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agitation in Alzheimer’s disease (AD), but the risks of bias arising from published trials and the number and design of unpublished studies are poorly understood.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 community5 and care home6 settings, agitation reduces quality of life,7 precipitates earlier institutionalization8 and more rapid disease progression9 and possibly earlier death.10 The best treatment evidence for agitated people with dementia who do not respond to non-pharmacological approaches11 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.

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 tool24 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 in 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
pharmacological treatment categories. The majority of published studies (65%; \( N = 13 \)) did not report significant findings for their pre-specified primary measures, and \( \approx 33\% \) 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 \( \approx 3.3 \) (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.
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): 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 α1-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. 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.

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 reported a positive finding, but on closer inspection, the pre-specified primary outcome from the primary analysis was not significant.
| Drug type | Drug name | NCT identifier | Study start or registration (year) | Repurposed and novel pharmacological treatment strategies for agitation in AD from included studies |
|-----------|-----------|----------------|-----------------------------------|-------------------------------------------------------------------------------------------------|
| Repurposed | Risperidone | NCT00249158 | 1998 | 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. |
| Repurposed | Haloperidol versus trazodone versus behavioral program | NCT00000179 | 1999 | Participants needed to have stopped psychotropic medications >2 weeks before enrolment. |
| Repurposed | Risperidone versus gabapentin | NCT0018291 | 2001 | 12 weeks |
| Repurposed | Risperidone versus olanzapine versus quetiapine | NCT0015548 | 2001 | 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. |

(Continues)
| Drug type | Drug name | Trial status | NCT identifier | Study start or registration (year) | Significant positive primary findings at endpoint versus placebo or comparator | Comments |
|-----------|-----------|--------------|----------------|-----------------------------------|--------------------------------------------------------------------------------|----------|
| Risperidone | 9 | NCT00626613 | 2008 | – | 12 weeks | NA; NA | NA; NA | ≥ 60 | NA; NA | NPI; NA | – |
| Quetiapine | 1 | NCT00621647 | 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) | 333 (66.3) | 82.3% | 55 (81.3) | NA (5.3) | Lower US, multisite, 1 |
| Brexpiprazole | 1 | NCT01922258 Study 1 | 2013 | Yes | Fixed doses. It was safe; 2 weeks 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) | 55-90 (73.9) | 5-22 (mild [≥ 18]) 9% | 57.3% | Caregiver who spent ≥ 2 h/d for 4 d/wk with the patient. | CMAI; NPI-NH A/Adomain 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 | NCT018626-40 Study 1 | 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) | 55-90 (73.8) | 5-22 (mild [≥ 18]) 20% | moderate 7% | Caregiver who spent ≥ 2 h/d for 4 d/wk with the patient. | CMAI; ≥ 4 on the NPI-NH A/AA 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)
| Drug type | Drug name | Trial status | NCT identifier | Study start or registration (year) | Significant positive primary findings at endpoint versus placebo or comparator | 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/multi site and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none |
|-----------|-----------|--------------|----------------|-----------------------------------|-------------------------------------------------------------------------|--------------------------|-----------------------------|---------------------------------|-------------------------------|-------------------------------|------------------------------------------|-------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------|
| Brexipiprazole 5 | Brexpiprazole | 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. |
| Brexipiprazole 5 | Brexpiprazole | NCT03620981 | 2018 | – | 10 weeks | NINCDS-ADRDA and DSM-5; Hospital or 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. |
| Aripiprazole 8 | Aripiprazole | 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. |
| Lumateperone 3 | Lumateperone | NCT02817706 | 2016 | No | 4 weeks | NA; Com | NA | 177 | ≥ 55 | NA | CMAI-C; Clinically significant agitation secondary to AD (NA) | – | US, multisite. |
| Pimavanserin 2, 8 | Pimavanserin | NCT02992132 | 2016 | No | Planned to recruit 43212 weeks participants. Study was underpowered. | NPI; NPI-12 total ≥ 20 (NA) | 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 (CMAI65.1) | – | US, Chile, Europe, UK. |
| Amisulpride 6 versus olanzapine* | Amisulpride versus olanzapine | NCT04341467 | 2020 | – | Open label. | KCD-10; NA | NA | Estimated 76AII ages <24 (NA) | NPI; NPI-12 total ≥ 20 (NA) | Lower | – | China, single site (NA) |
| Citalopram versus perphenazine | Citalopram versus perphenazine | T000009204 | 1995 | Yes, for citalopram | 17 days | DSM-IV; Hospital | NA | 85 (61), 63.7% | NA (79.9) | NA (7.6) | NBR5; score ≥3 on NBR5 agitation or psychosis items (5.6.3) | – | Lower US, single site (NA) |
| Citalopram versus risperidone* | Citalopram versus risperidone | T01438060 | 2000 | No | Significant increase in 12 weeks side effect burden with risperidone but not citalopram. | NA; Hospital | NA | 103 (91), 31.5% | NA (81.8) | NA (10.9) | NBR5; score ≥3 on 1 of the Lower agitation items (NBR5 total 57.0, NBR5 agitation 9.6) | – | US, single site (NA) |
| 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) | MMS E inclusion criteria (actual mean MMS E) | Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score) | Location(s), single/multisite and [industry]: | Quality                                      |
|------------------|---------------------------|--------------|------------------------------|----------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|----------------------------------|-----------------------------------|-----------------------------|---------------------------------|---------------------------------|---------------------------------------------------------------------------------------------|---------------------------------|----------------------------------|
| Citalopram       | Citalopram                | Yes          | NCT00898807                 | 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 ≥6, 46.0% at least several hours a week with the patient | NA (78.5)           | NA(28.5)                         | NA(15.7) | NRS 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 (NRS agitation 7.6, NPI A/A 7.9, NPI total 37.3, CMAI 28.2) | Higher US, Canada [NA]          |                                    |
| Escitalopram     | Escitalopram*             | –            | NCT00260624                 | 2003                             | Open label and non-randomized.                                                    | Available and reliable caregiver.                                                                                                                                             | 12 weeks                    | NA; NA                           | Estimated 20≥61 (NA) NA%                        | NA                          | NA                              | NA                              | NRS agitation factor; Agitation present at screening and baseline, not responsive to non-pharmacological treatment and lasting ≥2 weeks prior to enrolment. | US, multisite                  |                                    |
| Escitalopram     | Escitalopram versus risperidone* | No          | NCT01119638                 | 2008                             | Higher rate of discontinuation and adverse effects with risperidone.              | DSM-IV; hospital                                                                                                                                                    | 6 weeks                     | NA                              | 40, NA%                            | 55-95(NA)                    | 5-24(NA)                        | NA                              | NPI; Signs and symptoms of Lower 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). | Israel, single site [NA]        |                                    |
| Drug type | Drug name | NCT identifier | Study start or registration (year) | Trial status | NCT identifier | Significant positive primary findings at endpoint versus placebo or comparator | AD criteria; inclusion setting | Comments | Duration of drug treatment | AD criteria; inclusion setting | Definitions 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) | Location(s), single/multisite and [industry]: | Quality |
|------------|-----------|----------------|-----------------------------------|--------------|----------------|-------------------------------------------------|-----------------------------|----------------|--------------------------|-------------------------------|-----------------------------------------------|--------------------------|-----------------------------------------------|------------------------------------------------|------------------------------------------------------------------|------------------------------------------------|--------|
| Escitalopram | 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 | Estimated 392 | 18-109 (NA) | 5-28 (NA) | 5-2 (NA) | 18-109 (NA) | 5-2-2 (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 | 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 carers. | Estimated 222 | ≥ 18 (NA) | NA | CMAI; score ≥45 (NA) | – | UK, multisite [NA] |
| Donepezil | Donepezil 1 | NCT00142324 | 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 27.7, CGIC 4.3) | Higher UK, multisite [NA] |
| Memantine | Memantine 1, 8 | NCT00857649 | 2003 | No | | 12 weeks | NINCDS-ADRDA; Com (long term care facility and NH) | NA | 369, 58.3% | ≥ 50 (75) | 5-15 (12) | NPI; NPI A/A score ≥1 and NPI A/A score ≥5 at screening and baseline (30.1) | Canada, multisite1 |
| Memantine | Memantine 7 | NCT00977916 | 2004 | – | NA | NA, NA | NA | 34, NA% | ≥ 50 (NA) | NA | NPI; NPI A/A score ≥4 | – | US, multisite1 |
| Memantine* | Memantine* 1 | NCT00411167 | 2006 | Yes | Open label. | 3 months | DM 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, multisite2 |

(Continues)
| Drug type       | Drug name | NCT identifier | Trial status | NCT start or registration (year) | Significant positive primary findings at endpoint versus placebo or comparator Comments | Study start or registration (year) | 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) | MME inclusion criteria (actual mean MME) | Primary agitation scale; definition of agitation to be eligible; (actual baseline agitation score) Comments | Location(s), single, multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none |
|-----------------|-----------|----------------|--------------|----------------------------------|------------------------------------------------------------------------------------------|----------------------------------|-----------------------------|-------------------------------|-------------------------------------------|---------------------------------|--------------------------------------|---------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Memantine*      | 9         | NCT00703430    | Open label.  | 2008                             | NA; NA Availability of a caregiver to ensure treatment compliance and provide information for assessments | 2008                             | 12 weeks                    | NA; NA                        | Estimated 50≥50 (NA) NA%                     | NA                              | 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 site² |
| Repurposed (other) | Acetaminophen | NCT00012857    | 7            | 2001                             | Each arm lasted 2 weeks (crossover). Participants needed to have a documented painful condition and be unable to report pain consistently or reliably. | 2001                             | 4 weeks                     | NA; NH                        | Estimated 66≥55 (NA) NA%                     | NA                              | NA                                   | NA                                    | CMAI: > 1 episode of agitation/td (NA)                                   | US, multisite [NA] |
| Prazosin        | 1         | NCT00161473    | Yes          | 2001                             | Adverse effects and blood pressure changes were similar between the groups.                 | 2001                             | 8 weeks                     | NA                           | NINCDS-ADRDA, NH or Com                  | NA                              | NA                                   | NA                                    | 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    | No           | 2010                             | Actual recruitment was less than anticipated recruitment of 120 so likely to have been underpowered. | 2010                             | 12 weeks                    | NA; Com                       | Caregiver spends 10 h/wk caring for participant. | 20, 65.0% | NA                                   | NA                                    | ADCS-C GIC and NPI: Disrupted agitated behaviors ≥ twice per week (NPI 42.4, BPRS 9.1) | US multisite [NA] |

(Continues)
| 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 ≥5 times/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 | 24 months | NINCDS-ADRDA; Com | NA | 313, 58.7% | >54 (75.8) | 12-20 (16.9) | Time to endpoint defined as Lower 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) | - | US, multisite [NA] |
| Valproate added to atypical antipsychotic versus increasing doses of atypical antipsychotic* | NCT00208819 | 2003 | - | Open label | NA; Hospital stay | NA | Estimated 50±65 (NA) | NA | NA | CMAI, PAS; NA (NA) | - | US single site2 |
| 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) |
| Drug type | Drug name | Trial status | NCT identifier | Study start or registration (year) | Significant positive primary findings at endpoint versus placebo or comparator | Comments |
|-----------|-----------|--------------|----------------|------------------------------------|--------------------------------------------------------------------------------|----------|
| Gabapentin enacarbil | 5 NCT03082755 | 2017 | – | Aiming 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) |
| Levetiracetam* | NCT04004702 | 2020 | – | Open label non-randomized. Participants with epileptiform discharge on EEG will receive levetiracetam. | 12 months | NINCDS-ADRDA; NA Caregiver willing and estimated 65 NA <26 (NA) NPI; NPI-12 score ≥4 – US, single site (NA) |
| Dronabinol (THC) | 1 NCT01608217 | 2012 | No | 3 weeks | NINCDS-ADRDA; NH and Com Caregiver available who was in touch with the patient ≥ 2 time/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) Estimated 160 | 60-95 (NA) NA NPI and PIS; 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 | 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) | 39 (NA); 23%> 55 (87.0) ≤24 (6.5) CMAI; Clinically significant agitation with NPI-C A/A score ≥ 3 (CAMI 67.9; NPI-NH 34.3, NPI-NH A/A 7.1CG3.7) – Higher Canada, single site (NA) |
| Drug type | Drug name | Trial status | NCT identifier | Study start or registration (year) | Significant primary findings at endpoint vs 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 caregivers: Estimated 112 | ≥ 35 (NA) | ≤ 24 (NA) | | CMAI; Consensus definition of agitation as per IPA guidelines | Canada (NA) |
| THC-free cannabinoid | 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 site² |
| AVP-923   | 1 | NCT01584440 | 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 CGI scale for agitation (NPI A/A 7.1, NPI total 39.6) | US, multisite¹ |
| Sodium benzoate | 1 | NCT02103673 | 2014 No | | 6 weeks | NINCDS-ADRDA; NA | NA | | ≥ 50 (75.5) | 5–26 (17.6) | BEHAVE-AD; BEHAVE-AD ≥ 2 (BEHAVE-AD 10.9) | Lower Taiwan, multisite [NA] |
| Novel Mibampator | 1 | NCT00843518 | 2009 No | Up to 28 days washout 12 weeks period preceding treatment | Reliable and actively involved caregiver who can communicate in English and is willing to comply with protocol requirements. | NINCDS-ADRDA; Com | | | > 60 (77.5) | 6–26 (17) | NPI A/A; Clinically significant lower and persistent verbal or physical agitation and/or aggression behaviors that are disruptive to daily functioning or potentially harmful and occurred ≥ 3 d/week 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, CMAI 69.2) | US, multisite¹ |

(Continues)
| Drug type | Drug name | Trial status | NCT identifier | Study start or registration (year) | 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/multi site and [industry]: |
|-----------|-----------|--------------|----------------|-----------------------------------|----------------------------|-----------------------------|---------------------------------|---------------------------------|----------------------------------------|---------------------------------------------|-------------------------------------|----------|------------------------------------------------|
| ELND-005  | 2         | NCT01735630  | 2012           | No                                | 12 weeks                   | NIA-AA, NA                  | NA                              | 350, 55.7%                      | 50-95 (76.1)                           | 5-24 (NA)                                  | NPI-CA/A defined as NPI-A/A subscore ≥ 4 (NA) | –        | US, UK, Canada, Europe1 |
| 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-CA/A; NPI-AA ≥ 2 at screening, agitation defined as per IPA guidelines and symptoms present for ≥4 weeks before the screening visit (NA) | –        | Europe (Finland), multisite1 |
| 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, multisite1 |
| 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 Canada1 |
| AVP-786   | 5         | NCT03393520  | 2017           | –                                 | 12 weeks                   | NIA-AA; Com (NH, assisted living or outpatients) | 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)                             | NA                                  | CMAI; Consensus definition – 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, UK1 |

(Continues)
| Drug type | Drug name | Trial status | NCT identifier | Study start or registration (year) | Significant positive primary findings at endpoint versus placebo or comparator | 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) | Comments | Quality | Location(s), single/multisite and [industry]: 1 = full sponsorship, 2 = part sponsorship, NA = none |
|-----------|-----------|--------------|----------------|-----------------------------------|--------------------------------------------------------------------------------|-----------------------------|----------------------------------|-------------------------------------|------------------------------------------|-------------------------------------------|-----------------------------------------------|---------|---------|---------------------------------------------------------|
| AVP-786   | 5         | NCT04408755  | 2020           | –                                 | Reliable caregiver able and willing to comply with study procedures and spends ≥2 h/d for 4 d/wk with the participant. | 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 |
| AVP-786   | 6         | NCT04464564  | 2020           | –                                 | Reliable caregiver able and willing to comply with study procedures and spends ≥2 h/d for 4 d/wk with the participant. | 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      |
| MP-101    | 3         | NCT03044249  | 2017           | No                                | Included other dementias.                                                  | NA/NA                        | Reliable caregiver spends ≥4 h/d ≥4 d/wk with the patient. | ≥84 (NA)                            | 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) | CMAI; Consensus definition – agitation in cognitive disorders from the IPA (NA) | NA      | US and Canada |
| AXS-05 versus 5 bupropion | NCT03226522 | 2017           | –                              | 5 weeks                       | NA/AA/NA                                                                | NA                           | Estimated 435                          | 65-90 (NA)                               | NA                                        | CMAI; Consensus definition – agitation in cognitive disorders from the IPA (NA) | US and Australia |

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’s 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; NBRSS, Neurobehavorial 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; PAIN95-EC, Positive and Negative Symptom Scale-Excited Component; PAS, Pittsburgh Agitation Scale; RMBPC, Revised Memory and Behavior Problem Checklist; THC, tetrahydrocannabinol; THCV-1, cannabidiol.

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, and update earlier reviews of novel pharmacological agents. 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. 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. 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 QTc 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.

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. As participant dropout was common, future trials could consider using participant dropout as the primary or secondary endpoint, which was done in one study, 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, 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. 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. 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 (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 brexipiprazole, 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. 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. For example, the benefit of brexipiprazole 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. This has led to
recommendations to incorporate adjunctive rating scales for overall clinical improvement such as the CGI into future studies.\textsuperscript{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.\textsuperscript{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,\textsuperscript{36} which can affect the reliability of findings. We support recent calls to measure and investigate potential biomarkers of agitation,\textsuperscript{15} 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 under-enrollment 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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.