-A/A
Reference	**Tariot et al. 2011** (30)	

Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	313
	Inclusion criteria	Diagnosis of possible or probable AD per NINCDS/ADRDA; weight >39 kg; community residence; MMSE 12-20; absence of agitation with NPI A/A <1
	Exclusion criteria	None stated
	Statistical measures	Cox proportional hazards
Treatments	**Treatment type**	Valproate
	Treatment duration	24 months
	Concomitant medication	Cholinesterase inhibitors, memantine, antidepressants, antianxiety medications
Patients	**Age, years**	Mean (SD)*: 75-77 (7-8)
	AD diagnostic criteria	NINCDS/ADRDA

	AD severity measure	MMSE
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	NPI, CMAI
Reference	**Mowla and Pani 2010** (21)	
Study details	**Design**	Single-center, randomized, double-blind
	Comparator	Risperidone
	Patient no.	48
	Inclusion criteria	Diagnosis of AD per *DSM-IV*; MMSE 10-26; NPI part 1 score >1; no medication in prior 4 weeks
	Exclusion criteria	Non-AD dementia; organic diseases; other psychiatric disorder including MDD
	Statistical measures	Mann-Whitney test
Treatments	**Treatment type**	Topiramate

	Treatment duration	8 weeks
	Concomitant medication	None
Patients	**Age, years**	Mean (SD): 75 (3)
	AD diagnostic criteria	*DSM-IV*
	AD severity measure	MMSE
	Agitation as primary or secondary end point	Primary
	Agitation measure	NPI-A/A, CMAI
Reference	**Gehrman et al. 2009** (22)	
Study details	**Design**	Multicenter, randomized, blinded rater
	Comparator	Placebo
	Patient no.	41

	Inclusion criteria	Resident in nursing home; diagnosis of probable AD per NINCDS/ADRDA; MMSE 0-18
	Exclusion criteria	None stated
	Statistical measures	ANOVA
Treatments	**Treatment type**	Melatonin
	Treatment duration	10 days
	Concomitant medication	Not stated
Patients	**Age, years**	Range 61-95
	AD diagnostic criteria	NINCDS/ADRDA
	AD severity measure	MMSE
	Agitation as primary or secondary end point	Secondary
	Agitation measure	ABRS, CMAI

Reference	**Sommer et al. 2009** (23)	
Study details	**Design**	Phase 3, multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	103
	Inclusion criteria	Nursing home residents; AD or vascular dementia per ICD-10; MMSE 0-20; agitation for ≥1 week; NPI nursing home score ≥6; stable treatment
	Exclusion criteria	Renal or hepatic impairment; cardiac symptoms; other neurologic disorder; severe psychiatric disorder; non-AD dementia
	Statistical measures	Repeated-measures model, LOCF
Treatments	**Treatment type**	Oxcarbazepine
	Treatment duration	8 weeks
	Concomitant medication	Paracetamol, psychotropic drugs at stable doses
Patients	**Age, years**	Range: 63-98

	AD diagnostic criteria	*ICD-10*
	AD severity measure	MMSE
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	NPI-A/A, BARS
Reference	**Wang et al. 2009** (24)	
Study details	**Design**	Single-site, double-blind, randomized, parallel-group
	Comparator	Placebo
	Patient no.	24
	Inclusion criteria	Community or nursing home residents; diagnosis of possible or probable AD per NINCDS/ADRDA; agitation ≥twice weekly for 2 weeks; BPRS score ≥4 for one of anxiety, tension, hostility, uncooperativeness or excitement; stable treatment
	Exclusion criteria	Low BP; orthostatic hypotension; uncontrolled psychotic disorder; bipolar disorder or schizophrenia;

		unstable medical condition contributing to cognitive or behavioral impairment
	Statistical measures	Mann-Whitney, linear mixed-effects
Treatments	**Treatment type**	Prazosin
	Treatment duration	8 weeks
	Concomitant medication	Previously prescribed medication at stable dose
Patients	**Age, years**	Mean (SD): 81 (11)
	AD diagnostic criteria	NINCDS/ADRDA
	AD severity measure	MMSE
	Agitation as primary or secondary end point	Primary
	Agitation measure	CGIC, NPI, BPRS
Reference	**Streim et al. 2008** (25)	

Study details	**Design**	Multicenter, randomized, double-blind, flexible-dose
	Comparator	Placebo
	Patient no.	256
	Inclusion criteria	Diagnosis of AD per *DSM-IV*; psychotic symptoms for ≥1 month; institutionalized; ambulatory; available caregiver able to participate; MMSE 6-22; NPI nursing home score ≥6 for delusions or hallucination
	Exclusion criteria	Axis 1 disorder; non-AD dementia; psychosis before dementia; MDD; seizures; unstable thyroid pathology; refractory to antipsychotic drugs; substance abuse; suicidality; any medical or laboratory measurement precluding participation
	Statistical measures	Mixed-effects model, hierarchical sequential testing
Treatments	**Treatment type**	Aripiprazole
	Treatment duration	10 weeks
	Concomitant medication	Trazodone, zolpidem, temazepam, lorazepam, anticholinergics, cognition enhancers, antidepressants
Patients	**Age, years**	Range: 55-95

	AD diagnostic criteria	*DSM-IV*
	AD severity measure	MMSE
	Agitation as primary or secondary end point	Secondary
	Agitation measure	CGIS, BPRS, CMAI, NPI
Reference	**Howard et al. 2007** (26)	
Study details	**Design**	Phase 4, multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	272
	Inclusion criteria	Diagnosis of possible or probable AD per NINCDS/ADRDA; clinical agitation for ≥2 days/week for 2 weeks; CMAI ≥39; community dwelling or in nursing home; stable treatment
	Exclusion criteria	Neuroleptic agents or cholinesterase inhibitors; severe, unstable or uncontrolled medical condition; delirium; non-AD dementia; evidence of poor medication compliance

	Statistical measures	ANCOVA
Treatments	**Treatment type**	Donepezil
	Treatment duration	4 weeks psychosocial treatment, 12 weeks drug treatment
	Concomitant medication	Psychotropic agents at stable doses
Patients	**Age, years**	Mean (SD)*: 84-85 (7-8)
	AD diagnostic criteria	NINCDS/ADRDA
	AD severity measure	CMAI
	Agitation as primary or secondary end point	Secondary
	Agitation measure	NPI, CGI
Reference	**Mahlberg et al. 2007** (27)	
Study	**Design**	Single-center, randomized, single-blind

details	**Comparator**	Placebo
	Patient no.	20
	Inclusion criteria	Diagnosis of probable AD per NINCDS-ADRDA; inpatient of geriatric psychiatry unit; agitated behavior; stable clinical state and medication
	Exclusion criteria	Delirium; MDD; suicidality; substance abuse; seizures; urinary retention; asthma; cardiac symptoms; use of cholinesterase inhibitor in previous 6 weeks
	Statistical measures	Mann-Whitney test
Treatments	**Treatment type**	Rivastigmine
	Treatment duration	2 weeks
	Concomitant medication	Risperidone, donepezil
Patients	**Age, years**	Mean (SD)*: 78-83 (7-10)
	AD diagnostic criteria	NINCDS/ADRDA
	AD severity measure	MMSE, FAST

	Agitation as primary or secondary end point	Secondary
	Agitation measure	NPI-A/A
Pooled study		
Reference	**Wilcock et al. 2008** (28)	
Study details	**Design**	Pooled analysis of 3 double-blind, parallel-group RCTs
	Comparator	Placebo
	Patient no.	593
	Inclusion criteria	Moderately severe or severe AD; MMSE 3-14 or 5-14; agitation or psychosis at baseline
	Exclusion criteria	None stated
	Statistical measures	LOCF, observed case, ANOVA
Treatments	**Treatment type**	Memantine (n = 2), memantine + donepezil (n = 1)

	Treatment duration	24-28 weeks
	Concomitant medication	Not stated
Patients	**Age, years**	Mean (SD): 77 (8)
	AD diagnostic criteria	Not stated
	AD severity measure	MMSE
	Agitation as primary or secondary end point	Secondary
	Agitation measure	NPI

Abbreviations: ABRS, Agitated Behavior Rating Scale; AD, Alzheimer's disease; ANCOVA, analysis of covariance; ANOVA, analysis of variance; BARS, Brief Agitation Rating Scale; BP, blood pressure; BPRS, Brief Psychiatric Rating Scale; CGII, Clinical Global Impressions-Improvement; CGIS, Clinical Global Impressions-Severity; CMAI, Cohen-Mansfield Agitation Inventory; *DSM*, *Diagnostic and Statistical Manual*; FAST, Functional Assessment Staging; *ICD, International Statistical Classification of Diseases and Related Health Problems*; LOCF, last observation

carried forward; mADCS-CGIC, modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change; MMSE, Mini Mental State Examination; NBRS-A, Neurobehavioral Rating Scale Agitation subscale; NIA-AA, National Institute on Aging-Alzheimer Association; NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; NINDS/AIREN, National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche en l'Enseignement en Neurosciences; NMDA, *N*-methyl-D-aspartate; NPI A/A, Neuropsychiatric Inventory Agitation/Aggression domain; RCT, randomized controlled trial; SD, standard deviation; SPCD, sequential parallel comparison design; SSRI, selective serotonin reuptake inhibitor; THC, tetrahydrocannabinol. *Means and/or standard deviations for treatment groups in study. †Sum of the subscale scores for agitation-aggression, hallucinations, and delusions (29).

Supplemental Table 2. Overview of clinical trials meeting search criteria (N=18) (12)

Phase 2		
NCT no.	**NCT01735630**	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	350
	Inclusion criteria	Diagnosis of probable AD by NIA-A/A; MMSE score 5-24; NPI-A/A ≥4; lack of response to non-pharmacological treatment
	Exclusion criteria	Agitation attributable to cause other than AD; diagnosis of MDD; persistent psychotic symptoms necessitating hospitalization
Treatments	**Treatment type**	ELND005
	Treatment duration	12 weeks
	Concomitant medication	Not stated

Patients	**Age, years**	50-95
	AD diagnostic criteria	NIA-A/A
	AD severity measure	MMSE
	Agitation Criteria	NPI A/A
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	NPI (caregiver) A/A, mADCS-CGIC
NCT no.	**NCT02992132**	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	432
	Inclusion criteria	Diagnosis of probable AD by NIA-A/A; meets IPA criteria for agitation; living at home or in assisted living; caregiver ≥3 times weekly who agrees to participate

	Exclusion criteria	Agitation attributable to cause other than AD; antipsychotic medication within 2 weeks; medical condition that would impair participation; cardiac symptoms; psychotic disorder
Treatments	**Treatment type**	Pimavanserin
	Treatment duration	12 weeks
	Concomitant medication	Antipsychotics not allowed
Patients	**Age, years**	>50
	AD diagnostic criteria	NIA-A/A
	AD severity measure	Not stated
	Agitation Criteria	IPA
	Agitation as primary or secondary end point	Primary
	Agitation measure	CMAI
NCT no.	**NCT02129348**	

Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	80
	Inclusion criteria	Diagnosis of possible or probable AD by NIA; MMSE 5-26; NPI A/A >4; availability of informant
	Exclusion criteria	Medications with renal effects in combination with lithium; psychotic disorder; MDD or suicidality; substance abuse; major neurologic disorder; stroke with neurologic effects; cardiac symptoms; unstable illness
Treatments	**Treatment type**	Lithium
	Treatment duration	12 weeks
	Concomitant medication	Some antipsychotics and antidepressants allowed, lorazepam, hypnotics
Patients	**Age, years**	55-95
	AD diagnostic criteria	NIA-A/A
	AD severity measure	MMSE, CGI

	Agitation Criteria	NPI A/A
	Agitation as primary or secondary end point	Primary
	Agitation measure	NPI
NCT no.	**NCT03226522**	
Study details	**Design**	Multicenter, randomized, double-blind, parallel-group
	Comparator	Active (bupropion) and placebo
	Patient no.	435
	Inclusion criteria	Diagnosis of probable AD by NIA-A/A; meets IPA criteria for agitation
	Exclusion criteria	Non-Alzheimer's dementia; conditions or behavior precluding participation
Treatments	**Treatment type**	AXS-05
	Treatment duration	5 weeks
	Concomitant	Not stated

	medication	
Patients	**Age, years**	65-90
	AD diagnostic criteria	NIA-A/A
	AD severity measure	Not stated
	Agitation Criteria	IPA
	Agitation as primary or secondary end point	Primary
	Agitation measure	CMAI
NCT no.	**NCT02792257**	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	160
	Inclusion criteria	Diagnosis of AD; meets IPA criteria for agitation; NPI-C A/A ≥4; fluent in English and able to give consent;

		able to stay in hospital for study duration
	Exclusion criteria	Serious or unstable medical condition; seizure disorder; baseline delirium
Treatments	**Treatment type**	Dronabinol
	Treatment duration	3 weeks
	Concomitant medication	Not stated
Patients	**Age, years**	60-90
	AD diagnostic criteria	Not stated
	AD severity measure	Not stated
	Agitation Criteria	IPA, NPI
	Agitation as primary or secondary end point	Primary
	Agitation measure	PAS, NPI

NCT no.	NCT02471196	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	308
	Inclusion criteria	Consent from patient and participating caregiver; diagnosis of probable AD with brain imaging; MMSE 10-24; meets IPA criteria for agitation; NPI A/A ≥4
	Exclusion criteria	MHIS >4; unstable concomitant medications; use of antipsychotics, anticholinergics and other specified medication; cardiac or cerebrovascular symptoms; malignancy; suicidality; brain abnormalities that could affect cognition; residence in skilled nursing facility
Treatments	**Treatment type**	ORM-12741
	Treatment duration	12 weeks
	Concomitant medication	Some stable medications allowed; antipsychotics and anticholinergics excluded
Patients	**Age, years**	55-90

	AD diagnostic criteria	Not stated
	AD severity measure	MMSE
	Agitation Criteria	IPA, NPI
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	NPI, mADCS-CGIC, CMAI
NCT no.	**NCT02351882**	
Study details	**Design**	Multicenter, randomized, double-blind, crossover
	Comparator	Placebo
	Patient no.	40
	Inclusion criteria	Major neurocognitive disorder owing to AD per *DSM-V*; MMSE ≤24; NPI A/A ≥3; stable medications
	Exclusion criteria	Psychotropic medication; cardiovascular symptoms; other psychiatric disorder or neurologic condition; substance abuse

Treatments	**Treatment type**	Nabilone
	Treatment duration	6 weeks, 1 week washout, 6 weeks
	Concomitant medication	Stable cholinesterase inhibitors and memantine allowed; psychotropic medications excluded
Patients	**Age, years**	>55
	AD diagnostic criteria	*DSM*-5
	AD severity measure	MMSE
	Agitation Criteria	NPI
	Agitation as primary or secondary end point	Primary
	Agitation measure	CMAI
NCT no.	**NCT01126099**	
Study	**Design**	Phase 1/2: phase 1, randomized, double-blind; phase 2, open-label

details	**Comparator**	Placebo
	Patient no.	20
	Inclusion criteria	Probable or possible AD; agitated behavior ≥2× weekly; stable medication for 2 weeks; caregiver for 10 hours/week who agrees to participate
	Exclusion criteria	Cardiovascular symptoms; unstable medical condition; exclusionary medications; psychoactive medications; psychiatric conditions or behavior precluding participation
Treatments	**Treatment type**	Prazosin
	Treatment duration	12 weeks (double-blind phase)
	Concomitant medication	Stable medication allowed
Patients	**Age, years**	No age limit
	AD diagnostic criteria	Not stated
	AD severity measure	Not stated
	Agitation Criteria	Not stated

	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	ADCS-CGIC, NPI, BPRS
Phase 3		
NCT no.	**NCT02817906**	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	360
	Inclusion criteria	Diagnosis of probable AD; clinically significant agitation secondary to AD; ability to attend clinic visits
	Exclusion criteria	Conditions or behavior precluding participation
Treatments	**Treatment type**	ITI-007 (lumateperone)
	Treatment duration	4 weeks
	Concomitant	Not stated

	medication	
Patients	**Age, years**	>55
	AD diagnostic criteria	Not stated
	AD severity measure	CGI-S
	Agitation Criteria	Not stated
	Agitation as primary or secondary end point	Primary
	Agitation measure	CMAI
NCT no.	**NCT02168920**	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	880
	Inclusion criteria	Major neurocognitive disorder owing to AD per *DSM-V*; diagnosis of probable AD per NINCDS/ADRDA;

		hospitalized or in care facility; MMSE 1-22
	Exclusion criteria	Dementia other than AD; MHIS ≥5; psychologic conditions or behavior precluding participation; cardiac or cerebrovascular symptoms; weight <30 kg; seizure disorder; suicidality; motor dysfunction
Treatments	**Treatment type**	Aripiprazole
	Treatment duration	10 weeks
	Concomitant medication	Not stated
Patients	**Age, years**	55-89
	AD diagnostic criteria	*DSM*-5, NINCDS/ADRDA
	AD severity measure	CGIS, CGII, MMSE
	Agitation Criteria	Not stated
	Agitation as primary or secondary end point	Primary
	Agitation measure	CMAI

NCT no.	NCT02442765	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	380
	Inclusion criteria	Diagnosis of probable AD by NIA-A/A; meets IPA criteria for agitation; significant agitation for ≥2 weeks; outpatients or care home residents; CGIS ≥4; MMSE 6-26; caregiver ≥4× weekly who agrees to participate
	Exclusion criteria	Non-AD dementia; clinically significant or unstable medical conditions; myasthenia gravis
Treatments	**Treatment type**	AVP-786
	Treatment duration	12 weeks
	Concomitant medication	Not stated
Patients	**Age, years**	50-90
	AD diagnostic criteria	NIA-A/A

	AD severity measure	MMSE
	Agitation Criteria	IPA
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	CMAI, NPI A/A
NCT no.	**NCT02442778**	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	470
	Inclusion criteria	Diagnosis of probable AD by NIA-A/A; meets IPA criteria for agitation; significant agitation for ≥2 weeks before baseline; outpatients or care home residents; CGIS ≥4; MMSE 6-26; caregiver ≥4× weekly who agrees to participate
	Exclusion criteria	Non-AD dementia; clinically significant or unstable medical conditions; myasthenia gravis
Treatments	**Treatment type**	AVP-786

	Treatment duration	12 weeks
	Concomitant medication	Not stated
Patients	**Age, years**	50-90
	AD diagnostic criteria	NIA-A/A
	AD severity measure	MMSE
	Agitation Criteria	IPA
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	CMAI, NPI A/A
NCT no.	**NCT03108846**	
Study details	**Design**	Multicenter, randomized, double-blind, pretreatment psychosocial intervention
	Comparator	Placebo

	Patient no.	392
	Inclusion criteria	Probable or known AD; agitation
	Exclusion criteria	MDD
Treatments	**Treatment type**	Escitalopram
	Treatment duration	12 weeks
	Concomitant medication	Not stated
Patients	**Age, years**	18-109
	AD diagnostic criteria	Not stated
	AD severity measure	Not stated
	Agitation Criteria	Not stated
	Agitation as primary or secondary end point	Primary

	Agitation measure	mADCS-CGIC
NCT no.	**NCT01862640**	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	433
	Inclusion criteria	Diagnosis of probable AD per NINCDS-ADRDA; MMSE 5-22; agitation for ≥2 weeks; NPI-NH ≥4; failed trial of non-pharmacological treatment; brain imaging
	Exclusion criteria	Non-AD dementia; clinically significant or unstable medical conditions; axis 1 disorder; uncontrolled diabetes or hypertension; seizures
Treatments	**Treatment type**	Brexpiprazole
	Treatment duration	12 weeks
	Concomitant medication	Not stated
Patients	**Age, years**	55-90

	AD diagnostic criteria	NINCDS/ADRDA
	AD severity measure	MMSE
	Agitation Criteria	NPI (patients must also have failed nonpharmacological intervention)
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	CMAI, CGIS
NCT no.	**NCT01922258**	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	270
	Inclusion criteria	Diagnosis of probable AD per NINCDS-ADRDA; MMSE 5-22; agitation for ≥2 weeks; NPI-NH ≥4; failed trial of nonpharmacological treatment; brain imaging
	Exclusion criteria	Non-AD dementia; clinically significant or unstable medical conditions; axis 1 disorder; uncontrolled diabetes or hypertension; seizures

Treatments	**Treatment type**	Brexpiprazole
	Treatment duration	12 weeks
	Concomitant medication	Not stated
Patients	**Age, years**	55-90
	AD diagnostic criteria	NINCDS/ADRDA
	AD severity measure	MMSE
	Agitation Criteria	NPI (patients must also have failed non-pharmacologic intervention)
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	CMAI, CGIS
NCT no.	**NCT03031184**	
Study	**Design**	Multicenter, randomized, double-blind, pragmatic

details	**Comparator**	Placebo
	Patient no.	471
	Inclusion criteria	Diagnosis of probable AD per NINCDS-ADRDA; agitation that has not responded to treatment; CMAI ≥45; suitable informant who consents to participate
	Exclusion criteria	Antidepressants, anticonvulsants or antipsychotics; cardiac symptoms; history of bone marrow depression or hepatic porphyria; suicidality; childbearing
Treatments	**Treatment type**	Carbamazepine, mirtazapine
	Treatment duration	12 weeks
	Concomitant medication	Stable cholinesterase inhibitors or memantine allowed; antidepressants, antipsychotics, anticonvulsants excluded
Patients	**Age, years**	>18
	AD diagnostic criteria	NINCDS/ADRDA
	AD severity measure	Not stated
	Agitation Criteria	CMAI

	Agitation as primary or secondary end point	Primary
	Agitation measure	CMAI
Phase 4		
NCT no.	**NCT03082755**	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Placebo
	Patient no.	136
	Inclusion criteria	CDR score 2 or 3; diagnosis of AD; nighttime agitation per CMAI; RLS diagnosis; sleep disturbance; table medication; ambulatory
	Exclusion criteria	Opioids; current RLS treatment; Parkinson disease or motor dysfunction; seizures; psychosis; alcohol consumption; renal dysfunction; suicidality; any condition precluding participation
Treatments	**Treatment type**	Gabapentin, enacarbil
	Treatment duration	8 weeks

	Concomitant medication	Stable medication allowed; opioids excluded
Patients	**Age, years**	>55
	AD diagnostic criteria	CDR
	AD severity measure	CDR, MMSE
	Agitation Criteria	CMAI
	Agitation as primary or secondary end point	Primary and secondary
	Agitation measure	CMAI, mADCS-CGIC
NCT no.	**NCT00018291**	
Study details	**Design**	Multicenter, randomized, double-blind
	Comparator	Risperidone
	Patient no.	130

	Inclusion criteria	Diagnosis of probable AD per *DSM-IV* and NINCDS-ADRDA; ≥2-week history of agitation; stable medication; MHIS ≤4
	Exclusion criteria	Neurologic disorder other than AD; delirium; non-AD dementia; substance abuse; serious or unstable medical condition that precludes participation; non-AD agitation; psychotropic medications; cardiac symptoms
Treatments	**Treatment type**	Gabapentin
	Treatment duration	12 weeks
	Concomitant medication	Antipsychotics, antidepressants, anxiolytics, anticonvulsants, hypnotics all excluded
Patients	**Age, years**	>50
	AD diagnostic criteria	*DSM-IV*, NINCDS/ADRDA
	AD severity measure	Not stated
	Agitation Criteria	ASI
	Agitation as primary or	Primary

	secondary end point	
	Agitation measure	Not stated

Abbreviations: AD, Alzheimer's disease; ADCS-CGIC, Alzheimer Disease Cooperative Study-Clinical Global Impression of Change; ASI, agitation screening inventory; BPRS, Brief Psychiatric Rating Scale; CDR, clinical dementia rating; CGII, Clinical Global Impressions-Improvement; CGIS, Clinical Global Impressions-Severity; CMAI, Cohen-Mansfield Agitation Inventory; mADCS-CGIC, modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change; *DSM*, *Diagnostic and Statistical Manual*; IPA, International Psychogeriatric Association; mADCS-CGIC, modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change; MDD, major depressive disorder; MHIS, Modified Hachinski Ischemia Score; MMSE, Mini-Mental State Examination; NIA-AA, National Institute on Aging-Alzheimer Association; NPI A/A, Neuropsychiatric Inventory Agitation/Aggression domain; NPI-C A/A, NPI-Clinician Rating Scale Agitation/Aggression Domains; PAS, Pittsburgh Agitation Scale; RLS, restless legs syndrome.