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Efficacy, acceptability and tolerability of second-generation antipsychotics for behavioural and psychological symptoms of dementia: a systematic review and network meta-analysis

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ABSTRACT

Background Behavioural and psychological symptoms of dementia (BPSD) are highly prevalent in people living with dementia. Second-generation antipsychotics (SGAs) are commonly used to treat BPSD, but their comparative efficacy and acceptability are unknown.

Methods The standard mean difference (SMD) was used to pool the fixed effects of continuous outcomes. We calculated ORs with corresponding 95% credible intervals (CI) for the categorical variable. Efficacy was defined as the scores improved on the standardised scales. Acceptability was defined as the all-cause dropout rate. Tolerability was defined as the discontinuation rate due to adverse effects (AEs). The relative treatment rankings were reported with the surface under the cumulative curve. The AE outcomes included mortality, cerebrovascular adverse events (CVAEs), falls, sedation, extrapyramidal symptoms and urinary symptoms.

Results Twenty randomised controlled trials with a total of 6374 individuals containing 5 types of SGAs (quetiapine, olanzapine, risperidone, brexpiprazole and aripiprazole) with intervention lengths ranging from 6 weeks to 36 weeks were included in this network meta-analysis. For the efficacy outcome, compared with the placebo, brexpiprazole (SMD=−1.77, 95% CI −2.80 to −0.74) was more efficacious, and brexpiprazole was better than quetiapine, olanzapine and aripiprazole. Regarding acceptability, only aripiprazole (OR=0.72, 95% CI 0.54 to 0.96) was better than the placebo, and aripiprazole was also better than brexpiprazole (OR=0.61, 95% CI 0.37 to 0.99). In terms of tolerability, olanzapine was worse than placebo (OR=6.02, 95% CI 2.87 to 12.66), risperidone (OR=3.67, 95% CI 1.66 to 8.11) and quetiapine (OR=3.71, 95% CI 1.46 to 9.42), while aripiprazole was better than olanzapine (OR=0.25, 95% CI 0.08 to 0.78). Quetiapine presented good safety in CVAE. Brexpiprazole has better safety in terms of falls and showed related safety in sedation among included SGAs.

Conclusion Brexpiprazole showing great efficacy in the treatment of BPSD, with aripiprazole showing the highest acceptability and olanzapine showing the worst tolerability. The results of this study may be used to guide decision-making.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous network meta-analyses revealed the efficacy and safety of commonly used second-generation antipsychotics (SGAs) to treat behavioural and psychological symptoms of dementia (BPSD).

WHAT THIS STUDY ADDS

⇒ The present study provides the first updated evidence to determine the efficacy, acceptability and tolerability of SGAs in the treatment of BPSD, particularly by incorporating three timely brexpiprazole trials, which have not been jointly analysed before.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study may be used to guide decision-making.

INTRODUCTION

Societies across the globe are ageing. The population aged over 60 years is estimated to rise to 2 billion by 2050.[1] By then, the number of people living with dementia is expected to reach 150 million.[2] The growing population with dementia is considered one of the greatest global challenges that brings public health crises and strains families. Dementia is a neurodegenerative disorder characterised by both cognitive and functional impairment. Behavioural and psychological symptoms of dementia (BPSD) (eg, delusion, agitation and apathy) are common in dementia patients and are implicated in a cycle of negative events including deterioration of family, increased caregiver burden, institutionalisation and risk of death.[3] Effective, safe and acceptable treatments for BPSD are sorely needed. Antipsychotics are considered to have a high risk of side effects in the treatment of BPSD. Previous randomised clinical trials suggest that second-generation antipsychotics (SGAs) offered modest improvement in BPSD but may cause serious adverse events, of which the most prominent are sedation, extrapyramidal symptoms (EPS), and increased risk of cerebrovascular events and mortality.[4] It is therefore the Food and Drug Administration (FDA) issued a black box warning about antipsychotics in earlier years.[2 5] The use of

SGAs might seem unjustifiable given that their off-label use lacks strong scientific evidence and is generally associated with adverse events. It is still used in approximately 12.3%–37.5% of patients for the treatment of BPSD.[6] SGAs were preferred by clinicians over typical antipsychotics since SGAs carry a relatively small risk of side effects.[7] Although some antidepressants may have fewer and less severe adverse effects (AEs) than antipsychotic medications, treatment may still be complicated by cardiac conduction-delaying effects and effects on reducing agitation are not evident until after 6–9 weeks of treatment.[8]

Evidence-based medicine has been trying to determine which antipsychotic is most beneficial and safe for the management of BPSD, but pairwise meta-analyses may have great limitations to this matter.[9] A previous study demonstrated that SGAs may improve neuropsychiatric performance, but the adverse events also developed major concerns for clinicians.[10] The efficacy and acceptability of specific drugs were not well known. Network meta-analysis (NMA) enables simultaneous comparison of multiple interventions and generates evidence from direct and indirect comparisons within a network of trials which may be helpful for insight. In the early years, Yunusa *et al*[11] first performed a NMA for BPSD treatment, in which effectiveness outcomes were separately measured by the improvement of neuropsychological scales, while the safety outcomes conducted different AEs (eg, mortality, cerebrovascular adverse events (CVAEs)), but not involving acceptability and tolerability. Recently, novel antipsychotics such as brexpiprazole have been studied to treat dementia-related psychosis and agitation. The present study aims to provide the first updated evidence to determine the efficacy, acceptability and tolerability of different SGAs by using NMA to evaluate the results of randomised placebo-controlled or head-to-head comparative trials on BPSD.

METHODS

This study was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)[12] guidelines (PRISMA checklist). Any amendments to this study will be reflected in an update to the PROSPERO registration (CRD42022363511).

Eligibility criteria

This NMA included Alzheimer's dementia (AD), vascular dementia and mixed dementia, defined by the study authors (including medical history and/or diagnostic and statistical manual diagnosis). There were no restrictions based on patient's age or the severity of dementia, but patients with Parkinson's dementia and Lewy body dementia, other mental comorbidities unrelated to dementia (eg, depression, delirium, schizophrenia), or uncontrolled physical illness (any physical disease in the acute phase, eg, cardiovascular and cerebrovascular accidents, infectious) or poorly controlled chronic disease (eg, poorly controlled hypertension and diabetes, residual symptoms of cerebral vascular events convalescence) were excluded. Any type and any course of SGA in the treatment of BPSD were included. Eligible comparator groups within studies include the efficacy and acceptability of randomised placebo-controlled or head-to-head comparative trials on BPSD. Our primary outcomes were efficacy and acceptability. Efficacy was defined as the change of endpoint score as measured with a standardised scale (eg, Cohen-Mansfield Agitation Inventory (CMAI), Neuropsychiatric Inventory (NPI), Brief Psychiatric Rating Scale (BPRS)). Acceptability was defined as all-cause dropout rate (the number of participants discontinuing the treatment due to any reason out of the total number of participants), and it encompassed efficacy and tolerability.[13] The secondary outcome was discontinuation due to AEs, which only reflected tolerability (the number of people discontinuing the treatment due to AEs out of the total number of participants). The AE outcomes included mortality, CVAEs, falls, sedation, EPS and urinary symptoms. Only randomised controlled trials (RCTs) were included in our systematic review.

Search strategy

We systematically searched for eligible trials of combinations of SGAs and BPSD among the following databases for citations published in English from database inception to December 2023: PubMed, Embase, Web of Science and Cochrane Trial Register. The full search strategy is presented in online supplemental material 1. For the meta-analysis retrieved, we searched the reference lists to include additional eligible studies. Two reviewers were involved in record selection, data collection and risk of bias evaluation, independently. Study authors were contacted for additional information or missing data if necessary.

Data collection

We extracted the characteristics of the included studies. Relevant information consisted of article characteristics (eg, first author, year of publication), participant characteristics including age, sex, sample size, type of dementia and baseline Mini-Mental State Examination (MMSE) Score, and intervention characteristics (eg, type and dose of SGA, intervention period). All continuity variables are described using mean and SD.

Data analysis

Stata/SE (V.15.1) and a frequentist framework were used to perform the NMA. The standard mean difference (SMD) was used to pool the fixed effect of continuous outcomes. We calculated ORs with corresponding 95% credible intervals (CIs) for the categorical variable. The random-effects model was used when performing the NMA. We presented the results of each comparison based on direct and indirect evidence in a two-dimensional graph and tabular form. We employed the surface under the cumulative ranking curve (SUCRA) to represent the probability of efficacy, acceptability and tolerability for each treatment compared with a hypothetical treatment. We evaluated the heterogeneity of each comparison by quantifying I^2 statistics, and the visualised form was presented by a predictive interval (PI) plot, where differences between CI and PI indicated the size of heterogeneity.[14 15] Inconsistency was evaluated using global and local network methods. We evaluated local inconsistency by node-splitting and loop-specific methods and global inconsistency using a design-by-treatment test.[15] For bias assessment, we assessed selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases of studies included by using risk of bias 2 (ROB2) recommended by the Cochrane Collaboration.[16] For transitivity assessment, we evaluated the credibility of transitivity in our data by comparing the distribution of potential effect modifiers (eg, age, sex, baseline MMSE and treatment duration).[17] Publication bias is represented by the funnel plot. The sensitivity analysis of the conclusions for two primary outcomes was performed by excluding studies with a high risk of bias.[18] We used the Confidence In Network Meta-Analysis (CINeMA) approach to evaluate the credibility of each study.

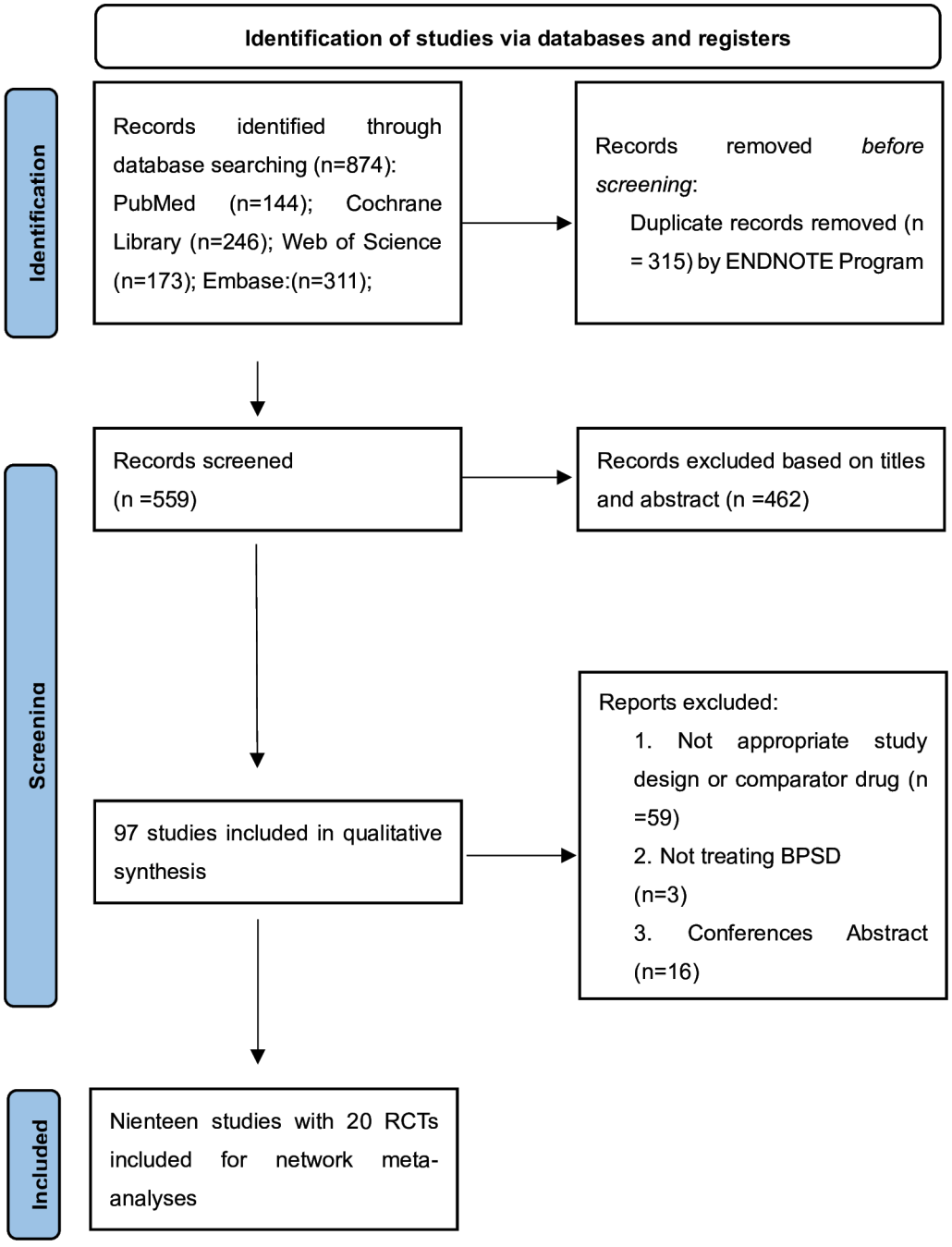

Figure 1 Flow diagram of the selection process. BPSD, behavioural and psychological symptoms of dementia; RCT, randomised controlled trial.

RESULTS

The PRISMA flow chart for eligible studies is shown in figure 1. The primary database search yielded 874 studies of which 315 were excluded for duplication and 462 were excluded after the title and abstract screening. Full texts of 97 studies were independently assessed by two authors, of which 77 were excluded due to some reasons . Nineteen studies with 20 RCTs met the inclusion criteria in the systematic review and meta-analysis.[19–38] Of these, 19 RCTs (except for Paleacu *et al*[34]) were included for efficacy meta-analysis.

STUDY CHARACTERISTICS

The characteristics of the studies included are summarised in table 1. Briefly, these studies were published between 1999 and 2023, and their sample sizes varied from 40 to 652 participants with a total of 6374 individuals with intervention lengths ranging from 6 weeks to 36 weeks. The included studies contained five types of SGAs (quetiapine, olanzapine, risperidone, brexpiprazole and aripiprazole). A network plot of comparisons between eligible interventions is shown in figure 2. Only three closed loops existed in the network (quetiapine vs olanzapine vs placebo, risperidone vs quetiapine vs placebo and risperidone vs olanzapine vs placebo). The primary outcomes were measured by the CMAI, NPI, Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), BPRS and Positive and Negative Syndrome Scale (PANSS). Most studies were set in nursing homes. The CINeMA results showed that four of eight comparisons were rated as low confidence of evidence and another four comparisons as very low (online supplemental materials 7).

Table 1 Characteristics of the included studies

Study	Sample size (female)	Participants	Age, years, mean (SD)	Intervention	Duration	Primary efficacy outcome	Target symptom	Baseline MMSE	Trial setting
Ballard *et al*[37]	62 (51)	AD	83.8 (7.7)	Quetiapine (50–100 mg/day) versus placebo	6 weeks	CMAI	Agitation	N/A	NH
Brodaty *et al*[26]	345 (248)	AD, VD, MD	83 (9.84)	Risperidone (0.5–2 mg/day) versus placebo	12 weeks	CMAI	Agitation	5.46 (0.46)	NH
Brodaty *et al*[28]	93 (79)	AD, MD	83.5 (7.1)	Risperidone (0.5–2 mg/day) versus placebo	12 weeks	BEHAVE-AD	Psychosis	5.7 (5.67)	NH
Daniel *et al*[19]	345 (195)	AD	74 (7.5)	Brexpiprazole (2 mg/day or 3 mg/day) versus placebo	12 weeks	CMAI	Agitation	15.6 (3.7)	NH
De Deyn *et al*[27]	229 (133)	AD, VD	81	Risperidone (0.5–4 mg/day) versus placebo	12 weeks	BEHAVE-AD	Psychosis	8.6	NH
De Deyn *et al*[24]	652 (489)	AD	76.6 (10.4)	Olanzapine (1.0 mg/day, 2.5 mg/day, 5.0 mg/day or 7.5 mg/day) versus placebo	10 weeks	NPI	Psychosis	13.7 (5.1)	NH
De Deyn *et al*[20]	208 (150)	AD	81.5	Aripiprazole (2,5 mg/day,10 mg/day or 15 mg/day) versus placebo	10 weeks	NPI	Psychosis	14.24	Outpatient
Deberdt *et al*[21]	494 (324)	AD, VD, MD	78.3 (7.3)	Olanzapine (2.5–10 mg/day) versus risperidone (0.5–2 mg/day) versus placebo	12 weeks	NPI	Psychosis	14.4 (5.6)	Outpatient and NH
Grossberg *et al*[23]	433 (239)	AD	74.1 (8)	Brexpiprazole (1 mg/day or 2 mg/day) versus placebo	12 weeks	CMAI	Agitation	N/A	NH
Grossberg *et al*[23]	270 (170)	AD	74 (7.8)	Brexpiprazole (0.5–2 mg/day) versus placebo	12 weeks	CMAI	Agitation	N/A	NH
Katz *et al*[22]	625 (424)	AD, VD, MD	82.7 (7.7)	Risperidone (0.5 mg/day, 1.0 mg/day or 2.0 mg/day) versus placebo	12 weeks	BEHAVE-AD	Psychosis	6.6 (6.3)	NH
Mintzer *et al*[29]	473 (364)	AD	83.4 (7.2)	Risperidone (0.5–1.5 mg/day) versus placebo	8 weeks	BEHAVE-AD	Psychosis	13.2 (4.97)	NH
Mintzer *et al*[35]	487 (315)	AD	82.5 (7.04)	Aripiprazole (2 mg/day, 5 mg/day or 10 mg/day) versus placebo	10 weeks	NPI	Psychosis	N/A	NH
Paleacu *et al*[34]	40 (26)	AD	82.2 (6.4)	Quetiapine (50–300 mg/day) versus placebo	6 weeks	N/A	N/A	14.4 (6.5)	NH
Rainer *et al*[38]	72 (42)	AD, VD, MD	77.8 (5.3)	Quetiapine (50–400 mg/day) versus risperidone (0.5–4 mg/day)	8 weeks	NPI	Psychosis	18.3 (4.4)	Outpatient
Schneider *et al*[30]	421 (235)	AD	77.9 (7.5)	Olanzapine (2.5 mg/day or 5 mg/day) versus quetiapine (25 mg/day or 50 mg/day) versus risperidone (0.5 mg/day or 1 mg/day) versus placebo	36 weeks	BPRS	Psychosis	15 (5.8)	Outpatient
Street *et al*[31]	206 (126)	AD	82.8 (6.5)	Olanzapine (5 mg/day, 10 mg/day or 15 mg/day) versus placebo	6 weeks	NPI	Psychosis	6.7 (6.5)	NH
Streim *et al*[33]	256 (195)	AD	83 (6.63)	Aripiprazole (2–15 mg/day) versus placebo	10 weeks	NPI	Psychosis	13.6 (87)	NH
Tariot *et al*[32]	190 (145)	AD, VD	83.2 (6.71)	Quetiapine (25–100 mg/day) versus risperidone	10 weeks	BPRS (total and agitation subscale)	Psychosis and agitation	12.8 (5.3)	NH
Zhong *et al*[25]	333 (247)	AD, VD	83 (7.2)	Quetiapine (100 mg/day or 200 mg/day) versus risperidone	10 weeks	PANSS	Psychosis	5.3 (3.9)	NH

AD, Alzheimer's dementia; BPRS, Brief Psychiatric Rating Scale; CMAI, Cohen-Mansfield Agitation Inventory; MD, mixed dementia; MMSE, Mini-Mental State Examination; NH, nursing home; NPI, Neuropsychiatric Inventory; PANSS, Positive and Negative Syndrome Scale; VD, vascular dementia.

Risk of bias assessment

According to the ROB2 assessment, 45% (9/20) of the included studies demonstrated a low risk of bias, while 2 studies indicated a high risk of bias for intention-to-treat analysis. The sources of high risk and unclear risk of bias were majorly from the selection of reported and randomisation processes. The detailed bias results are presented in online supplemental materials 2,3. The present generally stacked funnel plot suggests a low risk of publication bias (online supplemental materials 4).

EVALUATION OF INCONSISTENCY

The global inconsistencies for efficacy (χ^2=0.89, p=0.989) and acceptability (χ^2=6.86. p=0.351) were not statistically significant. However, the tolerability showed statistical significance (χ^2=13.56, p=0.035). The local inconsistencies for efficacy (p>0.05) and acceptability (p>0.05) were not statistically significant while two of six loops for tolerability showed statistical significance. The detailed results are presented in online supplemental materials 5,6.

TRANSITIVITY ASSESSMENT

The mean age of all participants was 79.90 years, and most were women (4197/6234 (67.32%)). Most of the patients had a diagnosis of AD with a mean MMSE Score of 11.32. The mean intervention duration is 11.3 weeks. The distribution of age, sex and diagnosis was comparable between studies (table 1). Thus, the transitivity assumption of this study is generally tenable.

Efficacy, acceptability and tolerability outcomes

For the efficacy outcome, compared with placebo, brexpiprazole (SMD=−1.77, 95% CI −2.80 to −0.74) was more efficacious, and brexpiprazole was better than quetiapine, olanzapine and aripiprazole (table 2). Regarding acceptability, only aripiprazole (OR=0.72, 95% CI 0.54 to 0.96) was better than placebo, and

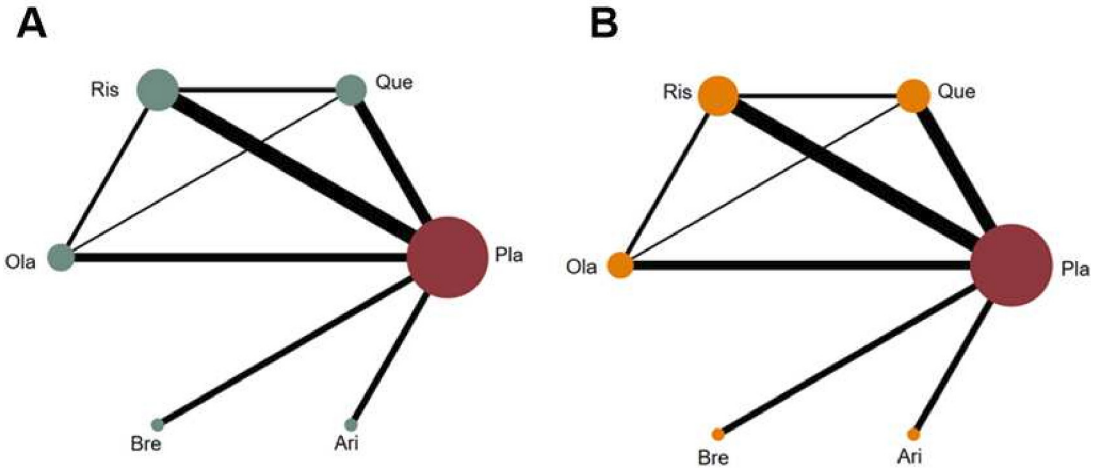

Figure 2 Network of eligible comparison. (A) Efficacy (19 RCTs). (B) Acceptability and tolerability (20 RCTs). The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of each node is proportional to the number of randomly assigned participants. Pla=Placebo, Que=quetiapine, Ola=olanzapine, Ris=risperidone, Bre=brexpiprazole, Ari=aripiprazole, RCT=randomised controlled trial.

aripiprazole was also better than brexpiprazole (OR=0.61, 95% CI 0.37 to 0.99). In terms of tolerability, olanzapine was worse than placebo (OR=6.02, 95% CI 2.87 to 12.66), risperidone (OR=3.67, 95% CI 1.66 to 8.11) and quetiapine (OR=3.71, 95% CI 1.46 to 9.42), while aripiprazole was better than olanzapine (OR=0.25, 95% CI 0.08 to 0.78). No significant tolerability differences were observed between olanzapine and brexpiprazole (table 3 and online supplemental materials 8). The sensitivity analysis showed that after removing two studies with a high risk of bias, the efficacy and acceptability results are generally in line with the primary outcomes (online supplemental materials 9).

Cumulative probability plots and SUCRAs are presented in online supplemental materials 10–12. In terms of efficacy, all SGAs were better than placebo, and brexpiprazole was the best among all five SGAs followed by risperidone, quetiapine, olanzapine and aripiprazole. For acceptability, aripiprazole (mean rank 1.2) and risperidone (mean rank 3.1) were better than placebo (mean rank 3.7). In terms of tolerability, all included SGAs were worse than placebo, of which aripiprazole, quetiapine and risperidone ranked as the first three among all SGAs.

AE outcomes

Mortality has been reported in a total of four trials involving quetiapine, risperidone and olanzapine. The NMA showed that none of the included AAPs were significantly different from the placebo or from each other (online supplemental material 13). According to SUCRA, placebo had the highest probability of safety, followed by olanzapine, risperidone and quetiapine (online supplemental material 13).

CVAEs have been reported in a total of five trials involving quetiapine, risperidone and olanzapine. NMA showed that risperidone had a significantly increased risk of CAVEs compared with placebo (OR=4.01, 95% CI 1.48 to 10.90) and quetiapine (OR=4.65, 95% CI 1.12 to 19.38). According to SUCRA, the quetiapine has the highest probability of safety, followed by placebo, olanzapine and risperidone (online supplemental material 14).

Falls were reported in 15 trials involving quetiapine, risperidone, olanzapine, brexpiprazole and aripiprazole. The NMA showed that none of the included AAPs were significantly different from the placebo or from each other. According to SUCRA, brexpiprazole had the highest probability of safety, followed by quetiapine, risperidone, placebo, aripiprazole and olanzapine (online supplemental material 15).

Sedation was reported in 16 trials involving quetiapine, risperidone, olanzapine, brexpiprazole and aripiprazole. NMA showed that compared with placebo, quetiapine (OR=5.04, 95% CI 3.24 to 7.83), olanzapine (OR=3.68, 95% CI 2.43 to 5.55), risperidone (OR=2.51, 95% CI 1.91 to 3.31) and aripiprazole (OR=2.74, 95% CI 1.25 to 6.02) had a significantly increased risk of sedation. Risperidone showed a significantly decreased risk of sedation compared with quetiapine (OR=0.50, 95% CI 0.32 to 0.79). Olanzapine showed a significantly increased risk of sedation compared with risperidone (OR=1.46, 95% CI 1.01 to 2.12). According to SUCRA, placebo had the highest probability of safety, followed by brexpiprazole, risperidone, aripiprazole, olanzapine and quetiapine (online supplemental material 16).

Table 2 Results of network meta-analysis (NMA) for efficacy outcome

Brexpiprazole					
–1.16 (–2.36 to 0.05)	Risperidone				
–1.33 (–2.60 to –0.06)	–0.17 (–1.03 to 0.68)	Quetiapine			
–1.44 (–2.77 to –0.12)	–0.29 (–1.23 to 0.65)	–0.12 (–1.15 to 0.92)	Olanzapine		
–1.61 (–3.07 to –0.15)	–0.45 (–1.66 to 0.75)	–0.28 (–1.54 to 0.99)	–0.16 (–1.49 to 1.16)	Aripiprazole	
–1.77 (–2.80 to –0.74)	–0.62 (–1.24 to 0.01)	–0.44 (–1.17 to 0.29)	–0.33 (–1.16 to 0.51)	–0.16 (–1.19 to 0.87)	Placebo

Note: Comparisons are based on SMD (95% CI) between treatments. The bold font in the cell represents statistical significance.
CI, credible interval; SMD, standard mean difference.

Table 3 Results of network meta-analysis (NMA) for acceptability and tolerability

Aripiprazole	**0.61 (0.37 to 0.99)**	0.69 (0.46 to 1.05)	0.75 (0.53 to 1.07)	0.71 (0.47 to 1.08)	**0.72 (0.54 to 0.96)**
0.87 (0.23 to 3.34)	Brexpiprazole	1.14 (0.70 to 1.87)	1.25 (0.80 to 1.94)	1.17 (0.71 to 1.93)	1.19 (0.80 to 1.76)
0.25 (0.08 to 0.78)	0.29 (0.08 to 1.01)	Olanzapine	1.09 (0.79 to 1.51)	1.03 (0.69 to 1.53)	1.04 (0.78 to 1.39)
0.92 (0.33 to 2.54)	1.05 (0.33 to 3.33)	**3.67 (1.66 to 8.11)**	Risperidone	0.94 (0.67 to 1.33)	0.95 (0.78 to 1.16)
0.93 (0.31 to 2.82)	1.07 (0.31 to 3.67)	**3.71 (1.46 to 9.42)**	1.01 (0.46 to 2.25)	Quetiapine	1.01 (0.75 to 1.37)
1.51 (0.64 to 3.59)	1.73 (0.62 to 4.81)	**6.02 (2.87 to 12.66)**	1.64 (0.97 to 2.78)	1.62 (0.81 to 3.24)	Placebo

Note: The orange cell represents the acceptability (OR, 95% CI) and the grey cell represents the tolerability (OR, 95% CI). The bold font in the cell represents statistical significance.
CI, credible interval; OR, odds ratio.

EPS was reported in nine trials involving quetiapine, risperidone, olanzapine and brexpiprazole. The NMA showed that risperidone (OR=2.35, 95% CI 1.62 to 3.39) and olanzapine (OR=2.57, 95% CI 1.43 to 4.63) had a significantly increased risk of EPS compared with placebo. Risperidone (OR=2.90, 95% CI 1.22 to 6.90) and olanzapine (OR=3.18, 95% CI 1.24 to 8.17) also showed a significantly increased risk of EPS compared with quetiapine. According to SUCRA, quetiapine had the greatest probability of safety, followed by placebo, brexpiprazole, risperidone and olanzapine (online supplemental material 17).

Urinary symptoms were reported in 13 trials involving quetiapine, risperidone, olanzapine, brexpiprazole and aripiprazole. The NMA showed that quetiapine (OR=2.73, 95% CI 1.34 to 5.54) showed a significantly increased risk of urinary symptoms compared with placebo. According to SUCRA, placebo had the highest probability of safety for urinary symptoms, followed by aripiprazole, olanzapine, brexpiprazole, risperidone and quetiapine (online supplemental material 18).

DISCUSSION

This research extends previous NMAs, regardless of the number of articles or the variety of drug types. The present study compares the efficacy, acceptability and tolerability of SGA treatment for BPSD. Data were analysed from 21 trials, which included 6374 patients with dementia randomly assigned to five SGAs or placebo. Evaluations of heterogeneity, inconsistency, risk of bias through various domains, and up-to-date tools and implementation of sensitivity analysis make our results generally robust (online supplemental material 9,10). Instead of investigating efficacy outcomes by different tools separately, we extracted the primary outcome from the original study and standardised the results with SMD across five valid scales, of which eight were NPI, four were BEHAVE-AD, four were CMAI, three were BPRS and one was PANSS, with the aim to evaluate the efficacy from another perspective. We also investigated the acceptability and tolerability of SGAs.

The first strong point of this study is that we enriched this topic by including three timely brexpiprazole trials, which have not been jointly analysed before. It has been recently licensed by the FDA for the treatment of agitation due to AD.[39] We found that brexpiprazole was significantly more efficacious than placebo, quetiapine, olanzapine and aripiprazole. Notably, the efficacy outcomes of the included brexpiprazole trials were measured by CMAI that strongly related to aggressive behaviour, which means brexpiprazole may provide important benefits for caregivers and healthcare systems, since both caregiver burden and healthcare and social care costs increase with agitation severity.[40] Meanwhile, agitation is also associated with more rapid cognitive decline and increases the risk of patients settling in residential care settings.[41]

For acceptability, aripiprazole was better than placebo and brexpiprazole. No statistically significant difference is observed in the comparison between other SGAs. A previous NMA on the treatment of BPSD[11] involving aripiprazole, olanzapine, quetiapine and risperidone evaluated outcomes from different scales separately and found that compared with placebo, aripiprazole improved the NPI, CMAI and BPRS. Interestingly, our acceptability (reflecting the mixed effects of efficacy and safety) also showed that aripiprazole is the only and the best SGA, which means aripiprazole may have rich potential in the treatment of BPSD. This provides further evidence for clinical guidance.

We also found that for tolerability, olanzapine was worse than placebo and also worse than risperidone, quetiapine and aripiprazole. A previous study illustrated that olanzapine was not only associated with improvement over placebo, but also significantly increased the risk of CAVEs and sedation.[11] This raises the red flag again for the use of olanzapine for BPSD. Although no significant tolerability differences were observed between olanzapine and brexpiprazole, brexpiprazole did not show any worse tolerability than placebo. Brexpiprazole has a good effect on agitation, indicating that brexpiprazole may be a good strategy in the management of BPSD.

The AE results of the present study were generally in line with the previous study. There is no single safe SGA, and each SGA presents a different risk of AEs. Our results suggest that quetiapine presents good safety in case of CVAE and brexpiprazole has better safety in terms of falls. As in the previous study, each included SGA has an increased risk of sedation, while brexpiprazole showed related safety in sedation among included SGAs. In terms of EPS, quetiapine had the greatest probability of safety, which is in line with the previous study. People living with Parkinson's disease should avoid the use of risperidone and olanzapine due to the high risk of EPS.

Overall, this study found that aripiprazole was the most acceptable SGA for BPSD, brexpiprazole was the most effective, and olanzapine was the most likely to cause adverse reactions. Our results show that brexpiprazole, as a new drug, can decrease the risk of falls and has a relatively low risk of sedation in the included SGA. However, the treatment of BPSD is not limited to SGA, and some studies have also explored the potential effects of antidepressants. A novel medication acting on 5-hydroxytryptamine (5-HT) named pimavanserin has shown efficacy in patients with hallucinations and delusions associated with Parkinson's disease psychosis and is approved for that indication.[42] It has also recently been studied in dementia-related psychosis. In future, medications that act across different targets can be included in comprehensive analyses.

Our study had several strengths. To our knowledge, this NMA is the first to update the evidence for SGA treatment of BPSD and to include brexpiprazole in the joint analysis. We enrich the evidence on this topic from new perspectives such as acceptability,

tolerance and efficacy. The conclusion based on a vast majority of subjects was substantially consistent with previous reviews, and we further verified the accuracy of contemporary clinical guidelines and provided information about brexpiprazole.

Several limitations of this study should also be considered. First, we did not consider the dose in the analysis since most studies lack relative information. In some trials, a relatively large difference between the virtual and predefined doses in some comparator groups was observed. In addition, it was formidable to define a precise cut-off value for low and high doses of each drug in practical trials. High-quality studies covering different SGAs and different doses of RCTs are needed to develop a dose–effect meta-analysis. Second, all of the included studies included individuals with AD, and only a small number of studies partially included other types of dementia, which limited sensitivity analysis for different types of dementia. Most studies implemented in nursing homes should also be considered as a limitation. We also need to realise that the patients in long-term trials were more likely to experience side effects and decreased drug tolerance.

It is important to further explore the findings from a real-world setting to capture adverse drug events that RCTs are not powered to detect. We hope that including all types of SGA interventions in our NMA may help clinicians make informed decisions when managing BPSD. Despite these limitations, the findings from this NMA represent the most comprehensive analysis of the available evidence.

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