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Efficacy and safety of brexpiprazole for agitation in Alzheimer's disease: A systematic review and meta-analysis

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Abstract

Agitation represents one of the most debilitating neuropsychiatric dimensions of Alzheimer's disease (AD), imposing a profound burden on patients' quality of life and escalating caregiver burnout. While brexpiprazole has emerged as a frontline pharmacological candidate for managing these symptoms, a definitive consensus on its clinical utility has remained elusive. To address this, a comprehensive systematic review and meta-analysis were conducted, synthesizing data from four high-quality randomized controlled trials encompassing 1,413 participants. The analysis revealed that brexpiprazole yields a statistically significant reduction in agitation severity, as evidenced by a mean difference (MD) of −3.89 in Cohen–Mansfield Agitation Inventory scores (95% CI: −5.87 to −1.90; $p = 0.0001$). This primary finding is bolstered by moderate-certainty evidence and complemented by a significant, albeit modest, improvement in Clinical Global Impressions-Severity ratings (MD: −0.29; $p = 0.002$). Notably, the impact on the Neuropsychiatric Inventory-Nursing Home scores did not reach statistical significance, suggesting that the drug's efficacy may be more pronounced in specific behavioral domains than in global neuropsychiatric health. Safety remains a critical consideration; the data indicate a heightened risk of treatment-emergent adverse events (risk ratio: 1.12; $p = 0.04$), supported by high-certainty evidence. Despite this risk, discontinuation rates were not significantly different from placebo, suggesting that the side effect profile is generally manageable. Ultimately, while brexpiprazole demonstrates clear therapeutic benefits for AD-related agitation, clinicians must prioritize vigilant monitoring and individualized risk-benefit assessments to mitigate potential adverse outcomes. Further long-term longitudinal research is warranted to validate these findings over extended durations.

Keywords: Alzheimer disease; Agitation; Brexpiprazole; Antipsychotic agents; Neuropsychiatric symptoms

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, functional impairment, and a wide range of neuropsychiatric

symptoms (NPS), which substantially worsen patient outcomes and increase caregiver burden.[1] Neuropsychiatric manifestations such as anxiety, depression, psychosis, aggression, and agitation occur in up to 97% of individuals with AD over the course of the illness.[2] Among these, agitation represents one of the most challenging and distressing symptoms, encompassing excessive motor activity, emotional distress, verbal or physical aggression, and restlessness. Agitation is associated with increased morbidity, accelerated institutionalization, and significantly reduced quality of life for both patients and caregivers.[2]

The pathophysiology of agitation in AD is complex and multifactorial. Neuroimaging and neuropathological studies suggest that agitation may be associated with volume reduction and dysfunction in the anterior and posterior cingulate cortex, insula, amygdala, and frontal cortex, regions involved in emotional regulation and behavioral control.[3] Additional contributing mechanisms include degeneration of monoaminergic neurotransmission, circadian rhythm disturbances, and increased frailty, all of which may exacerbate behavioral symptoms in advanced disease stages.[3] Despite its clinical importance, effective and well-tolerated pharmacological treatments for agitation in AD remain limited.

Atypical antipsychotics have been widely used off-label for the management of agitation and psychosis in patients with dementia due to AD. However, their use is associated with substantial safety concerns, particularly in elderly populations. Reported adverse effects include sedation, extrapyramidal symptoms, sleep disturbances, confusion, falls, and fractures, as well as metabolic abnormalities such as dyslipidemia and impaired glucose regulation.[4] In addition, several atypical antipsychotics have been associated with QT interval prolongation and an increased risk of cerebrovascular events and mortality, limiting their suitability for long-term use in high-risk individuals.[5]

Brexpiprazole is a second-generation antipsychotic with a distinct pharmacological profile, classified as a serotonin–dopamine activity modulator. It acts as a partial agonist at serotonergic (5-HT1A) and dopaminergic (D2) receptors, while antagonizing serotonergic (5-HT2A) and adrenergic (α1B/2C) receptors.[6] This receptor-binding profile differentiates brexpiprazole from other antipsychotics and may contribute to improved tolerability, with a lower risk of extrapyramidal symptoms and metabolic adverse effects.[7] Nevertheless, brexpiprazole carries a boxed warning for increased mortality and suicidal behavior in elderly patients with dementia-related psychosis, underscoring the importance of careful evaluation of its risk–benefit profile in this population.[8]

Previous randomized controlled trials (RCTs) have investigated the efficacy of brexpiprazole for agitation associated with AD. Several studies have reported significant reductions in agitation severity, as measured using validated instruments such as the Neuropsychiatric Inventory and the Cohen–Mansfield Agitation Inventory (CMAI). However, concerns regarding treatment-emergent adverse events—including sedation, metabolic disturbances, and cerebrovascular events—have complicated the interpretation of the overall clinical benefit of brexpiprazole in AD-related agitation.[9] Consequently, uncertainty remains regarding the balance between efficacy and safety across available trials.

Given the variability in reported outcomes and the clinical importance of informed therapeutic decision-making, a comprehensive synthesis of the existing evidence is warranted. Therefore, this systematic review and meta-analysis evaluated the efficacy and safety of brexpiprazole for agitation associated with dementia due to AD.

2. Methods

This systematic review and meta-analysis aimed to evaluate the efficacy and safety of brexpiprazole for the treatment of agitation associated with dementia due to AD. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] The protocol was prospectively registered in the International Prospective Register of Systematic Reviews database (CRD42024622841).

2.1. Eligibility criteria

2.1.1. Participants/population

Randomized controlled trials were included if they enrolled adults with dementia due to AD who exhibited clinically significant agitation, as defined by established diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, or International Classification of Diseases, Tenth Revision).

2.1.2. Intervention

Brexpiprazole was administered at any dose and for any treatment duration.

2.1.3. Comparator

Placebo or other pharmacological or non-pharmacological interventions.

2.1.4. Outcomes

Primary outcomes included:

- Reduction in agitation severity measured using validated agitation scales (e.g., CMAI).

- Overall response rate, defined as the proportion of patients achieving a clinically meaningful improvement.

Secondary outcomes included:

- Incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs).
- Treatment discontinuation due to adverse events.
- Changes in cognitive function and quality-of-life measures, when reported.

2.2. Exclusion criteria

Studies were excluded if they:

- Included participants with dementia due to causes other than AD (e.g., vascular dementia, frontotemporal dementia, or mixed dementia).
- Evaluated brexpiprazole in combination with other investigational interventions without isolating its effect.
- Lacked a placebo or an appropriate control group.
- Did not report agitation outcomes assessed using validated measurement tools.
- Did not provide data on key safety outcomes (AEs, SAEs, or treatment discontinuation).
- Were non-randomized studies, observational studies, case reports, case series, reviews, or conference abstracts without original data.
- Had insufficient randomization methods, incomplete data, or unavailable full-text articles.
- Were duplicate publications, interim analyses without final results, or studies not published in English.

2.3. Search strategy

A comprehensive and systematic search strategy was developed to identify studies evaluating the efficacy and safety of brexpiprazole for the treatment of agitation in AD. The following electronic databases were searched: PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials, Embase, and ClinicalTrials.gov. Medical subject headings, Emtree terms, and free-text keywords related to AD, agitation, and brexpiprazole were combined using Boolean operators. Search terms included combinations of "AD" OR "Alzheimer's dementia" OR "dementia," "agitation" OR "behavioural symptoms," "brexpiprazole," and "randomized controlled trial" OR "RCT" OR "clinical trial."

No restrictions were applied to the year of publication; however, the search was limited to studies published in English and conducted in human participants. The complete search string has been added to the supplementary file.

2.4. Study selection

Two reviewers independently screened the titles, abstracts, and full-text articles identified through the search against the predefined eligibility criteria. Discrepancies were resolved through discussion or consultation with a third reviewer. The study selection process was conducted in accordance with PRISMA guidelines to ensure a transparent and unbiased identification of eligible studies.

2.5. Data extraction

Two reviewers extracted the data by using a standardized form. The following details were obtained from each included study:

- Study characteristics: Author, publication year, country, study design, and sample size.
- Population demographics: Age range, gender distribution, diagnostic criteria for Alzheimer's disease, and baseline agitation severity.
- Intervention details: Dosage and duration of brexpiprazole treatment.
- Comparator details: Type of control (e.g., placebo or alternative interventions) and treatment regimen.
- Outcome measures: Primary outcomes (e.g., reduction in agitation symptoms assessed using validated scales such as the CMAI and overall response rate) and secondary outcomes (e.g., occurrence of AEs, SAEs, treatment discontinuation rates, cognitive function changes, and quality of life assessments).
- Study duration and follow-Up: Duration of the intervention and follow-up period after treatment.

A third reviewer was consulted to resolve any discrepancies in data extraction. For continuous efficacy outcomes, change-from-baseline values were preferentially extracted when reported. When change-from-baseline data were unavailable, endpoint values were used as reported by the original studies. Outcomes assessed at different but clinically comparable time points (e.g., week 10 and week 12) were pooled as short-term outcomes, reflecting similar treatment durations across trials. If standard deviations were not directly reported, they were calculated from available summary statistics or imputed using established methods in accordance with the Cochrane handbook. No outcome conversion or transformation was performed when outcomes were reported using the same measurement scale.

2.6. Risk of bias assessment

The risk of bias in the included RCTs was assessed using the Cochrane risk of bias 2 (RoB2), with each study evaluated individually across five key domains: the randomization

process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Based on these evaluations, studies were classified as having low, some concerns, or high risk of bias.[11]

2.7. Data synthesis and analysis

Review Manager 5.4 was used for analyzing the extracted data. For the primary outcome, reduction in agitation symptoms, mean differences (MD) or standardized mean differences with 95% confidence intervals (CIs) were calculated, depending on the scales used. For dichotomous outcomes such as overall response rate and adverse events, relative risk and 95% CIs were calculated. To account for potential heterogeneity among studies, a random-effects model was employed. Statistical heterogeneity was evaluated using the I^2 statistic, with thresholds of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively.[12]

Subgroup analyses were performed to investigate potential differences in efficacy and safety by factors such as brexpiprazole dosage, treatment duration, or baseline agitation severity. Additionally, sensitivity analyses were conducted to assess the robustness of the findings by excluding high-risk-bias studies.[13]

2.8. Quality of evidence

The Grading of Recommendations, Assessment, Development, and Evaluation approach was applied to assess the overall quality of evidence, taking into account factors such as study design, risk of bias, inconsistency, indirectness, imprecision, and potential publication bias.[14] The certainty of the evidence was categorized as high, moderate, low, or very low.

2.9. Ethical considerations

Since this study analyzed previously published data for the meta-analysis, neither ethical approval nor informed consent was required. However, it was expected that all included studies had obtained ethical approval from their respective institutional review boards. By adhering to robust methodological standards, this meta-analysis provides a comprehensive evaluation of the efficacy and safety of brexpiprazole for the management of agitation associated with AD.

3. Results

3.1. Study selection and characteristics

A total of four RCTs evaluated the efficacy and safety of brexpiprazole in patients with agitation associated with AD. One active-treatment extension study did not include a placebo comparator and was therefore excluded from quantitative meta-analysis (Figure 1). Across these studies, improvements were observed in key efficacy endpoints, including the CMAI total score, Clinical Global Impressions-Severity (CGI-S) score, and Neuropsychiatric Inventory-Nursing Home (NPI-NH) agitation/aggression score. The characteristics of the included studies are shown in Table 1.

3.2. Change in Cohen–Mansfield Agitation Inventory score at week 10–12 from baseline

Four RCTs involving 1,413 participants were included in the analysis.[15-17] Brexpiprazole was associated with a statistically significant reduction in CMAI scores compared with placebo (MD: −3.89; 95% CI: −5.87 to −1.90; p = 0.0001). Heterogeneity across studies was low to moderate (I^2 = 41%). Although the individual Grossberg *et al.*[15] trials did not reach statistical significance independently, their effect estimates were directionally consistent with benefit and contributed to the overall pooled effect. These findings indicate a clinically meaningful reduction in agitation severity with brexpiprazole (Figure 2A).

3.3. Change in Clinical Global Impressions-Severity score

Brexpiprazole demonstrated a statistically significant improvement in CGI-S scores compared with placebo (MD: −0.29; 95% CI: −0.47 to −0.11; p = 0.002). No heterogeneity was observed among the included studies (I^2 = 0%), indicating highly consistent findings. Although the magnitude of improvement was modest, the results support a clinically relevant reduction in clinician-rated agitation severity (Figure 2B).

3.4. Change in Neuropsychiatric Inventory-Nursing Home score

The pooled analysis showed a trend toward improvement in NPI-NH scores with brexpiprazole compared with placebo (MD: −1.05; 95% CI: −2.17 to 0.06); however, this difference did not reach statistical significance (p = 0.06). Substantial heterogeneity was observed across studies (I^2 = 76%), suggesting variability in treatment effects that may be related to differences in study populations, baseline symptom severity, or assessment methods. Consequently, the robustness of the pooled estimate for this outcome is limited (**Figure 2C**).

3.5. Treatment–emergent adverse events

Brexpiprazole was associated with a modest but statistically significant increase in treatment-emergent adverse events compared with placebo (risk ratio [RR]: 1.12; 95% CI: 1.01–1.24; p = 0.04). Heterogeneity was low (I^2 = 21%),

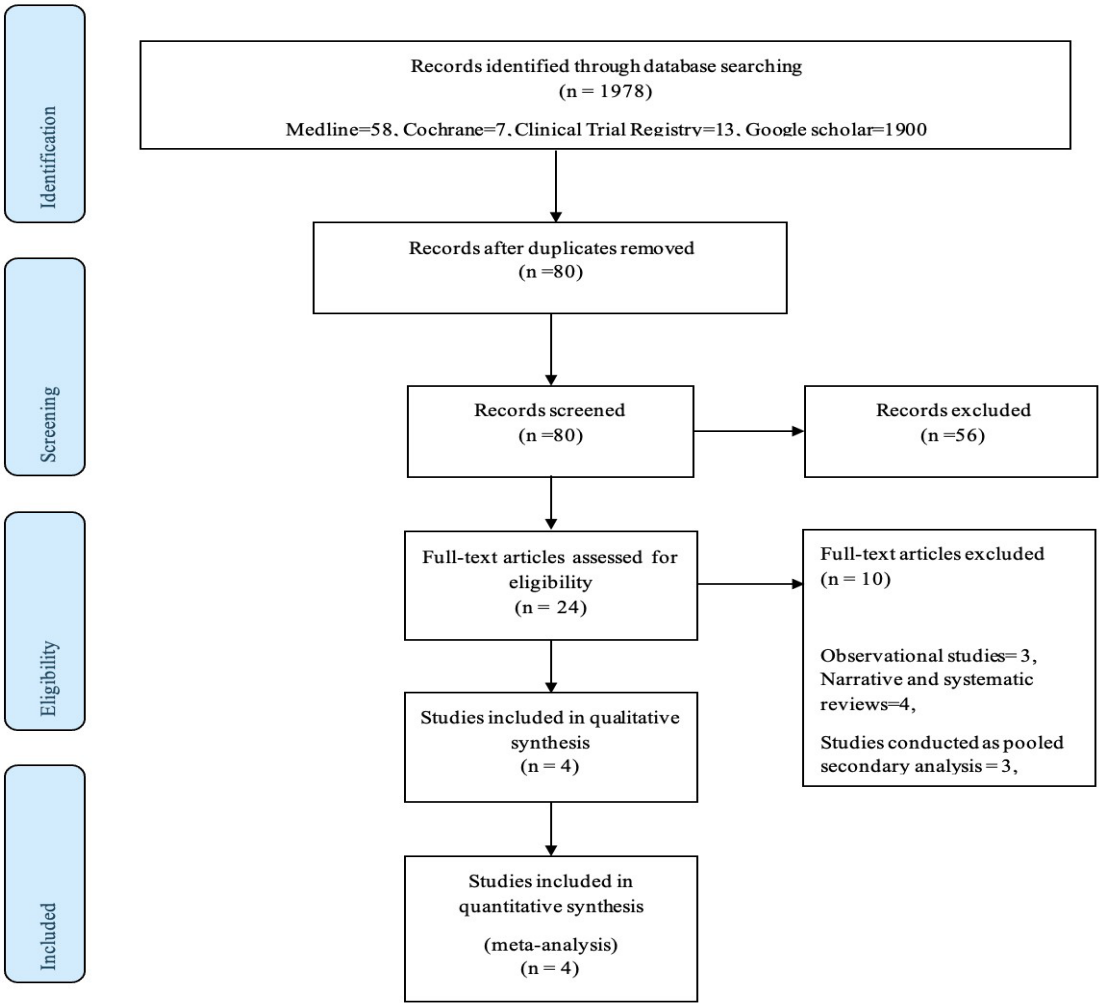


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection process. Image created by the authors.

indicating consistent findings across trials. A higher number of AEs occurred in the brexpiprazole group (547 events) compared with the placebo group (288 events), supporting a small increase in overall adverse event risk (Figure 3A).

3.6. Treatment discontinuation due to treatment–emergent adverse events

There was a non-significant trend toward a higher risk of treatment discontinuation due to adverse events with brexpiprazole compared with placebo (RR: 1.35; 95% CI: 0.85–2.15; p = 0.21). Heterogeneity was low (I^2 = 22%), and the findings were consistent across studies. Although discontinuations were numerically more frequent in the brexpiprazole group (93 events) than in the placebo group (38 events), this difference did not reach statistical significance (Figure 3B).

3.7. Sensitivity analyses

A sensitivity analysis was conducted for each outcome, revealing consistent findings across all measures. Additionally, when the analysis was performed with a fixed-effect model rather than a random–effects model, the results remained comparable, further supporting the robustness of the findings.

3.8. Risk of bias and evidence quality

Using the Cochrane RoB2 tool, "some concerns" were noted in two trials (Table 2). The funnel plots for both outcomes were symmetrical, but due to the small number of studies, publication bias could not be reliably assessed. (Figure S1–S5).

The overall certainty of evidence varied across outcomes. The reduction in CMAI scores was supported

Table 1. Characteristics of included studies

Study	Study type	Country- wise study sites	No. of participants	Average age in each arm, years (standard deviations)	Sex distribution in each arm, *n* female (%)	No. of arms	Study arms	Study outcome
Grossberg *et al*[15] (Study 1)	Randomized double-blind	81 sites in 7 countries: Russia (29.1% of randomized patients), the United States (27.9%), Ukraine (14.8%), Serbia (12.2%), Croatia (8.5%), Spain (4.4%), and Germany (3.0%).	433	(i) Placebo: 74.1 (8.0) (ii) Brexpiprazole 0.5 mg: 73.9 (9.1) (iii) Brexpiprazole 1 mg: 73.8 (8.8) (iv) Brexpiprazole 2 mg: 73.7 (8.1)	(i) Placebo: 70 (51.5) (ii) Brexpiprazole 0.5 mg: 12 (60.0) (iii) Brexpiprazole 1 mg: 78 (56.9) (iv) Brexpiprazole 2 mg: 79 (56.4)	4	(i) Tablet Placebo orally (ii) Tablet brexpiprazole 0.5 mg orally (iii) Tablet brexpiprazole 1 mg orally (iv) Tablet brexpiprazole 2 mg orally	(i) Change of CMAI total score from baseline to week 12 (ii) Change of CGI-S score as related to agitation from baseline to week 12 (iii) Change of NPI-NH agitation/aggression score (frequency × severity) from baseline to week 12
Grossberg *et al.*[15] (Study 2)	Randomized double-blind	62 sites in 9 countries: Ukraine (28.9%of randomized patients), the United States (22.6%),Russia (19.3%), Bulgaria (17.8%), Canada (4.8%),France (3.3%), Slovenia (2.2%), the United Kingdom(0.7%), and Finland (0.4%)	270	(i) Placebo: 74.0 (7.8) (ii) Brexpiprazole 0.5–2 mg: 73.5 (8.5)	(i) Placebo: 88 (64.2) (ii)Brexpiprazole 0.5–2 mg: 82 (61.7)	2	(i) Tablet placebo orally (ii) Tablet brexpiprazole 0.5–2 mg (iii)Brexpiprazole was initiated at 0.25 mg/day (days 1–3), increased to 0.5 mg/day (days 4–14), and further increased to a target dose of 1 mg/day (days 15–28; could be decreased back to 0.5 mg/day) orally	(i) Change of CMAI total score from baseline to week 12 (ii) Change of CGI-S score as related to agitation from baseline to week 12 (iii) Change of NPI-NH agitation/aggression score (frequency × severity) from baseline to week 12
Lee *et al.*[16]	Double-blind, placebo-controlled, fixed-dose, parallel-arm trial	123 Alzheimer disease clinical trial sites in Europe(Bulgaria, Hungary, Serbia, Slovakia, Spain, Ukraine) and the United States	345	(i) Placebo: 73.0 (7.0) (ii) Brexpiprazole 2 or 3 mg 74.5 (7.7)	(i) Placebo: 48.7: 51.3 (ii) Brexpiprazole 2 or 3 mg: 40.8:59.2	2	(i) Tablet placebo orally (ii) Tablet brexpiprazole 2 or 3 mg orally	Change in CMAI total score from baseline to week 12
Nakamura *et al.*[17]	Randomized double blind	120 sites nationwide in Japan	410	(i) Placebo: 80.5 (6.5) (ii) Brexpiprazole 1 mg: 79.3 (7.4) (iii) Brexpiprazole 2 mg: 80.2 (6.4)	(i) Placebo: 42.2:57.8 (ii) Brexpiprazole 1 mg: 38:62 (iii) Brexpiprazole 2mg: 29.1:70.9	3	(i) Tablet placebo orally (ii) Tablet brexpiprazole 1 mg (iii) Tablet brexpiprazole 1 mg 2 mg orally (iv) Brexpiprazole was initiated at 0.5 mg in week 1, increased to 1 mg in week 2(day 8), and further increased to 2 mg in week 3 (day 15) for the 2 mg group.	(i) Change in CMAI total score from baseline to Week 10 (ii) Change in CMAI subscale (aggressive behaviour, physically nonaggressive behaviour, and verbally agitated behaviour) scores from baseline to week 10 (iii) Change in CGI-S score from baseline to week 10 (iv) CGI-I score at week 10.

Abbreviations: CGI-I: Clinical Global Impressions-Global Improvement; CGI-S: Clinical Global Impressions-Severity; CMAI: Cohen–Mansfield Agitation Inventory; NPI-NH: Neuropsychiatric Inventory-Nursing Home.

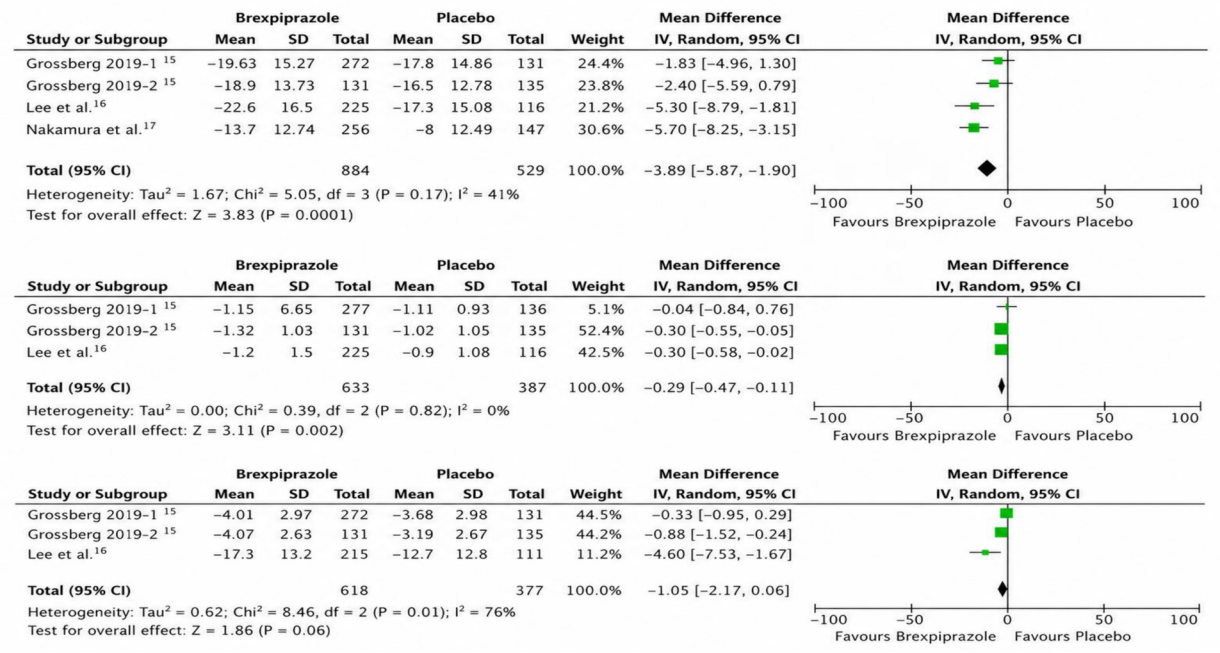


Figure 2. Forest plot of efficacy endpoints. (A) Change in CMAI score at week 10–12 from baseline. (B) Change in CGI-S score as related to agitation at week 10–12 from baseline. (C) Change in NPI-NH score at week 10–12 from baseline.
Abbreviations: CGI-S: Clinical Global Impressions–Severity; CI: Confidence interval; CMAI: Cohen–Mansfield Agitation Inventory; IV: Inverse-variance; NPI-NH: Neuropsychiatric Inventory-Nursing home. Image created by the authors.

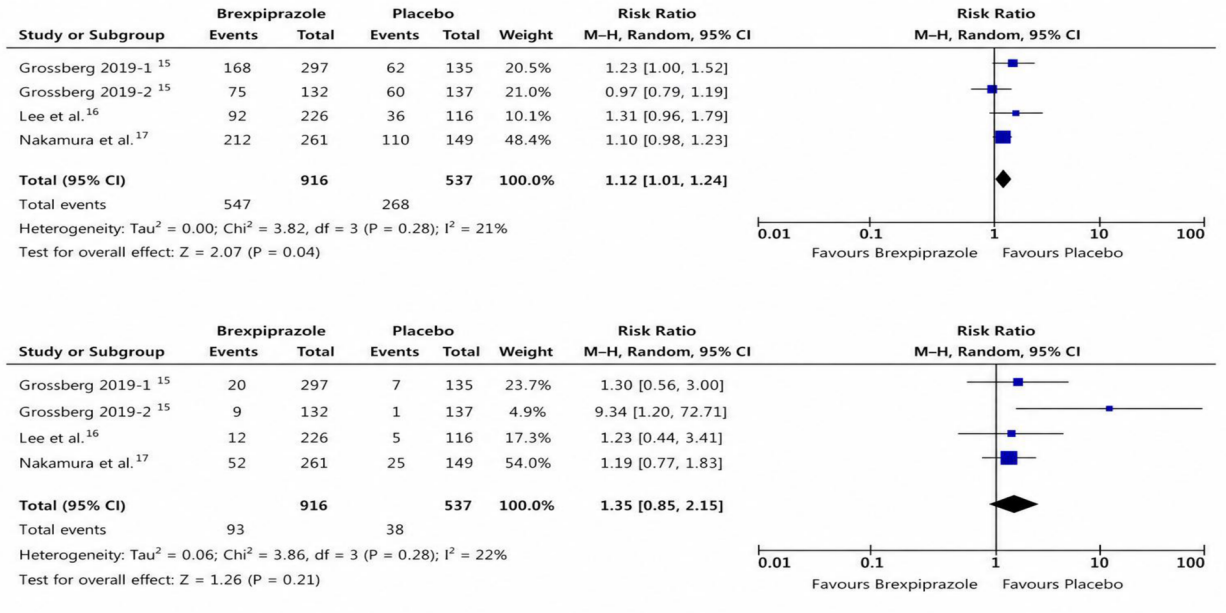


Figure 3. Forest plot of safety endpoints. (A) Treatment-emergent adverse event; (B) treatment discontinuation due to treatment-emergent adverse event.
Abbreviations: CI: Confidence interval; M–H: Mantel–Haenszel. Image created by the authors.

by moderate-certainty evidence, primarily downgraded due to imprecision, as the confidence interval ranged from a substantial benefit to a more modest effect. In contrast, the reduction in CGI-S scores had high-certainty evidence, reflecting consistent findings across studies with minimal heterogeneity. The effect on NPI-NH scores was based on moderate-certainty evidence, downgraded due to inconsistency, likely stemming from variations in study populations and assessment methods. For safety outcomes, the certainty of evidence was high for both treatment-emergent adverse events (TEAEs) and treatment discontinuation due to TEAEs, indicating robust and reliable findings. The increased risk of TEAEs was statistically significant, whereas the trend toward higher discontinuation rates did not reach significance (Table 3).

4. Discussion

This systematic review and meta-analysis synthesize current evidence on the efficacy and safety of brexpiprazole for the treatment of agitation associated with AD. Across four RCTs, brexpiprazole was associated with clinically meaningful improvements in agitation severity, accompanied by a modest increase in treatment-emergent adverse events. These findings add to the growing literature on pharmacological approaches to managing behavioral symptoms in AD and support brexpiprazole as a potential therapeutic option when non-pharmacological strategies are insufficient.

4.1. Efficacy outcomes

Brexpiprazole demonstrated a consistent reduction in agitation severity as measured by the CMAI, suggesting a meaningful improvement in core behavioral symptoms. Although the magnitude of effect was modest, it is comparable to reductions reported with other atypical antipsychotics used for agitation in AD.[18] Given the limited availability of effective pharmacological treatments in this setting, even moderate symptom improvement may be clinically relevant. The pharmacological profile of brexpiprazole, characterized by partial agonism at serotonin 5-HT1A and dopamine D2 receptors, may contribute to its efficacy while differentiating it from agents with stronger dopamine antagonism.[19,20]

Improvements in clinician-rated agitation severity, reflected by CGI-S scores, were consistent across trials and showed minimal heterogeneity, reinforcing the robustness of this finding. In contrast, changes in NPI-NH scores did not reach statistical significance and showed substantial heterogeneity. This variability may reflect differences in baseline symptom severity, study populations, or the broader symptom domains captured by the NPI-NH scale. These findings suggest that brexpiprazole may exert more consistent effects on core agitation behaviors than on composite neuropsychiatric symptom measures. Future studies should explore symptom-specific responses to better identify patient subgroups most likely to benefit from treatment.[21]

Table 2. Risk of bias summary

Trial (study)	RoB arising from the randomization process	RoB due to deviations from the intended intervention	RoB due to missing outcome data	RoB in the measurement of the outcome	RoB in the selection of the reported result	Overall RoB
Grossberg *et al.*[15] (Study 1)	Some concerns	Low	Low	Low	Low	Some concerns
Grossberg *et al.*[15] (Study 2)	Low	Low	Low	Low	Low	Low
Lee *et al.*[16]	Some concerns	Low	Low	Low	Low	Some concerns
Nakamura *et al.*[17]	Low	Low	Low	Low	Low	Low

Abbreviation: RoB: Risk of bias.

Table 3. Summary of findings

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With brexpiprazole		Risk with placebo	Risk difference with brexpiprazole
Change in CMAI score at week 10–12 from baseline											
1,413 (4 RCTs)	Not serious	Not serious	Not serious	Serious[a]	none	⊕⊕⊕◯ Moderate[a]	529	884	–	529	MD 3.89 lower (5.87 lower to 1.9 lower)
Change in CGI-S score as related to agitation at week 10–12 from baseline											
1,020 (3 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	387	633	–	387	MD 0.29 lower (0.47 lower to 0.11 lower)
Change in NPI-NH score at week 10–12 from baseline											
995 (3 RCTs)	Not serious	Serious[b]	Not serious	Not serious	None	⊕⊕⊕◯ Moderate[b]	377	618	–	377	MD 1.05 lower (2.17 lower to 0.06 higher)
TEAE											
1,453 (4 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	288/537 (53.6%)	547/916 (59.7%)	RR 1.12 (1.01 to 1.24)	288/537 (53.6%)	64 more per 1,000 (from 5 more to 129 more)
Treatment discontinuation due to TEAE											
1,453 (4 RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	38/537 (7.1%)	93/916 (10.2%)	RR 1.35 (0.85 to 2.15)	38/537 (7.1%)	25 more per 1,000 (from 11 fewer to 81 more)

Notes: [a]Very wide confidence interval; [b]I^2 is 76% and $p = 0.01$, significant heterogeneity. ⊕ denotes that evidence exists, and ◯ denotes the absence of evidence. Negative MD = improvement.
Abbreviations: CGI-S: Clinical Global Impressions-Severity; CI: Confidence interval; CMAI: Cohen–Mansfield Agitation Inventory; MD: Mean difference; NPI-NH: Neuropsychiatric Inventory-Nursing Home; RCT: Randomized controlled trial; RR: Risk ratio; TEAE: Treatment-emergent adverse event.

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4.2. Safety and tolerability

Brexpiprazole was associated with a small but statistically significant increase in treatment-emergent adverse events compared with placebo. Importantly, heterogeneity for safety outcomes was low, indicating consistent findings across studies. The observed increase in adverse events appears lower than that reported for several other atypical antipsychotics commonly used in dementia-related agitation, which have been associated with higher risks of sedation, extrapyramidal symptoms, and cerebrovascular events.[22]

Although treatment discontinuation due to adverse events was numerically higher in the brexpiprazole group, this difference was not statistically significant. This observation suggests that, while adverse events were more frequent, they were not consistently severe enough to necessitate treatment discontinuation. Nevertheless, given the known risks associated with antipsychotic use in older adults, careful monitoring remains essential, particularly during treatment initiation and dose escalation.

4.3. Certainty of evidence and interpretation

The certainty of evidence varied across outcomes. Moderate-certainty evidence supports a reduction in CMAI scores, with imprecision contributing to some uncertainty regarding effect size. High-certainty evidence for CGI-S outcomes strengthens confidence in brexpiprazole's effect on clinician-assessed agitation severity. In contrast, moderate-certainty evidence for NPI-NH outcomes reflects inconsistent findings across studies and underscores the need for more standardized outcome assessment. High-certainty evidence for safety outcomes supports the reliability of observed adverse event rates. Together, these findings underscore the importance of individualized risk–benefit assessment when considering brexpiprazole for agitation management in AD.

4.4. Comparison with existing therapies

Compared with other pharmacological treatments such as risperidone or quetiapine, brexpiprazole appears to offer a balanced efficacy–safety profile. Traditional atypical antipsychotics are associated with increased risks of cerebrovascular events and mortality, which have limited their use in dementia-related agitation.[21-24] Brexpiprazole's receptor activity profile may contribute to a more favorable tolerability profile, potentially reducing the risk of severe sedation and extrapyramidal symptoms.

Selective serotonin reuptake inhibitors have also been evaluated for agitation in AD, with variable results.[25-27] While agents such as citalopram have demonstrated modest efficacy, concerns regarding QT interval prolongation and limited benefit in severe agitation restrict their widespread use.[25] Within this context, brexpiprazole represents a targeted pharmacological option with demonstrated efficacy in reducing agitation severity.

4.5. Clinical implications

The findings of this meta-analysis have several practical implications. First, the consistency of efficacy across dosing strategies suggests that a cautious, individualized titration approach may be appropriate in clinical practice. Second, patient selection remains critical, particularly for individuals with comorbidities that may increase vulnerability to adverse effects. Finally, the modest increase in adverse events must be weighed against the substantial impact of agitation on patient well-being and caregiver burden. In carefully selected patients, the benefits of symptom reduction may outweigh the potential risks.

4.6. Limitations and future directions

Several limitations of this meta-analysis warrant consideration:

(a) Study duration: The included trials' duration (10–12 weeks) limits conclusions about long-term efficacy and safety. Future studies should assess longer-term outcomes to evaluate the durability of brexpiprazole's effects.
(b) Heterogeneity in NPI-NH outcomes: The substantial heterogeneity in NPI-NH results suggests a need for more standardized assessment approaches and subgroup analyses focusing on specific symptom domains.
(c) Limited geographic representation: While the studies included multiple countries, certain regions were underrepresented, potentially limiting generalizability.
(d) Comparison with non-pharmacological interventions: Future research should assess how brexpiprazole compares with non-pharmacological interventions such as behavioral therapy, caregiver training, and structured routines, which remain the cornerstone of agitation management in dementia care.

Further research should focus on:

- Identifying predictors of treatment response to enable personalized therapy.
- Investigating long-term safety and efficacy through extended follow-up studies.
- Examining the impact of brexpiprazole on caregiver burden and overall quality of life.
- Conducting head-to-head comparisons with other pharmacological and non-pharmacological interventions.

5. Conclusion

This systematic review and meta-analysis indicate that brexpiprazole is associated with clinically meaningful improvements in agitation among patients with AD, accompanied by a modest increase in TEAEs. Overall, the findings suggest a favorable balance between efficacy and safety when brexpiprazole is used judiciously. In the context of limited pharmacological options for agitation in AD, brexpiprazole represents a potential therapeutic option for selected patients. Nevertheless, careful patient selection, close monitoring, and individualized dose titration remain essential. Further well-designed studies with longer follow-up are needed to better define the long-term safety, durability of treatment effects, and the role of brexpiprazole within multimodal management strategies for agitation in Alzheimer's disease.

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Conflict of interest

The authors declare that they have no competing interests.

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