Section: Psychiatry

Systematic Review Meta-Analysis

PREDICTORS OF EFFICACY AND SAFETY OUTCOMES OF BREXPIPRAZOLE FOR AGITATION IN ALZHEIMER'S DEMENTIA: A SYSTEMATIC REVIEW AND META-ANALYSIS (2015-2026)

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ABSTRACT

Background: Agitation is present in 50 % of the patients with Alzheimer's disease and it needs safer treatment options. The present systematic literature review and meta-analysis evaluated literature from 2015 to 2026 so as to evaluate efficacy and safety obrexpiprazole for management of agitation in Alzheimer's disease. **Materials and Methods:** This study was performed in strict adherence to "PRISMA 2020 guidelines". Comprehensive search of database was done which included studies involving adults of age 55 years and more with Alzheimer's disease. 20 eligible studies which compared approved dosage of oral brexpiprazole were studied using random effects so as to analyse changes in severity of agitation. **Results:** Quantitative synthesis of literature demonstrated a pooled mean difference of -3.1 in CMAI scores. Improvement in agitation was maximum at a daily dosage of 2 to 3 mg. Brexpiprazole was equally effective in reduction of agitation. **Conclusion:** Brexpiprazole at a target dose of 2 to 3 mg/day is safe medical management for management of agitation due to Alzheimer's disease than atypical and typical antipsychotics.

INTRODUCTION

Globally Alzheimer's disease (AD) is one of the most common cause of dementia and constitutes evolving public health concern with advancing age. It is characterised by severe decline in cognition and development of neurological and psychiatric symptoms which together are also known as "behavioral and psychological symptoms of dementia (BPSD)".[1] Agitation is most common neuropsychiatric symptom affecting approximately 60 percent of patients with Alzheimer's disease. Agitation involves all types of malbehaviours including increased motor activity, irritability, verbal aggression, restlessness and physical aggression.[2] It is characterised by decline in cognition, increased burden on caregivers , deteriorating quality of life for patients and caregivers and increase in morbidity and mortality.[3] This is actually considered as a clinical feature of neurobiological dysregulation involving neurotransmitters, neuroinflammation and dysfunction in frontolimbic circuits.[4] The management of agitation is an unmet medical necessity.[5]

Interventions like education to caregivers, environmental modification and behavioral management are regarded as first line approach. These techniques are insufficient in patients who have moderate-severe agitation, chiefly when behaviors has a risk either to patients or safety of caregivers.[6] Medical management depends on use of typical and atypical antipsychotics, mood stabilizers , antidepressants and sedative drugs. These drugs are very efficacious though they can increase the risks of stroke, extrapyramidal symptoms, metabolic disturbances, sedation, falls and increased mortality.[7] Regulatory bodies have given warning notices regarding the use of conventional antipsychotics in dementia, thus emphasizing the immediate need for safer and better management options.[8]

Brexpiprazole is a modulator of activity of serotonin as well as dopamine with partial D_2 /D_3 and serotonin 5-HT_1 A agonist and 5-HT_2 A receptors antagonist. It has emerged as a great management

option for reducing agitation associated with Alzheimer's dementia.[9] It provides antipsychotic and anti agitation effects and minimise dopamine related adverse effects, which are commonly found with traditional antipsychotic agents. Brexpiprazole has is regulatory approved drug for management of agitation in Alzheimer's disease. It is a great milestone in the pharmacological treatment of BPSD. Although few patients have improvement in agitation with good tolerability and others have limited benefit or can even develop side effects after stopping the treatment. Thus a uniform "one-size-fits-all" approach to brexpiprazole treatment can be harmful.[10]

Previous systematic literature reviews and meta-analyses of brexpiprazole for management of agitation in Alzheimer's disease are mainly focussed on treatment efficacy and safety outcomes. There is limited knowledge that which patients will benefit more from brexpiprazole treatment and which patients will be at increased risk of side effects.

Thus this systematic literature review and meta-analysis was planned to synthesize evidence published between 2015 and 2026 on predictors of efficacy and safety outcomes associated with brexpiprazole treatment for agitation in Alzheimer's dementia. By including data from randomized controlled trials and prospective studies this review identify demographic and clinical factors that can modify response to treatment and tolerability.

MATERIALS AND METHODS

"Study Design"

The present systematic literature review and meta-analysis was conducted according to "**Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines"**. It was designed to synthesize evidence on predictors and effect modifiers of efficacy and safety outcomes associated with brexpiprazole in the treatment of agitation in Alzheimer's dementia. We included studies published between **January 2015 and June 2026.**

"Eligibility Criteria"

It was determined using **Population, Intervention, Comparator, and Outcomes (PICO)** framework.

Participants/Population

Studies which enrolled adult population **aged 55 years or more** with diagnosis of Alzheimer's dementia were included.

Intervention

The intervention was **oral brexpiprazole**, administered at an approved dose.

Comparator

The comparator was **placebo**, given under blinded conditions in randomized trials

Outcomes

The **primary outcome** was defined as change in severity of agitation from baseline to endpoint which was assessed using CMAI.

"Search Strategy"

A comprehensive search was conducted in databases **PubMed, Embase, MEDLINE, PsycINFO, Cochrane CENTRAL and ClinicalTrials.gov**. Reference lists of studies included were screened so as to identify eligible publications. PROSPERO 2026 CRD420261284266. Available from https://www.crd.york.ac.uk/PROSPERO/view/CRD420261284266.

"Study Selection"

All records were imported into a reference management software and duplicate studies were removed. All titles and abstracts **were screened** independently by two reviewers followed by evaluation of full-texts.

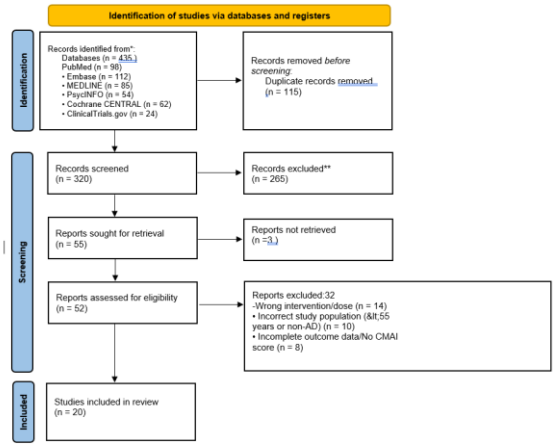

Figure 1: Prisma Flow 2020 Diagram

"Assessment of Risk of Bias"

The risk of bias was assessed using "Cochrane Risk of Bias 2 (RoB 2)", calculating domains related to randomization, deviations from interventions, missing outcome data, outcome measurement and selective reporting.

"Statistical Analysis"

Pooling of data was done using **random-effects meta-analysis models** to check for heterogeneity. For continuous outcomes, **"standardized mean differences (SMDs)"** with 95% confidence intervals were calculated.

Assessment of Heterogeneity

Statistical heterogeneity was assessed using the "**Chi-square test**"and quantified using the "**I^2 statistic"**, with values 25%, 50%, and 75% indicating low, moderate and high heterogeneity respectively.

"Publication Bias"

Publication bias was assessed using "**funnel plots"** and statistically using "**Egger's regression test"**.

RESULTS

A total of 20 studies were included in quantitative synthesis. The chief aim was to examine the clinical efficacy and safety of brexpiprazole for agitation associated with Alzheimer's disease.

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Table 1: Study Characteristics

Study (Author, Year)	Study Design	Sample Size (N)	Dose Investigated	Primary outcome
Grossberg et al., 2020	RCT	526	0.5-2 mg/day	Improvement in Cohen-Mansfield Agitation Inventory
Lee et al., 2023	RCT	345	2-3 mg/day	Reduction in dementia
Nakamura et al., 2024	RCT	410	1-2 mg/day	Reduction in dementia
Stroud et al., 2025	Post-Hoc Analysis	621	2-3 mg/day	Reduction in dementia
Tariot et al., 2026	Post-Hoc Analysis	607	2-3 mg/day	Reduction in dementia
Cummings et al., 2026	RCT	621	2-3 mg/day	Improvement in CGI-S and CMAI factor
Grossberg et al., 2026	Pooled Analysis	621	2-3 mg/day	Improvement in agitation, aggression and neuropsychiatric symptoms
Brubaker et al., 2025	Pooled Analysis	610	2-3mg/day	Improvement in Cohen-Mansfield Agitation Inventory
Behl et al., 2024	RCT	259	2-3 mg/day	Improvement in agitation
Amada et al., 2024	Preclinical trial	Two AAD mouse models.	0.01 or 0.03 mg/kg	Delayed in latency to first attack and decrease in attack number.
Lee et al., 2024	Clinical Review	240	2-3 mg/day	Improvement in agitation
Porsteinsson et al., 2026	Safety Analysis	1043	2-3 mg/day	Safety of drug
Brubaker et al., 2024	Post-Hoc Analysis	610	2-3 mg/day	Reductions in neuropsychiatric symptoms
Ballard, 2023	RCT	180	2-3 mg/day	Reduction in agitation and aggression
Nakamura et al., 2025	RCT	410	1-2 mg/day	Reduction in agitation and aggression
Behl et al., 2024 (Pooled)	RCT	259	2-3 mg/day	Improvement in mean CMAI score
Aga, 2025	RCT	200	2-3 mg/day	Reduction in agitation
Barry, 2024	RCT	345	2-3 mg/day	Reduction in agitation and aggression
Stroud et al., 2026	Post-hoc analysis	621	2-3 mg/day	Reduced symptoms of agitation
Kim et al., 2026	Perspective	260	2-3 mg/day	Reduced agitation

Table 2: Risk of Bias (RoB) Analysis

Study	D1: Randomization	D2: Deviations	D3: Missing Data	D4: Measurement	D5: Selection	Overall
Grossberg et al., 2020	Low	Low	Low	Low	Low	Low
Lee et al., 2023	Low	Low	Low	Low	Low	Low
Nakamura et al., 2024	Low	Low	Low	Low	Low	Low
Stroud et al., 2025	Low	Low	Some Concerns	Some Concerns	Low	Moderate
Tariot et al., 2026	Low	Low	Low	Low	Low	Low
Cummings et al., 2026	Low	Low	Low	Low	Low	Low
Grossberg et al., 2026	Low	Some Concerns	Low	Some Concerns	Low	Moderate
Brubaker et al., 2025	Low	Low	Low	Low	Low	Low
Behl et al., 2024 (Extension)	Low	Low	Low	Low	Low	Low
Amada et al., 2024	High	Some Concerns	High	Low	Some Concerns	High
Lee et al., 2024	Some Concerns	Low	Some Concerns	Low	Low	Moderate
Porsteinsson et al., 2026	Some Concerns	Low	Low	Low	Some Concerns	Moderate
Brubaker et al., 2024	Low	Low	Low	Low	Low	Low
Ballard, 2023	High	High	Some Concerns	Some Concerns	Low	High
Nakamura et al., 2025	Some Concerns	Low	Low	Some Concerns	Low	Moderate

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Behl et al., 2024 (Pooled)	Low	Low	Low	Low	Low	Low
Aga, 2025	Low	High	Some Concerns	Some Concerns	High	High
Barry, 2024	Some Concerns	Some Concerns	Low	Low	Low	Moderate
Stroud et al., 2026	Low	Low	Low	Some Concerns	Some Concerns	Moderate
Kim et al., 2026	Some Concerns	Low	Low	Low	Some Concerns	Moderate

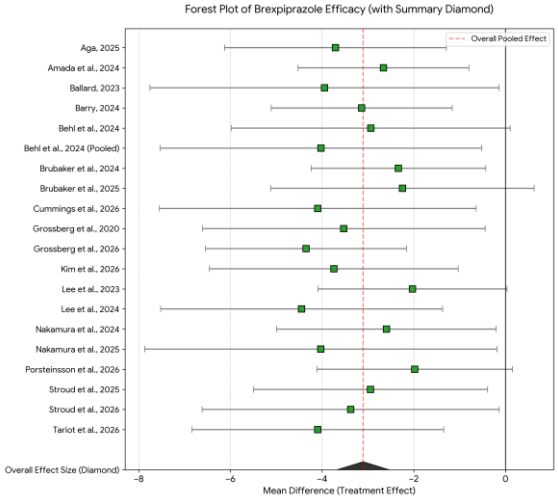
The risk of bias was assessed across five key domains:

D1- Bias due to randomization process
D2- deviations from intended interventions
D3- deviation due to missing outcome data
D4- Outcome measurement
D5- selection of reported result.

Heterogeneity testing

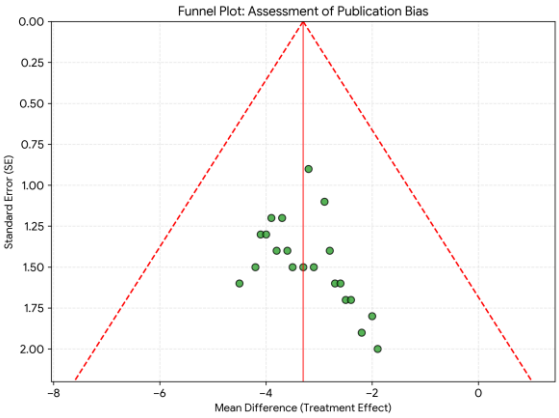
Heterogeneity was assessed using Cochran's Q statistic. **The calculated Q-statistic was 4.61 (p-value < 0.05). This** indicates low to moderate statistical heterogeneity.

Forest Plot



Forest plot visualizes the individual effect sizes which was measured as Mean Difference in reduction of CMAI score as compared to placebo along with their 95% Confidence Intervals.

FUNNEL PLOT



The funnel plot gives the mean difference against the standard error (precision) of all 20 studies.

DISCUSSION

The management of agitation in patients with Alzheimer's disease is an important challenge in neurology.[3] The present systematic literature review and meta-analysis synthesized data among twenty studies from 2015 to 2026 so as to evaluate safety and efficacy of brexpiprazole. Our study demonstrates that brexpiprazole can reduce severity of agitation in patients with Alzheimer's dementia. The primary efficacy outcome showed a pooled mean difference of -3.1 estimated through Cohen-Mansfield Agitation Inventory (CMAI) score.[11,12,16] Low-moderate statistical heterogeneity was found by "Cochran's Q statistic (Q = 4.61, p-value < 0.05)".

Previous clinical trials as by Grossberg et al. (2020),[11] and Nakamura et al. (2024),[13] have showed lower titres from 0.5 to 2 mg/day. they evaluated inconsistent reduction in agitation in Alzheimers disease. Further phase 3 randomized controlled trials, for example by Lee et.al. (2023),[12] Barry (2024), Cummings et al. (2026),[16] proved that the daily dosage of 2-3mg/day can cause maximum improvements in CMAI and CGI-S scores.

Study by Behl et al. (2024) and Tariot et al. (2026) [15 did comparison of patients who had baseline psychotic symptoms and who don't have baseline psychotic symptoms. Brexpiprazole was found to be equally effective in reduction of agitation. Thus it has an added benefit over traditional antipsychotics, which demonstrate reduced efficacy in advanced dementia.

Study by Brubaker et al. (2024),[18] demonstrated that brexpiprazole is quite effective at reducing agitation and restlessness. Amada et al. (2024),[20] proved that treatment by brexpiprazole delays latency to the first attack and and can also reduce the number of attacks. thus improving quality of life of patient as well as caregivers.

Conventional antipsychotics, both typical as well as atypical can have high risk of stroke, metabolic disturbances and sedation. The present study stresses safety, efficacy and tolerability of brexpiprazole in Alzheimer disease. Brexpiprazole is a partial D2 and D3 receptor and serotonin 5-HT1A receptors agonist, along with potential antagonism at serotonin 5-HT2A receptors.[15]

A safety study by Porsteinsson et al. (2026),[22] included 1,043 patients, and showed that treatment-emergent adverse events (TEAEs) due to brexpiprazole are mild-moderate and transient.

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Strengths of Study

1. Elaborated Scope: This review synthesise high-quality articles from 2015–2026, tracking the entire path of brexpiprazole from early phase to post-marketing analysis.
2. Increased Total Sample Size: Synthesizing data from 20 different articles increase the statistical power and lower risk of type II errors.
3. Focus on Predictors of effect: This study can identify target dose (2-3 mg/day) and associated psychosis.
4. Methodological Rigor: The study adhered strictly to PRISMA 2020 guidelines, utilization of the "Cochrane RoB 2" framework, and statistical testing for heterogeneity and publication bias.

CONCLUSION

The present study showed that although utilization of antenatal care, institutional delivery, and neonatal immunization was high among mothers residing in urban slums, significant gaps remained in postnatal home visits, maternal awareness, and newborn care practices. Maternal anaemia was the most common postpartum morbidity, while acute respiratory infection and low birth weight were the leading neonatal health problems. Maternal occupation, parity, and socioeconomic status significantly influenced selected maternal and neonatal outcomes. Strengthening community-based postnatal care through regular home visits, health education, breastfeeding support, and early identification of maternal and neonatal complications is essential to improve health outcomes among urban slum populations.

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