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RESEARCH ARTICLE

Pharmacological treatment trials of agitation in Alzheimer's disease: A systematic review of ClinicalTrials.gov registered trials

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Abstract

Introduction: There is increasing emphasis on the importance of optimizing and standardizing clinical trials of agitation in Alzheimer's disease (AD), but the risks of bias arising from published trials and the number and design of unpublished studies are poorly understood.

Methods: Using the ClinicalTrials.gov database, we systematically reviewed all registered investigational clinical trials for agitation in AD to describe the landscape of agitation drug treatment trials and to assess their quality and generalizability.

Results: We included 52 clinical studies registered over the past 25 years. Within published randomized controlled trials (RCTs), there was a high rate of participant dropout, poor reporting of randomization procedures, and inconsistent definitions of the sample included for analysis. There was also evidence of publication and funder bias.

Discussion: We discuss factors that limit the internal and external validity of published RCTs and make additional recommendations for the conduct and reporting of future clinical trials of agitation in AD.

KEYWORDS
agitation, Alzheimer's disease, clinical trials, dementia, systematic review

1 | INTRODUCTION

Agitation, defined as observed or inferred evidence of emotional distress associated with excessive motor activity, and verbal or physical aggression,[1] is a common, distressing, and difficult-to-treat neuropsychiatric syndrome. In Alzheimer's disease (AD), the most common cause of dementia,[2] agitation prevalence increases with disease severity,[3] affecting around 80% of care home residents.[4] As well as substantially increasing the costs of patient care in community[5] and care home[6] settings, agitation reduces quality of life,[7] precipitates earlier institutionalization[8] and more rapid disease progression[9] and possibly earlier death.[10] The best treatment evidence for agitated people with dementia who do not respond to non-pharmacological approaches[11] is short-term use of atypical antipsychotic drugs, which are moderately effective but associated with significant harms (sedation, falls, parkinsonism, stroke) and increased mortality.[12,13] There has been a move away from antipsychotic prescribing in the past decade.[14] The need for effective and safer pharmacological treatments for

agitation in AD, to understand the neurobiology underlying this condition and investigate valid biomarkers as targets of new prevention or treatment monitoring strategies, is clear.[15]

Clinical trials generate important data on drug safety and efficacy, which can have significant medical, financial, and political implications. Yet, the search for effective drug therapies for agitation in AD may have been limited by the methodological heterogeneity of studies, leading to several published recommendations of ways to optimize clinical trial methodology in this field.[16–18] For example, although a consensus "provisional" definition of agitation in cognitive disorders now exists,[1] there is no standardized tool to assess agitation, no consensus definition of what constitutes a caregiver and a lack of agreed severity thresholds for baseline agitation in AD for qualification for entry into clinical trials. Earlier reviews have described the methodologies of ongoing or completed randomized controlled trials (RCTs)[16,17] or novel pharmacological treatments,[19,20] but have not systematically assessed study quality. Given increasing awareness of the limitations of RCTs, in terms of internal and external validity,[21,22] and including concerns about publication and funder bias,[23] it would be important to assess the risk of bias within reported RCTs, understand the extent and nature of unpublished studies, and discuss how the conduct and reporting of future clinical trials could be further optimized.

ClinicalTrials.gov is the largest clinical trials database and is run by the US National Library of Medicine at the National Institutes of Health (NIH). It has been publicly available since February 2000, with mandated registration, results, and adverse events reporting for all clinical trials since 2007. The present study aimed to systematically review all registered investigational clinical trials for agitation in AD (including unpublished, ongoing, or terminated studies, and not limited to RCTs), to describe the landscape of agitation drug treatment trials and to assess their quality and generalizability.

RESEARCH IN CONTEXT

1. Systematic review: The authors searched ClinicalTrials.gov for all registered drug intervention studies that assessed agitation in patients with Alzheimer's disease (AD).
2. Interpretation: Our findings are consistent with those from previous reviews that found methodological heterogeneity in studies and update an earlier review of novel pharmacological agents. We incorporated unpublished registered studies and assessed the quality of published randomized controlled trials to report on the landscape of pharmacological treatment trials of agitation in AD.
3. Future directions: The study identified several potential sources of selection, exclusion, and reporting biases and made recommendations to further improve the internal and external validity of future agitation clinical trials in AD.

2 | METHODS

To identify relevant studies, two authors (AB and KL) independently searched ClinicalTrials.gov initially up to November 26, 2019 using the search terms "Alzheimer's disease" AND ("neurobehavioral" OR "agitation" OR "aggression" or "BPSD" or "neuropsychiatric"). The search was updated on September 28, 2020. AB and KL independently screened studies for inclusion based on the following criteria: drug intervention studies that assessed agitation in patients with AD were included; observational studies and studies that used non-pharmacological interventions or did not primarily aim to measure agitation or time in relation to agitation symptoms were excluded.

Each of the included studies was assessed by two authors (out of AB, JM, TE, MK, and KL), who independently extracted data on study characteristics and methodology and, for completed studies, the outcomes. All published, completed controlled intervention studies were also assessed for quality using the freely available online NIH Quality Assessment of Controlled Intervention Studies tool[24] and given a dichotomous quality assessment rating of higher or lower quality. This was based on the accompanying guidance that assessed a study to have a "fatal flaw" if it had a high dropout rate (> 20% of the number allocated to treatment) or included no intention-to-treat analysis. We did not assess the quality of unpublished studies due to insufficient information available to make informed judgments. Discrepancies were resolved by discussion and/or re-extraction of the relevant data by AB or KL. If a hyperlink to the published study was not available on ClinicalTrials.gov, the registry number (NCT identifier) and/or study authors' names were searched using PubMed and Google Scholar. If no published results were obtained, the email address associated with the ClinicalTrials.gov registration, if available, was used to request information on study status or outcomes. If no relevant results were obtained, the study was classified as unpublished. Study characteristics were described using means and standard deviations (SD) or frequencies and proportions, as appropriate.

3 | RESULTS

The searches identified 608 potential studies, 52 of which met inclusion criteria for data extraction (Figure 1).

3.1 | Characteristics of included studies

Of the 52 included studies that started (or were registered, for those few without declared start dates) between 1995 and 2020, 30 (58%) were completed to study end, 20 (38%) were published, 16 (31%) were ongoing, 4 (8%) had been terminated early, and 2 (4%) had unknown status (Figure 2). Table 1 shows the extracted data from included studies, divided into repurposed and novel

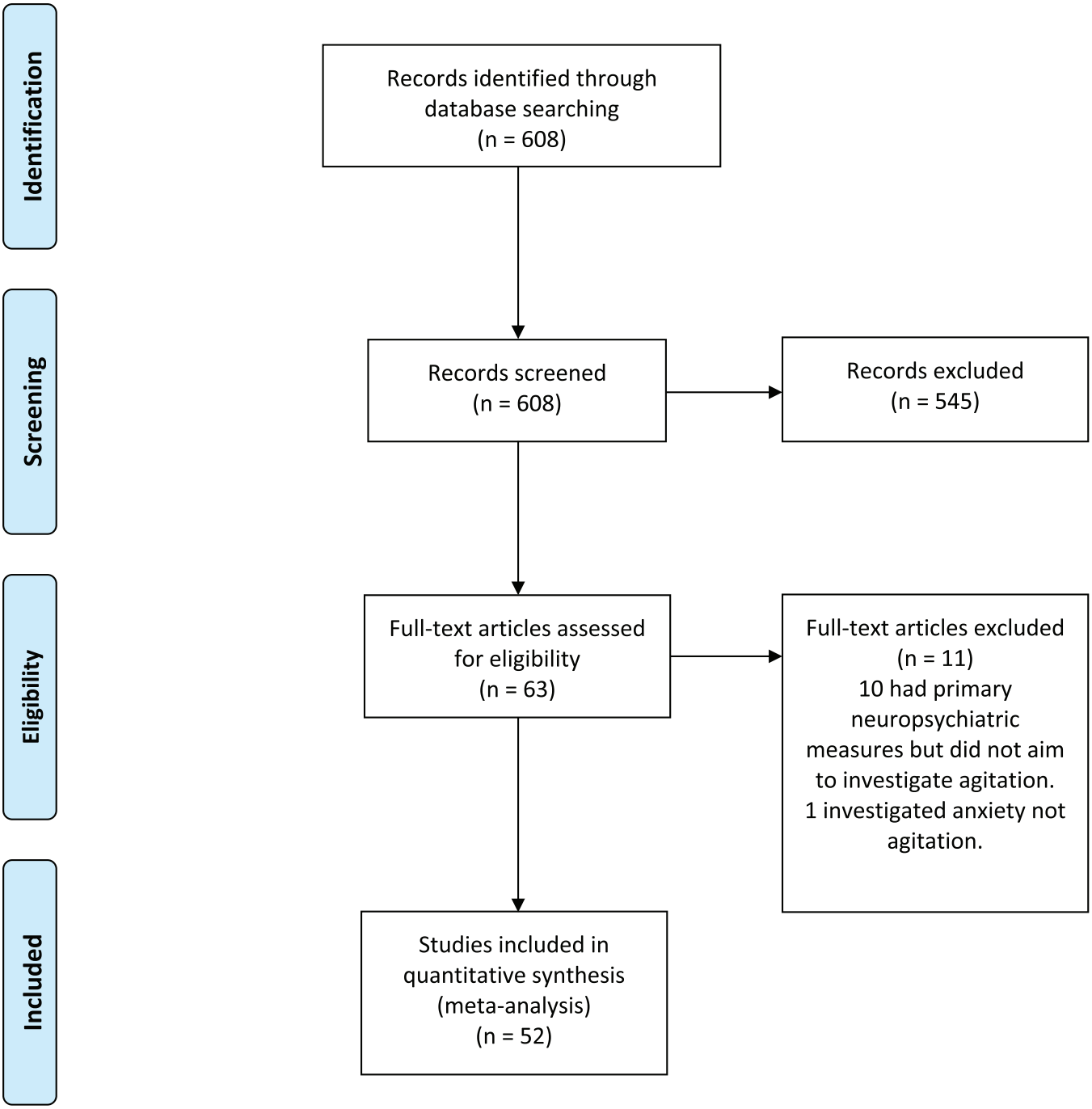

FIGURE 1 PRISMA flowchart

pharmacological treatment categories. The majority of published studies (65%; N = 13) did not report significant findings for their prespecified primary measures, and ≈33% of completed studies (that had started by 2015) remained unpublished (N = 11), of which only three had posted results on ClinicalTrials.gov. The average duration of completed studies (time between study start and completion dates) was ≈3.3 (SD 1.9) years.

Additional study characteristics relating to methodologies, inclusion criteria, and agitation outcome measures are summarized in Table S1 in supporting information.

3.1.1 | Location and sponsorship

Most studies (67%; N = 35) were conducted in the United States (US). Other countries/regions of trials sites were: Canada (N = 10), United Kingdom (N = 6) and other European countries (N = 7), China/Taiwan (N = 4), Australia/New Zealand (N = 3), Japan (N = 2), South Africa (N = 1), Israel (N = 1), and Chile (N = 1). More than half of all registered studies (54%; N = 28) were fully or partially sponsored by industry but proportionally fewer of these were published (40%; N = 8 of 20). All trials of novel agents were fully sponsored by pharmaceutical companies.

FIGURE 2 Investigated drugs by trial start date and size (number of Alzheimer's disease participants), grouped by study status. (Active_not = active, not recruiting; Completed_pub = completed and published; Completed_unpub = completed and unpublished; Not_yet = active and not yet recruiting). The published memantine 2003 study was terminated early

3.1.2 | Data from published studies

We extracted actual participant data reported in the 20 published studies. The mean number of participants was 198 (SD 142) who were treated for an average of 15.8 (SD 21.9) weeks. On average, participants were 79.2 (SD 4.1) years old with a Mini-Mental State Examination (MMSE) score of 11.7 (SD 4.3); 53.5% (SD 18.9%) were female; and most were community dwelling, including in long term care facilities (residential and nursing care homes and assisted living facilities). Only three studies enrolled hospital inpatients. Seven studies enrolled participants who on average had moderate dementia (MMSE 13 to 18) and eight enrolled participants with severe dementia (MMSE < 12). Study populations with mild dementia (MMSE > 18) were only identified in two brexpiprazole studies, in which they made up 9% and 23% of the study population, respectively. All but one study measured baseline cognitive impairment using the MMSE, five studies also used the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and three also used the Clinical Dementia Rating (CDR) scale. Four of the eight studies that enrolled severe AD patients measured cognition using the Severe Impairment Battery (SIB). In terms of mean baseline agitation levels measured using the three most commonly reported outcomes, where reported, these were Neuropsychiatric Inventory (NPI) total 34.6 (SD 6.1), Cohen–Mansfield Agitation Inventory (CMAI) total 61.6 (SD 14.1), and NPI-agitation/aggression 8.5 (SD 4.1), which indicated moderate agitation severity.

Compared to studies with no industry funding, a lower proportion of studies that were fully or partially sponsored by pharmaceutical companies reported negative findings, (67% vs. 50%). In addition, one of the industry-sponsored studies[25] reported a positive finding, but on closer inspection, the pre-specified primary outcome from the primary analysis was not significant.

3.2 | Pharmacological treatment strategies

Most (79%; N = 42) studies investigated or were investigating repurposed drugs (already approved for other conditions), and 10 studies of six novel agents were registered in the past decade (Table 1). The most common types of pharmacological treatment under investigation for agitation in AD included (see Table S2 in supporting information for a detailed summary): antipsychotics (including six studies of risperidone and four of brexpiprazole), antidepressants (three studies each of citalopram and escitalopram and one mirtazapine study), dextromethorphan-containing compounds (seven studies), anti-dementia drugs (four memantine studies and one donepezil study), cannabinoids (five studies), and an α_1-blocker (three prazosin studies).

3.3 | Quality ratings of published controlled intervention studies

Approximately half of all published controlled intervention studies (52%, N = 10 of 19) were judged to be of lower quality due to their reported dropout rates at the endpoint being > 20% of the number allocated to treatment (Table 1 and Table S3 in supporting information). Of these, two studies also had a difference in dropout rate of > 15% between treatment groups at endpoint. Four studies had < 50 participants in each arm despite reporting having at least 80% power to detect a difference in the primary outcome between groups.

All published controlled intervention studies were described as randomized trials, but several (16%; N = 3) did not adequately describe their randomization method and only one third (N = 6) reported concealment of treatment allocation. The majority (N = 14) of published controlled intervention studies used a modified intention-to-treat (mITT) approach, in which only randomized participants who had taken at least one dose of study medication, and/or had a baseline and/or at least one post-baseline assessment (had to be endpoint data in one study), were included in the final primary analysis.

For trials that included a run-in period, it has been suggested that incomplete reporting of any excluded patients during this period could affect study validity.[26] Of seven published RCTs that described a run-in or screening period prior to randomization, during which certain concomitant medications were stopped and/or placebo was provided, two trials did not report the number of excluded participants during this period. None of the studies reported the reasons for excluding these participants, or their baseline characteristics.

Eleven published studies reported allowing the use of rescue medication, most commonly lorazepam, during the study. Of these, two studies did not provide data on how/whether these medications were used, and three did not statistically compare rates of use between groups. Of the six studies that compared rates of rescue medication initiation between groups, four reported no significant differences, one reported more frequent use in the placebo group (vs. risperidone), and one in the drug (mibampator) versus placebo group.

TABLE 1 Repurposed and novel pharmacological treatment strategies for agitation in AD from included studies

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
Repurposed (antipsychotic, antidepressant, antidementia drugs)	Risperidone	1	NCT00249158[36]	1998	No	No difference at endpoint but significant differences at earlier timepoints. Higher rate of serious adverse events in risperidone group versus placebo. Up to 7 days washout and placebo run-in period.	12 weeks	DSM-IV; NH	Nurses in NH	384 (180), 71.8%	55 (83.0)	23 (5.5)	CMAI total aggression score; CMAI four on one aggressive item, or three on Two items, or teo on Three items, or two aggressive items occurring at frequency of two, and one at frequency of three; (33.6)	Lower	Australia, NZ,[1]
	Haloperidol versus trazadone versus behavioral program	1	NCT00000179[37]	1999	No	Participants needed to have stopped psychotropic medications >2 weeks before enrolment.	16 weeks	NINCDS-ADRDA; Com	Spouse or adult relative who had 5 h/d contact with the patient.	149, 55.3%	NA (74.8)	NA (13)	ADCS-CGIC; 2-week history of Two agitated behaviors occurring weekly and rated by caregiver as distressing or requirement help; (NA)	Lower	US, multisite, [NA]
	Risperidone versus gabapentin*	7	NCT00018291	2001	–		12 weeks	DSM-IV; Com (long term care facilities)	NA	130, NA%	≥50 (NA)	NA	NA; ≥2-week history of ≥2 agitated behaviors from the Agitation Screening Inventory (a shortened version of the RMBPC), occurring ≥once weekly, and rated as at least moderately distressing (NA)	–	US, single site [NA]
	Risperidone versus olanzapine versus quetiapine	1	NCT00015548[27]	2001	No	Atypical antipsychotic drugs had greater adverse effects versus placebo.	36 weeks	DSM-IV or on the basis of history, examination, brain imaging and MMSE; Com (home or assisted living)	Study partner or caregiver who had regular contact with the patient.	421, 55.8%	NA (78.1)	5-26 (15.1)	Time to antipsychotic discontinuation; Nearly daily psychosis, aggression or agitation in the previous week or at least intermittently for 4 weeks. In week before assignment, BPRS severity at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior, or NPI frequency "often" or "more frequently" and severity at least "moderate" for delusions, hallucinations, agitation, or "aberrant motor behavior" (BPRS 27.7, NPI 36.7)	Higher	US, multisite, [NA]

(Continues)

TABLE 1 (Continued)

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
	Risperidone	9	NCT00626613	2008	–		12 weeks	NA; NA	NA	NA	≥60	NA	NPI; NA	–	Taiwan, single site[2]
	Quetiapine	1	NCT00621647[23]	2002	No	Factorial assignment. It was reported that 200 mg/d was more clinically effective versus placebo, but it showed significant improvement in secondary but not primary measures/analyses versus placebo.	10 weeks	DSM-IV or NINCDS-ADRDA; NH and Com (assisted living)	NA	333 (263), 82.3%	55 (83.2)	NA (5.3)	PANSS-EC; Agitation not directly due to a medical condition and required antipsychotic medication in the opinion of the investigator, PANSS-EC score > 14 total and > 4 or 1 of 5 items at screening and randomization (23.0)	Lower	US, multisite,[1]
	Brexpiprazole	1	NCT01922258 Study 1[32]	2013	Yes	Fixed doses. It was safe and well-tolerated (five patients died during the study, all in the brexpiprazole group, though not considered related to treatment). Washout phase up to 42 days preceding treatment.	12 weeks	NINCDS-ADRDA; NH or Com (assisted living, residential care or home)	Caregiver who spent ≥2 h/d for 4 d/wk with the patient.	433, 54.9%	55-90 (73.9)	5-22 (mild [>18] 9%; moderate [13–18] 57.3%; severe [<12] 33.7%)	CMAI; NPI-NH A/A domain ≥4 and require pharmacotherapy for agitation in the investigator's judgment (CMAI 71.2; NPI-NH A/A 7.5).	Higher	US, Europe,[1]
	Brexpiprazole	1	NCT01862640 Study 2[32]	2013	No	Flexible doses. Post-hoc analyses showed improvement in patients titrated to brexpiprazole 2 mg/d versus similarly titrated placebo patients. Higher rate of discontinuation due to adverse event in the brexpiprazole group. Washout phase up to 42 days preceding treatment.	12 weeks	NINCDS-ADRDA; NH or Com (assisted living, residential care or home)	Caregiver who spent ≥2 h/d for 4 d/wk with the patient.	270, 63.0%	55-90 (73.8)	5-22 (mild [>18] 23.0%; moderate [13–18] 47.5%; severe [<12] 29.5%)	CMAI; ≥4 on the NPI-NH A/A domain and require pharmacotherapy for agitation in the investigator's judgment (CMAI 70.0, NPI-NH A/A 7.5)	Higher	US, Canada, UK, Europe,[1]

(Continues)

TABLE 1 (Continued)

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
	Brexpiprazole	5	NCT03548584	2018	–		12 weeks	NA; institutionalized or non-institutionalized	Caregiver spends ≥2 h/d for 4 d/wk) with the patient.	Estimated 225	55-90 (NA)	5-22	CMAI; NA (NA)	–	US, single site,[1]
	Brexpiprazole	5	NCT03620981	2018	–		10 weeks	NINCDS-ADRDA and DSM-5; Hospital or Com (care facility or home)	NA	Estimated 407	55-90 (NA)	1-22	CMAI; Consensus definition of agitation in cognitive disorders from the IPA (NA)	–	Japan, multisite,[1]
	Aripiprazole	8	NCT02168920	2014	–		10 weeks	DSM-V and NINCDS-ADRDA;Hospital or care facility	NA	150, NA%	55-89 (NA)	1-22 (NA)	CMAI; NA	–	Japan, multisite[1]
	Lumateperone	3	NCT02817906	2016	No		4 weeks	NA; Com	NA	177	≥55	NA	CMAI-C; Clinically significant agitation secondary to AD (NA)	–	US, multisite[1]
	Pimavanserin	2, 8	NCT02992132	2016	No	Planned to recruit 432 participants. Study was underpowered.	12 weeks	NIA-AA; Com (at home or assisted living or care facility)	Caregiver is in contact with the patient ≥3 times a week on three separate days	111, 52.3%	≥50 (76.8)	NA	CMAI; Consensus definition of agitation in cognitive disorders from the IPA guidelines (CMAI 65.1)	–	US, Chile, Europe, UK[1]
	Amisulpride versus olanzapine*	6	NCT04341467	2020	–	Open label.	8 weeks	ICD-10; NA	NA	Estimated 76	All ages	<24 (NA)	NPI; NPI-12 total ≥20 (NA)		China, single site [NA]
	Citalopram versus perphenazine	1	NCT00009204[38]	1995	Yes, for citalopram	Side effect scores were similar among the treatment groups. A 5-day washout period preceded treatment.	17 days	DSM-IV; Hospital	NA	85 (61), 63.7%	NA (79.9)	NA (7.6)	NBRS; score ≥3 on NBRS agitation or psychosis items (56.3)	Lower	US, single site [NA]
	Citalopram versus risperidone*	1	NCT01438060[39]	2000	No	Significant increase in side effect burden with risperidone but not citalopram.	12 weeks	NA;Hospital	NA	103 (91), 31.5%	NA (81.8)	NA (10.9)	NBRS; score ≥3 on ≥1 of the agitation items, (NBRS total 57.0, NBRS agitation 9.6)	Lower	US, single site [NA]

(Continues)

TABLE 1 (Continued)

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
	Citalopram	1	NCT00898807[25]	2009	Yes	Citalopram 30 mg/d associated with worse cognition and QT interval prolongation. A trained clinician conducted standardized psychosocial interventions during the study.	9 weeks	NINCDS-ADRDA; "academic medical centers"	Caregiver who spent at least several hours a week with the patient	186, 46.0%	NA (78.5)	5-28 (15.7)	NBRS agitation and mADCS-CGIC in agitation; Clinically significant agitation for which a physician determined that medication was appropriate and occurred "very frequently" or "frequently" with "moderate" or "marked" severity on the NPI A/A domain (NBRS agitation 7.6, NPI A/A 7.9, NPI total 37.3, CMAI 28.2)	Higher	US, Canada [NA]
	Escitalopram*	7	NCT00260624	2003	–	Open label and non-randomized.	12 weeks	NA; NA	Available and reliable caregiver.	Estimated 20 NA%	≥61 (NA)	NA	NBRS agitation factor; Agitation present at screening and baseline, not responsive to non-pharmacological treatment and lasting ≥2 weeks prior to enrolment.	–	US, multisite[2]
	Escitalopram versus risperidone*	1	NCT01119638[40]	2008	No	Higher rate of discontinuation and adverse effects with risperidone.	6 weeks	DSM-IV; hospital	NA	40, NA%	55-95 (NA)	5-24 (NA)	NPI; Signs and symptoms of psychosis, aggression, or agitation severe enough to disrupt functioning and justifies treatment with drugs, in the opinion of study physicians. Symptoms occur nearly daily during the week prior to enrolment; a frequency rating of "often" or "more frequently" and a severity rating of at least "moderate" are required for delusions, hallucinations, agitation, or aberrant motor behavior in NPI (NA).	Lower	Israel, single site [NA]

(Continues)

TABLE 1 (Continued)

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
	Escitalopram	5	NCT03108846	2018	–	Patients who did not respond to a 3-week structured psychosocial program for patients and carers were randomized.	12 weeks	NIA-AA; NA	Caregiver who spends at least several hours per week with the participant, supervises their care, and willing to accompany them to study visits	Estimated 392	18-109 (NA)	5-28 (NA)	mADCS-CGIC; Consensus definition of agitation in cognitive disorders from the IPA, clinically significant A/A and medication for agitation is appropriate as assessed by the study physician, and NPI frequency is "Very frequently," or"Frequently" AND the severity is "Moderate" or "Marked" (NA)	–	US, Canada [NA]
	Mirtazapine	4	NCT03031184	2017	–	Originally included carbamazepine but this arm was dropped on the basis of safety and efficacy due to challenges in recruitment.	12 weeks	NINCDS-ADRDA; NA	Availability of paid or family carer.	Estimated 222	≥18 (NA)	NA	CMAI; score ≥45 (NA)	–	UK, multisite [NA]
	Donepezil	1	NCT00142324[41]	2003	No	Patients with CMAI score >39 after up to 4 sessions/4 weeks of a psychosocial treatment program were randomized.	12 weeks	NINCDS-ADRDA; Com (residential care or home)	Caregiver who was in agreement with the patient's assent to participate.	272 (84.5)	>39 (84.7)	NA (8.2)	CMAI; Clinical agitation (causing distress to the patient and at least moderate management problems for caregivers on ≥2 d/wk for a 2-week period, together with a CMAI score ≥39) (CMAI 61.6, NPI 23.7, CGIC 4.3)	Higher	UK, multisite [NA]
	Memantine	1, 8	NCT00857649[42]	2003	No		12 weeks	NINCDS-ADRD and DSM-IV; Com	NA	369, 58.3%	≥50 (75)	5-15 (12)	NPI; NPI score ≥13 and NPI A/A score ≥1 at screening and baseline (30.1)		Canada, multisite[1]
	Memantine	7	NCT00097916	2004	–		NA	NA; NA	NA	34, NA%	≥50 (NA)	NA	NPI; NPI A/A score ≥4	–	US, multisite[1]
	Memantine*	1	NCT00401167[43]	2006	Yes	Open label.	3 months	DSM-IV; Com (long term care facility and NH)	NA	31, 6%	≥65 (85.8)	0-15 (8.7)	NPI-NH total; NPI-NH ≥10 and NPI-NH A/A score ≥1 (NPI-NH A/A 6.6, NPI total 31.1, CMAI 64.1)	–	Canada, multisite[2]

(Continues)

TABLE 1 (Continued)

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
	Memantine*	9	NCT00703430	2008	–	Open label.	12 weeks	NA; NA	Availability of a caregiver to ensure treatment compliance and provide information for assessments	Estimated 50, NA%	≥50 (NA)	NA	CMAI; CMAI score ≥4 on ≥1 aggressive item, or a score of 3 on ≥2 aggressive items, or a score of 2 on ≥3 aggressive items, or 2 aggressive items occurring at a frequency of 2 and 1 at a frequency of 3 (NA).	–	China, single site[2]
Repurposed (other)	Acetaminophe	7	NCT00012857	2001	–	Each arm lasted 2 weeks (crossover). Participants needed to have a documented painful condition and be unable to report pain consistently or reliably.	4 weeks	NA; NH	NA	Estimated 66, NA%	≥55 (NA)	NA	CMAI; > 1 episode of agitation/d (NA)	–	US, multisite [NA]
	Prazosin	1	NCT00161473[44]	2001	Yes	Adverse effects and blood pressure changes were similar between the groups.	8 weeks	NINCDS-ADRDA; NH or Com	NA	24, 40.5%	NA (80.7)	NA (11.7)	NPI, BPRS and CGIC; Exhibited agitation and aggression at least twice weekly for 2 weeks, score ≥4 on ≥1 of the following BPRS items: anxiety, tension, hostility, uncooperativeness, or excitement (NPI 46, BPRS 45)	Lower	US, multisite [NA]
	Prazosin	2	NCT01126099	2010	No	Actual recruitment was less than anticipated recruitment of 120 so likely to have been underpowered.	12 weeks	NA; Com	Caregiver spends 10 h/wk caring for participant.	20, 65.0%	NA (80.7)	NA	ADCS-CGIC and NPI; Disrupted agitated behaviors ≥ twice per week (NPI 42.4, BPRS 9.1)	–	US multisite [NA]

(Continues)

TABLE 1 (Continued)

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
	Prazosin	4	NCT03710642	2018	–		12 weeks	NINCDS-ADRDA; Com (long term care facility)	NA	186	NA	NA	ADCS-CGIC; Have ≥1 of irritability, physically and/or verbally aggressive behavior, physically resistive to necessary care, and/or pressured motor activity, any combination at least moderately severe rating ≥5times/wk for ≥4 weeks, they cause participant and caregiver distress and/or interfere with essential care or disrupt the environment (NA)	–	US, multisite [NA]
	Valproate	1	NCT00071721[45]	2003	No	Valproate treatment did not delay emergence of agitation or psychosis and was associated with significant toxic effects. A caregiver training program was offered to all families.	24 months	NINCDS-ADRDA; Com	NA	313, 58.7%	>54 (75.8)	12-20 (16.9)	Time to endpoint defined as NPI score >3 on A/A and/or psychosis domains; Absence of agitation or psychosis since illness onset, score <1 on NPI delusions, hallucinations, and A/A items (NA)	Lower	US, multisite [NA]
	Valproate added to atypical antipsychotic versus increasing doses of atypical antipsychotic*	7	NCT00208819	2003	–	Open label.	Duration of hospital stay	NA; Hospital	NA	Estimated 50 NA%	≥65 (NA)	NA	CMAI, PAS; NA (NA)	–	US single site[2]
	Lithium	7	NCT02129348	2014	–		12 weeks	NIA-AA; NA	Availability of informant.	77, NA%	NA	5-26 (NA)	NPI-A/A; NPI-A/A > 4 (NA)	–	US, multisite [NA]

(Continues)

TABLE 1 (Continued)

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
	Gabapentin enacarbil	5	NCT03082755	2017	–	Aimed to treat night-time agitation via medication for restless legs syndrome.	2 and 8 weeks	NA; NH	NA	Estimated 136	≥55 (NA)	NA (CDR score of 0.5-3)	CMAI (modified for night-time observation); Night-time agitation, defined as CMAI total score ≥35, diagnosis of restless legs syndrome and participant's physician opinion is that medication for agitation is appropriate (NA)	–	US, single site [NA]
	Levetiracetam	4	NCT04004702	2020	–	Open label non-randomized. Participants with epileptiform discharges on EEG will receive levetiracetam	12 months	NINCDS-ADRDA; NA	Caregiver willing and available to assist with medication administration and outcome measures	Estimated 65	NA	<26 (NA)	NPI; NPI-12 score ≥4	–	US, single site [NA]
	Dronabinol (THC)	1	NCT01608217[46]	2012	No		3 weeks	NINCDS-ADRDA; NH and Com	Caregiver available who was in touch with the patient ≥2 times/wk and supervised the patient's care.	50 (34), 50.2%	NA (78.5)	NA (15.0)	NPI; NPI-12 score ≥10, with symptoms reported on agitation, aggression, or aberrant motor behavior, existing ≥1 month prior to screening (NPI total 36.5, NPI A/A 6.0, CMAI 60.2)		Europe, multisite [NA]
	Dronabinol (THC)	5	NCT02792257	2017	–		3 weeks	NA; Hospital or Com (long term care or home)	NA	Estimated 160	60-95 (NA)	NA	NPI and PAS; Consensus definition of agitation in cognitive disorders from the IPA and severity of agitation defined by NPI-C A/A score > 4 (NA)	–	US, multisite [NA]
	Nabilone	1	NCT02351882[47]	2015	Yes	Crossover design. Nabilone was associated with more sedation versus placebo. There was a 1-week placebo run-in/washout period prior to each treatment phase.	14 weeks	DSM-5; Com (long-term care facility and outpatient geriatric psychiatry clinics)	NA	39 (NA), 23%	>55 (87.0)	≤24 (6.5)	CMAI; Clinically significant A/A with NPI A/A subscore ≥3 (CMAI 67.9; NPI-NH 34.3, NPI-NH A/A 7.1;CGIS 3.7)	Higher	Canada, single site [NA]

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TABLE 1 (Continued)

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
	Nabilone	6	NCT04516057	2020	–	Will include mixed AD/vascular dementia	8 weeks	DSM-5; NA	Available caregiver.	Estimated 112	≥55 (NA)	≤24 (NA)	CMAI; Consensus definition of agitation as per IPA guidelines	–	Canada [NA]
	THC-free cannabidiol	6	NCT04436081	2020	–	Will include mixed dementia.	15 weeks	NA; Com (not NH)	Caregiver must live with or have ≥4 h contact/d with participant.	Estimated 40	>50 (NA)	6-25 (NA)	CMAI; NPI-A/A > 3 (NA)	–	US, single site[2]
	AVP-923 (Nuedexta)	1	NCT01584440[48]	2012	Yes	Crossover design. AVP-923 was not ass. with cognitive impairment, sedation or clinically significant QTc prolongation, but was ass. with increased falls, diarrhea, urinary tract infection and dizziness versus placebo.	5 or 10 weeks	NINCDS-ADRDA; NH and Com (assisted living and home)	NA	220, 57.1%	50-90 (77.8)	8-28 (17.3)	NPI A/A subscore; Clinically significant agitation characterized by ≥1 of aggressive verbal, aggressive physical, or nonaggressive physical behaviors, that interfered with daily routine, were severe enough to warrant pharmacological treatment, scored ≥4 on the CGIS scale for agitation (NPI A/A 7.1, NPI total 39.6)	Higher	US, multisite[1]
	Sodium benzoate	1	NCT02103673[49]	2014	No		6 weeks	NINCDS-ADRDA; NA	NA	97 (85), 64.0%	≥50 (75.5)	5-26 (NA)	BEHAVE-AD; BEHAVE-AD ≥2 (BEHAVE-AD 10.9)	Lower	Taiwan, multisite [NA]
Novel	Mibampator	1	NCT00843518[50]	2009	No	Up to 28 days washout period preceding treatment.	12 weeks	NINCDS-ADRDA; Com	Reliable and actively involved caregiver who can communicate in English and is willing to comply with protocol requirements.	132, 50.7%	>60 (77.5)	6-26 (17)	NPI A/A; Clinically significant and persistent verbal or physical agitation and/or aggression behaviors that are disruptive to daily functioning or potentially harmful and occurred ≥3 d/wk over the past 4 weeks prior to study entry, NPI-10 item total score ≥10; NPI A/A ≥4 on one domain at screening and randomization (NPI A/A 18.5, NPI-10 total 30.8, CMAI 69.2)	Lower	US, multisite[1]

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TABLE 1 (Continued)

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
	ELND-005	2	NCT01735630	2012	No		12 weeks	NIA-AA; NA	NA	350, 55.7%	50-95 (76.1)	5-24 (NA)	NPI-C A/A; Clinically significant A/A defined as NPI A/A subscore ≥4 (NA)	–	US, UK, Canada, Europe[1]
	ORM-12741	7	NCT02471196	2015	–		12 weeks	NA; Com (nursing facility residence was an exclusion criterion)	Available caregiver	308, NA%	55-90 (NA)	10-24 (NA)	NPI-C A/A; NPI-A/A ≥4 at screening, agitation defined as per IPA guidelines and symptoms present for ≥4 weeks before the screening visit (NA)	–	Europe (Finland), multisite[1]
	AVP-786	7	NCT02442765	2015	–		12 weeks	NIA-AA; Com (NH, assisted living or outpatients)	Caregiver who must spend ≥2 h/d for 4 d/wk with the participant.	410, NA%	50-90 (NA)	6-26 (NA)	CMAI; Clinically significant, moderate/severe agitation at screening and ≥2 weeks prior to randomization definition of agitation as per IPA guidelines and CGIS score assessing agitation is ≥4 (NA)	–	US, multisite[1]
	AVP-786	7	NCT02442778	2015	–		12 weeks	NIA-AA; Com (NH, assisted living or outpatients	Caregiver who must spend ≥2 h/d for 4 d/wk with the participant.	522, NA%	50-90 (NA)	6-26 (NA)	CMAI; Clinically significant, moderate/severe agitation at screening and ≥2 weeks prior to randomization definition of agitation as per IPA guidelines and CGIS score assessing agitation is ≥4 (NA)	–	US and Canada[1]
	AVP-786	5	NCT03393520	2017	–		12 weeks	NIA-AA; Com	Reliable caregiver able and willing to comply with study procedures and spends ≥2 h/d for 4 d/wk with the participant.	Estimated 550	50-90	NA	CMAI; Consensus definition of agitation in cognitive disorders from the IPA and CGIS-Agitation score ≥4 at screening and for ≥2 weeks prior to baseline that interferes with daily routine and a prescription medication is indicated, in the opinion of the investigator (NA)	–	US, Australia, Europe, South Africa, UK[1]

(Continues)

TABLE 1 (Continued)

Drug type	Drug name	Trial status	NCT identifier	Study start or registration (year)	Significant positive primary findings at endpoint versus placebo or comparator	Comments	Duration of drug treatment	AD criteria; inclusion setting	Definition of caregiver if required	Total N assigned (AD), %Female	Inclusion age range (mean age) in years	MMSE inclusion criteria (actual mean MMSE)	Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score)	Quality	Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none
	AVP-786	5	NCT04408755	2020	–		12 weeks	NIA-AA; Com	Reliable caregiver able and willing to comply with study procedures and spends ≥2 h/d for 4 d/wk with the participant.	Estimated 750	50-90 (NA)	NA	CMAI; Clinically significant, moderate-to-severe agitation, meeting consensus definition of agitation as per IPA guidelines, for ≥2 weeks prior to screening that interferes with daily routine and requires pharmacotherapy as per Investigator's judgment. (NA)	–	US, multisite[1]
	AVP-786	6	NCT04464564	2020	–		12 weeks	NIA-AA; Com	Reliable caregiver able and willing to comply with study procedures and spends ≥2 h/d for 4 d/wk with the participant.	Estimated 750	50-90 (NA)	NA	CMAI; Clinically significant, moderate-to-severe agitation, meeting consensus definition of agitation as per IPA guidelines, for ≥2 weeks prior to screening that interferes with daily routine and requires pharmacotherapy as per Investigator's judgment. (NA)	–	NA[1]
	MP-101	3	NCT03044249	2017	No	Included other dementias.	10 weeks	NA;NA	Reliable caregiver spends ≥4 h/d ≥4 d/wk with the patient.	84 (NA)	≥50 (females ≥60 unless post-menopausal or congenitally or surgically sterile)	10-24 (NA)	NPI-A/A and/or NPI-psychosis; NPI score ≥4 on either delusions or hallucinations item, or ≥6 on combined delusions and hallucinations (psychosis subscale), or ≥4 on agitation/aggression (NA)	–	US and Canada[1]
	AXS-05versus bupropion	5	NCT03226522	2017	–		5 weeks	NIA-AA; NA	NA	Estimated 435	65-90 (NA)	NA	CMAI; Consensus definition of agitation in cognitive disorders from the IPA (NA)	–	US and Australia[1]

Abbreviations: A/A, agitation/aggression; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease; BPRS, Brief Psychiatric Rating Scale; CDR, Clinical Dementia Rating; CGI-C, Clinician's Global Impression of Change; CGI-S, Clinician Global Impression of Severity; CMAI, Cohen–Mansfield Agitation Inventory; CMAI-C, CMAI Community version; Com, community; DSM, Diagnostic and Statistical Manual of Mental Disorders; IPA, International Psychogeriatric Association; NA, not available; NBRS, Neurobehavioral Rating Scale; NH, nursing home; NIA-AA, National Institute on Aging and the Alzheimer's Association; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric Inventory; NPI-C, NPI Clinician Rating scale; NPI-NH, NPI Nursing Home version; PANSS-EC, Positive and Negative Symptom Scale-Excited Component; PAS, Pittsburgh Agitation Scale; RMBPC, Revised Memory and Behavior Problem Checklist; THC, tetrahydrocannabinol.

[a] Fixed-dose combination of dextromethorphan and quinidine sulfate.

[b] Scyllo-inositol believed to prevent amyloid beta aggregation.

[c] Alpha 2C adrenergic receptor antagonist.

[d] Deuterated, second-generation version of AVP-923/Nuedexta.

[e] Agonist of metabotropic glutamate receptor types 2 (mGluR2) and 3 (mGluR3).

[f] Fixed-dose combination of dextromethorphan and bupropion.

Trial status: 1 = completed and published; 2 = completed and unpublished but provided results; 3 = terminated due to statistical futility; 4 = active and not recruiting; 5 = recruiting; 6 = not yet recruiting; 7 = completed and no results available; 8 = terminated due to business or recruitment reasons, 9 = unknown status. All studies were placebo controlled apart from those indicated by (*) in the Drug names column.

4 | DISCUSSION

This review analyzed 52 clinical studies registered in the ClinicalTrials.gov database over the past 25 years to report on the landscape of pharmacological treatment trials of agitation in AD. Our findings are consistent with those from previous reviews that found methodological heterogeneity in studies,[16,17] and update earlier reviews of novel pharmacological agents.[19,20] We discuss our findings, which incorporated unpublished registered studies, the limitations and quality of published RCTs, and make additional recommendations for future studies in agitation in AD.

All published controlled studies were described as randomized, but random generation assignment was not always reported, and few studies adequately reported blinding to treatment allocation. As randomly generated assignments did not prevent unequal distribution of baseline differences between treatment groups in some studies, future studies may attempt to further mitigate the risk of selection bias by using larger samples and/or stratified randomization techniques.[22] We also recommend that future trials adequately describe their randomization process and transparently discuss the risks of selection bias that may be present in their methodology.

Many of the drugs that were reported to be more effective versus placebo were associated with significantly higher rates of adverse effects, which may have been specific enough to identify treatment allocation and consequently led to a degree of outcome rater unblinding. For example, the benefit of citalopram (around one point difference vs. placebo on the Neurobehavioral Rating Scale for agitation) was reported to be clinically significant, as a higher proportion of participants were judged to have moderate or marked improvement from baseline severity.[27] However, there was also a higher rate of adverse effects in this group, consistent with known selective serotonin reuptake inhibitor (SSRI)-mediated effects in the citalopram group, including prolonged QT_c intervals on electrocardiogram readings. We recommend that future studies transparently discuss the extent to which treatment-related adverse effects may have contributed to unblinding, or use tests for blinding to determine and report on the success of blinding, which is only rarely performed.[28]

A major issue, affecting more than half of published RCTs, was participant dropout rates of more than 20% of the number allocated to treatment, a proportion proposed to challenge study validity and increase the risk of attrition bias that may not be sufficiently addressed by ITT analyses.[29] As participant dropout was common, future trials could consider using participant dropout as the primary or secondary endpoint, which was done in one study,[30] as this may provide an integrated clinical outcome measure of drug efficacy, safety, and tolerability. Because the average time to study endpoint was 14 weeks, and some patients with agitation may require acute interventions to improve symptoms, another potential strategy to minimize dropout would be to shorten trial duration. This would have to be balanced against the need to obtain longer term data on efficacy and safety. A run-in period could potentially increase study power by excluding non-compliers or placebo-responders, but this may affect trial validity due to subsequent differences between the study and clinical populations,[26] which can only be meaningfully assessed if studies adequately report the number, reasons for exclusion, and baseline characteristics of the excluded participants.

Regarding data analysis, the intention-to-treat principle requires that all participants who are randomized must be included in the final analysis and analyzed according to the group to which they were originally assigned, regardless of the treatment received, withdrawals, or loss to follow-up. However, nearly all published RCTs used a mITT approach, that is, specified that only participants who had received at least one dose of medication and/or had a baseline and/or at least one follow-up measure were included in the primary analyses. Therefore, the analyzed population was inconsistently defined across different studies. It has been proposed that a mITT approach may increase the likelihood of post-randomization exclusions and subsequent attrition bias, and was associated with industry funding and authors' conflicts of interests.[31] Reporting of rescue medication initiation was inconsistent across published RCTs, and of those that did, only ≈half analyzed group differences in their use. Rescue medication potentially reduces the observed treatment effect in ITT analysis if their use substantially differs between groups and this should be explored through the use of sensitivity analyses.[32] Another potentially relevant aspect of data analysis identified was that many published RCTs only accounted for (differences in) group characteristics at baseline and assumed these remained constant throughout the study. While this may have been the case for participant sex and age, we recommend that variables such as MMSE scores are collected at study endpoint, to account for potential differential changes between groups at study end. We noted that the MMSE was used to measure cognition in almost all published trials, but other measures such as ADAS-Cog, SIB (in severe dementia), and CDR may provide greater precision[33,34] (and for the CDR, a more global measure of disease severity), but these were used in only a minority of studies.

We found evidence of publication bias, as although more than half of published studies reported negative findings, two thirds of completed studies were unpublished so the true proportion of negative findings was likely to be higher. We also found that a lower proportion of studies sponsored by pharmaceutical industries was published or reported negative findings, compared to those with no industry funding, supporting the presence of potential funder bias.

Pharmacological agents that were reported to show efficacy over placebo included 200 mg/d quetiapine, 2 mg/d brexpiprazole, 30 mg/d citalopram, AVP-923/Nuedexta, prazosin, and nabilone. On closer inspection, quetiapine only showed significant benefit over placebo in the pre-specified secondary and not the primary measures/analyses.[25] The prazosin and nabilone studies had < 50 participants and there were subsequent larger and ongoing RCTs investigating these drugs. Not all studies reported whether the significant differences in agitation scores between groups were clinically meaningful.[16] For example, the benefit of brexpiprazole over placebo was 3.77 points on the CMAI, but Clinical Global Impressions (CGI)-C scores (indicating clinical improvement) did not significantly differ between the groups.[35] This has led to

recommendations to incorporate adjunctive rating scales for overall clinical improvement such as the CGI into future studies.[18]

In terms of generalizability, most published studies enrolled community-residing patients living in North America who, on average, had moderate–severe dementia, moderate agitation symptoms, and were treated for 16 weeks. Thus, their findings may not apply to patients with more severe agitation or dementia symptoms or those living in other settings such as hospitals or health-care systems in other countries/regions, who may require more acute (or substantially longer term) treatment. More studies in these patient populations are needed.

The lack of standardized scales and caregiver definitions has been raised previously.[16] We found that although most studies used caregiver-provided ratings (N = 42 used CMAI or NPI) to measure agitation, only 15 defined a caregiver in terms of their level of contact with the participant. In addition to variability in caregiver relationships and its impact on the accuracy of retrospective agitation symptom reporting, it has also been reported that there is variability in how raters were trained to administer and score agitation scales,[36] which can affect the reliability of findings. We support recent calls to measure and investigate potential biomarkers of agitation,[18] which may augment or eventually replace existing rating scales.

Three studies were terminated early due to recruitment or funding issues and two other studies were underpowered due to underenrollment or a higher than expected dropout rate. As large clinical trials can be expensive, time-consuming, and burdensome on participants, the conduct of underpowered studies has previously been described as unethical.[37] Factors that could help increase the chance of successful recruitment and retention in future studies include consideration of study site selection; the qualities and enthusiasm of the lead investigator and study coordinator; and ensuring that patient and caregiver concerns, expectations, and burdens are adequately addressed.[38]

Drugs under investigation in active RCTs included brexpiprazole, mirtazapine, escitalopram, prazosin, gabapentin enacarbil (for nighttime agitation), cannabinoids (dronabinol, nabilone, and cannabidiol), and novel dextromethorphan-containing medications (AVP-786 and AXS-05), which were all placebo-controlled. A potential limitation in interpreting these studies in the future is that it will not be clear how the drug compares to conventional treatment, for example, risperidone, in terms of safety and efficacy. It may be more informative for future trials to compare a new drug to placebo and an antipsychotic such as risperidone, so that any positive findings can inform policy.

ClinicalTrials.gov is the largest database of registered clinical trials, providing useful information about unpublished clinical trials that were completed, terminated, or were currently active, relevant to our study. However, limitations of this study included that we may have missed studies that were not registered on ClinicalTrials.gov or for which the search terms used did not apply. Clinical trial registration has been mandated since 2007 and reporting of results mandated since 2008, so earlier studies or non–US-based studies may have been more likely to have been missed. We only assessed the quality of published controlled studies so cannot comment on the quality of other studies, including unpublished trials. The distinction between "lower" and "higher" quality studies was based on recommendations from the NIH Quality Assessment tool, which was not specific to agitation in dementia studies so, for example, the 20% dropout cut-off may have been too strict for this population. For unpublished trials, we were not able to verify the accuracy of the data reported on ClinicalTrials.gov or confirm whether the data was consistent with the actual study. We chose to focus on participant inclusion criteria so did not include analyses on participant exclusion criteria, such as medical conditions or concomitant medications, which have previously been shown to vary between studies,[17] and need to be evaluated for potential adverse effects/interactions depending on the specific drug under investigation. We also did not include observational studies, which can complement and enhance findings from RCTs. Although we assessed whether drug studies were fully or partially sponsored by pharmaceutical companies, we did not ascertain whether individual authors had documented conflicts of interests, thus we may have underestimated the potential for industry influence on study quality. Two AVP-786 trials that started in 2015 and were classed as unpublished, completed in 2019, so it is possible that these will be published in the near future.

In conclusion, the landscape of agitation clinical trials in AD has changed over time, with a recent emergence of novel therapies and newly repurposed drugs, although it remains to be seen whether these will be better and safer than conventional treatments. Given the increasing emphasis on the importance of standardized definitions and methodologies to optimize the methodology of agitation trials in AD, our review has identified several factors that may help to further improve the internal and external validity of future agitation clinical trials in AD.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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