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ORIGINAL RESEARCH

Comparison of the efficacy and safety of 4 and 2 mg/day brexpiprazole for acute schizophrenia: a meta-analysis of double-blind, randomized placebo-controlled trials

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Purpose: The purpose of this study was to compare the efficacy and safety of brexpiprazole 4 mg/day (B4) and 2 mg/day (B2) for treating acute schizophrenia.

Patients and methods: We performed three categorical meta-analyses (B4 vs placebo, B2 vs placebo, and B4 vs B2) of double-blind, randomized placebo-controlled trials (DBRCTs) that reported improvements in the Positive and Negative Syndrome Scale (PANSS) scores, response rate, Clinical Global Impression–Improvement and Severity (CGI-I and CGI-S) scores, discontinuation rate, and incidence of individual adverse events.

Results: We identified three DBRCTs with 1,444 patients. Both B4 and B2 were superior to placebo for PANSS total score (B4: standardized mean difference [SMD] =–0.30, 95% CI =–0.43, –0.17; B2: SMD =–0.30, 95% CI =–0.46, –0.13), PANSS negative score, response rate, CGI-S score, and CGI-I score. B2, but not B4, was superior to placebo for the PANSS positive score. However, there was considerable heterogeneity in the meta-analysis for B4's PANSS positive score, which disappeared after excluding a 2018 Japanese study from the meta-analysis that included more patients on a high-dose antipsychotic prior to their participation. A meta-analysis that excluded the data from the abovementioned patients showed B4 to be superior to the placebo in terms of the PANSS positive score (SMD =–0.22, 95% CI =–0.40, –0.03). B2, but not B4, was associated with a lower incidence of all-cause discontinuation compared with placebo. Both B4 and B2 were superior to placebo for discontinuation due to adverse events and schizophrenia, but both were associated with a higher incidence of weight gain compared with placebo. B4 was also associated with a higher risk of extrapyramidal symptoms than B2.

Conclusion: Both B4 and B2 benefitted patients with schizophrenia, particularly those who were not previously on high-dose antipsychotics. Both the regimens were well-tolerated, but carried a risk of weight gain and extrapyramidal symptoms, although the latter risk was higher for B4 than B2.

Keywords: schizophrenia, brexpiprazole 2 mg/day, brexpiprazole 4 mg/day, Positive and Negative Syndrome Scale score, response rate, safety outcomes, systematic review, meta-analysis

Introduction

Brexpiprazole was approved by the US Food and Drug Administration in July 2015 for the treatment of patients with schizophrenia and as an adjunctive treatment for patients with major depressive disorder. Its effect is thought to be mediated through a combination of partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2 receptors and antagonist activity at serotonin 5-HT_{2A} receptors.[1] Brexpiprazole demonstrates high

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affinity not only for these receptors but also for noradrenaline alpha$_{1B/2C}$ receptors.[1]

A recent systematic review and meta-analysis of double-blind, randomized placebo-controlled trials (DBRCTs) of brexpiprazole for the treatment of acute schizophrenia included one Phase II study and two Phase III studies.[2] The included Phase II study investigated brexpiprazole at 0.25 mg/day (fixed), 1.0±0.5 mg/day (flexible), 2.5±0.5 mg/day (flexible), and 5.0±1 mg/day (flexible), in comparison with placebo or aripiprazole 15±5 mg/day (flexible).[3] The included Phase III studies investigated fixed-dose brexpiprazole at 0.25 mg/day (Correll study), 1 mg/day (Kane study), 2 mg/day, and 4 mg/day, compared with placebo.[4,5] The meta-analysis showed that fixed-dose brexpiprazole 4 and 2 mg/day were both superior to placebo with regard to improvements in total, positive subscale, and negative subscale scores in the Positive and Negative Syndrome Scale (PANSS),[6] as well as the response rate.[2] The report concluded that both brexpiprazole 4 and 2 mg/day were effective in treating acute schizophrenia.[2]

Recently, a DBRCT of brexpiprazole for patients with acute schizophrenia as a Phase II/III study was conducted in Japan.[7] Surprisingly, this study found that brexpiprazole 2 mg/day, but not 4 mg/day, was superior to placebo for improvements in the PANSS total score and that neither brexpiprazole 4 nor 2 mg/day were superior to placebo for improvements in the PANSS positive subscale score and response rate.[7] On the basis of these findings, brexpiprazole 4 mg/day was not approved in Japan for the treatment of schizophrenia.

However, there were two notable differences in patient characteristics between the Japanese study[7] and the other two studies[4,5] (Table 1). First, fewer patients were included in the Japanese study than in other studies, suggesting that the lack of statistical significance for some efficacy outcomes may have been a type II error resulting from the small sample size. Second, the Japanese study included a higher proportion of patients who had been prescribed an antipsychotic polypharmacy or high-dose medication prior to participating in the study. In addition, the Japanese study showed a higher mean age than the Correll and Kane studies.

It is possible that most of those chronic patients on polypharmacy or high-dose prescriptions may have experienced dopamine supersensitivity psychosis, affecting their response to brexpiprazole. A recent meta-analysis of aripiprazole (which is also a dopamine D_2 receptor partial agonist) for chronic schizophrenia showed that, compared with switching to another antipsychotic, a switch to aripiprazole was associated with a higher risk of study discontinuation because of a lack of efficacy.[8] Dopamine supersensitivity results in exaggerated responsiveness of the dopamine system; this system is involved in causing psychosis, so the potential for psychosis rebound may be higher when switching to drugs such as a dopamine D_2 receptor partial agonist.[9,10] Indeed, the Japanese study showed similar discontinuation rates for brexpiprazole 4 mg/day (39.8%) and placebo (39.7%). In the other two studies, the active drug treatment arms showed a lower discontinuation rate than the placebo arm (Table 1). It is possible that the antipsychotic medication taken by patients in the Japanese study who had previously been on high-dose prescriptions may not have completely washed out during the screening phase (14 days). Higher dosages or longer treatment durations of dopamine antagonists prior to the Japanese study could lead to continued dopaminergic supersensitivity during the study. Therefore, such patients may not have been appropriate for a Phase II/III trial evaluating the efficacy and safety of a new antipsychotic.

The present study addresses two clinical questions raised by the results of the Japanese study: 1) Does brexpiprazole 4 mg/day have any benefit for the treatment of acute schizophrenia? 2) Are there differences in efficacy and safety between brexpiprazole 4 and 2 mg/day for the treatment of acute schizophrenia? The aim of this study, therefore, was to compare the efficacy (psychopathology, response rate, and clinical global impression) and safety (the discontinuation rate and the incidence of individual adverse events) of brexpiprazole 4 and 2 mg/day and placebo for the treatment of schizophrenia. To increase statistical power, we performed three categorical meta-analyses: brexpiprazole 4 mg/day vs placebo, brexpiprazole 2 mg/day vs placebo, and brexpiprazole 4 mg/day vs brexpiprazole 2 mg/day. Moreover, to address concerns about the potential dopamine supersensitivity, we also performed an additional meta-analysis that excluded the data from the patients who were on high-dose antipsychotics prior to the study.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[11] and was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/; CRD42018091230).

Search strategy and inclusion criteria

We performed a systematic literature review based on the PICO strategy (which considers participants/population, interventions, comparator/control, and outcomes) as follows.

Table 1 Study, patient, and treatment characteristics of the included double-blind, randomized, placebo-controlled trials

	Correll et al[4] (Phase III, NCT01396421)	Japan 2018[7] (Phase II/III, NCT01451164)	Kane 2015[5] (Phase III, NCT01393613)
Patients	Experienced an acute exacerbation of psychotic symptoms and marked deterioration of usual function and would benefit from hospitalization or continued hospitalization for treatment. BPRS T score ≥40 and score of ≥4 on two or more BPRS items (hallucinatory behavior, unusual thought content, conceptual disorganization, or suspiciousness)	Experienced an acute exacerbation of psychotic symptoms and marked deterioration of usual function and would benefit from hospitalization or continued hospitalization for treatment. BPRS T score ≥40 and score of ≥4 on two or more BPRS items (hallucinatory behavior, unusual thought content, conceptual disorganization, or suspiciousness)	Experienced an acute exacerbation of psychotic symptoms and marked deterioration of usual function and would benefit from hospitalization or continued hospitalization for treatment. BPRS T score ≥40 and score of ≥4 on two or more BPRS items (hallucinatory behavior, unusual thought content, conceptual disorganization, or suspiciousness)
14 days screening phase	Washout from previous antipsychotics (≥7 days) and prohibited concomitant medications	Washout from previous antipsychotics (≥7 days) and prohibited concomitant medications	Washout from previous antipsychotics (≥7 days) and prohibited concomitant medications
Countries (%)	United States (35.8), Ukraine (18.1), Romania (17.1), Serbia (11.8), Latvia (4.9), Malaysia (3.3), Japan (3.0), Poland (2.5), South Korea (2.4), and Canada (1.1)	Japan (100)	Colombia (NR), Croatia (NR), Mexico (NR), Philippines (NR), Russia (NR), Slovakia (NR), Taiwan (NR), and United States (NR)
Diagnosis	DSM-IV-TR diagnosis of schizophrenia confirmed by MINI	DSM-IV-TR diagnosis of schizophrenia confirmed by MINI	DSM-IV-TR diagnosis of schizophrenia confirmed by MINI
Number of patients (PBO/BRE2/BRE4)	184/182/180	116/115/113	184/186/184
Age (mean age ± SD: PBO/BRE2/BRE4)	18–65 years (39.7±10.8/39.6±10.2/40.8±11.0)	18–64 years (45.0±11.9/43.3±12.0/44.1±11.9)	18–65 years (39.3±10.8/36.9±10.9/38.6±11.0)
% male (PBO/BRE2/BRE4)	64.1/61.0/61.7	44.0/53.0/48.7	60.3/65.6/61.4
% antipsychotic polypharmacy and high-dose prescription patients[a] (PBO/BRE2/BRE4)	1.10/0.00/2.20	6.20/6.20/11.0	0.00/0.00/0.00
Mean PANSS T at baseline ± SD (PBO/BRE2/BRE4)	95.9±11.5/95.9±13.7/94.9±12.2	97.2±19.3/96.6±19.2/96.4±15.7	94.8±13.0/96.3±12.8/95.1±12.5
Result: % discontinuation rate due to all cause (PBO/BRE2/BRE4)	40.2/31.9/32.8	39.7/29.6/39.8	35.9/30.6/29.3
Result: PANSS T score[b]	BRE4 > PBO, BRE2 > PBO	BRE4 = PBO, BRE2 > PBO	BRE4 > PBO, BRE2 = PBO
Result: PANSS P score[b]	BRE4 > PBO, BRE2 > PBO	BRE4 = PBO, BRE2 = PBO	BRE4 > PBO, BRE2 = PBO
Result: PANSS N score[b]	BRE4 > PBO, BRE2 > PBO	BRE4 > PBO, BRE2 > PBO	BRE4 > PBO, BRE2 = PBO
Result: response rate[b,c]	BRE4 > PBO, BRE2 > PBO	BRE4 = PBO, BRE2 = PBO	BRE4 > PBO, BRE2 = PBO

Notes: [a]Criteria of antipsychotic polypharmacy and high-dose prescription patients were administration of >3 antipsychotic agents with a mean total chlorpromazine dose equivalence of >1,000 mg/day or administration of >3 antipsychotic agents with >2 antipsychotics having a chlorpromazine dose equivalence of >600 mg/day, from 30 days prior to informed consent to the day before hospital admission. [b]A>B: A was superior to B, A=B: A was similar to B. [c]Responder was defined as a ≥30% reduction in the PANSS total score from baseline or CGI-I score of 1 (very much improved) or 2 (much improved) at week 6.
Abbreviations: BPRS T, Brief Psychiatric Rating Scale total; BRE, brexpiprazole; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; MINI, Mini International Neuropsychiatric Interview; NR, not reported; PANSS (T, P or N), Positive and Negative Syndrome Scale (T: total, P: positive subscale, N: negative subscale); PBO, placebo.

The participants/population were patients with acute schizophrenia and/or schizophrenia spectrum disorder. The interventions were fixed-dose brexpiprazole treatment at 2 or 4 mg/day. The comparator/control was placebo treatment. The outcomes were efficacy and safety, as described in detail in the following section.

The analysis included only DBRCTs lasting ≥4 weeks that investigated fixed-dose brexpiprazole treatment in patients with acute schizophrenia. To identify relevant studies, two of the present authors (TK and YM) independently searched Scopus, MEDLINE, and the Cochrane library, without language restrictions, from inception to May 22, 2018. The search terms were "schizophrenia" and "brexpiprazole." The authors also searched ClinicalTrials.gov and the International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/). This ensured that the search was as comprehensive as possible and minimized the possibility of publication bias. Four authors (T Kishi, Y Matuda,

Y Matsui, and K Oya) independently assessed the identified studies based on the inclusion and exclusion criteria. In addition, the reference lists of the selected articles and reviews were searched for further relevant published and unpublished studies, including conference abstracts.

Data synthesis and outcome measures

The primary efficacy outcome was an improvement in the PANSS total score. The secondary efficacy outcomes, which were considered as important as the primary outcome, were improvements in the PANSS positive and negative subscale scores and the response rate at 6 weeks. The response rate was defined as a ≥30% reduction in the PANSS total score from baseline or a score of 1 (very much improved) or 2 (much improved) in the Clinical Global Impression–Improvement (CGI-I).[12] The PANSS scores have been used as outcome measures in many treatment efficacy studies and are increasingly used in clinical practice.[13] Other outcomes measured in this study were improvements in the Clinical Global Impression–Severity (CGI-S)[12] scores, the discontinuation rate due to all causes, adverse events, inefficacy, and the incidence of individual adverse events.

Data extraction

Seven authors (T Kishi, Y Matuda, Y Matsui, K Oya, I Nomura, M Okuya, and K Sakuma) independently extracted data from the selected studies. Only intention-to-treat or full analysis set analyses were used. When data necessary for the meta-analysis were missing, we contacted the authors of that study and requested unpublished data (personal communication to Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan; https://www.otsuka.co.jp/en/).

Meta-analysis methods

The meta-analysis was performed using Review Manager software.[14] We meta-analyzed only outcomes for which the data from all the three included DBRCTs were available. A random-effects model was used because of potential heterogeneity across the studies. Dichotomous outcomes were presented as risk ratios (RRs) with a 95% CI. Continuous outcomes were analyzed using the standardized mean difference (SMD). When intergroup differences with respect to treatment efficacy or adverse events based on RRs were significant, the number needed to treat (NNT) or the number needed to harm (NNH) was calculated from the risk difference (RD) using the following formula: NNT or NNH = 1/RD.

Heterogeneity was tested using the I^2 statistics, with I^2 ≥50% being considered to indicate considerable heterogeneity.[15] When we detected considerable heterogeneity in the primary and secondary outcomes, we performed sensitivity analyses to identify confounding factors for these outcomes.

As explained in the "Introduction" section, we performed a further meta-analysis with respect to PANSS scores, including only the patients who were not on high-dose antipsychotic prescriptions before participating in the study (with at least 6 weeks at a dose equivalent to 1,000 mg/day chlorpromazine).[16]

Because the Cochrane Handbook suggests using a funnel plot only when ≥10 studies are included in the meta-analysis,[15] we instead used Egger's regression to detect publication bias in the meta-analyses (Comprehensive Meta-Analysis software version 2; Biostat Inc., Englewood, NJ, USA). Finally, the methodological quality of the included articles was assessed according to the Cochrane Risk of Bias criteria (Cochrane Collaboration, http://www.cochrane.org/).

Results

Study characteristics

Of the 99 studies initially identified in our literature search, we excluded 27 after a review of the titles and abstracts, and 29 more after a full-text review (28 review articles and one study of flexible-dose brexpiprazole;[3] Figure S1). We did not retrieve any additional studies from the clinical trial registries (Figure S1). Finally, three DBRCTs[4,5,7] were selected for inclusion. The total numbers of patients in the various arms were as follows: brexpiprazole 4 mg/day: n=477; brexpiprazole 2 mg/day: n=483; and placebo: n=484. A summary of the included studies is presented in Table 1. The inclusion criteria, duration of the washout phase, study design, and process for diagnosis were almost identical in the three studies, and all lasted 6 weeks. All three studies were sponsored by pharmaceutical companies and were published in English. They were of a high-quality design (DBRCTs of fixed-dose brexpiprazole treatment, with intention-to-treat or full analysis set populations). The methodological quality of the included studies was assessed according to the Cochrane Risk of Bias criteria (Figure S2).

Compared with the Correll and Kane studies, the Ishigooka study (ie, the Japanese study) had a smaller sample size, with a higher mean age, a greater proportion of women, and a higher percentage of patients who were on antipsychotic polypharmacy and high-dose prescriptions before starting the trial (6.2% in the placebo arm, 6.2% in the brexpiprazole 2 mg arm, and a notable 11.0% in the brexpiprazole 4 mg arm). In addition, although both the Correll and Kane studies observed lower all-cause discontinuation with brexpiprazole

4 mg/day than with placebo, the Ishigooka study reported similar levels of discontinuation in the brexpiprazole 4 mg and placebo arms. In the Correll study, both brexpiprazole 4 and 2 mg/day were superior to placebo for all the efficacy outcomes. However, the Kane study reported that brexpiprazole 4 mg/day, but not 2 mg/day, was superior to placebo in all efficacy outcomes. Although the Ishigooka study showed that brexpiprazole 4 and 2 mg/day were both superior to placebo with regard to improvements in the PANSS negative subscale score, only brexpiprazole 2 mg/day was superior to placebo in improvements in the PANSS total score, and neither brexpiprazole 4 nor 2 mg/day was superior to placebo in improvements in the PANSS positive subscale score and response rate. Thus, the efficacy results of the studies included in the current meta-analysis were inconsistent. We therefore performed the following meta-analyses to obtain absolute evidence of the efficacy of brexpiprazole for the treatment of schizophrenia.

Efficacy outcomes

In our meta-analyses, both brexpiprazole 4 and 2 mg/day were superior to placebo in improvements in the PANSS total score (4 mg: SMD =–0.30, 95% CI =–0.43, –0.17, $P<0.00001$, I^2 =0%; 2 mg: SMD =–0.30, 95% CI =–0.46, –0.13, $P=0.0003$, I^2 =36%) (Table 2). They were also superior to placebo for the PANSS negative subscale score, CGI-S and CGI-I scores, and response rates (Table 2). The data in each treatment group showed no publication bias with respect to the primary outcome (Egger's test *P*-values: 4 mg/day, $P=0.189$; 2 mg/day, $P=0.849$).

In our meta-analyses for the PANSS positive subscale score, brexpiprazole 2 mg/day, but not 4 mg/day, was superior to placebo (Table 2). However, there was considerable heterogeneity in the meta-analysis of brexpiprazole 4 mg/day (I^2 =72%). We therefore performed a sensitivity analysis. After excluding the Ishigooka study from the primary meta-analysis of brexpiprazole 4 mg/day, the heterogeneity disappeared (I^2 =0%), and brexpiprazole 4 mg/day was observed to be superior to placebo (SMD =–0.30, 95% CI =–0.44, –0.15, $P<0.0001$).

Brexpiprazole 4 and 2 mg/day were both superior to placebo for the PANSS negative subscale score (Table 2). However, there was considerable heterogeneity in the brexpiprazole 2 mg/day meta-analysis (I^2 =53%). After excluding

Table 2 Efficacy outcomes

Outcome	Comparison	n	SMD	95% CI	*P*-value	I^2 (%)
PANSS total score	BRE 4 mg vs placebo	939	–0.30	–0.43, –0.17	<0.00001	0
	BRE 2 mg vs placebo	943	–0.30	–0.46, –0.13	0.0003	36
	BRE 4 mg vs BRE 2 mg	940	0.00	–0.19, 0.19	0.98	53[a]
PANSS positive score	BRE 4 mg vs placebo	939	–0.18	–0.42, 0.07	0.16	72[b]
	BRE 2 mg vs placebo	943	–0.17	–0.32, –0.02	0.03	30
	BRE 4 mg vs BRE 2 mg	940	–0.01	–0.23, 0.20	0.91	63[c]
PANSS negative score	BRE 4 mg vs placebo	939	–0.30	–0.43, –0.17	<0.00001	0
	BRE 2 mg vs placebo	943	–0.32	–0.51, –0.13	0.001	53[d]
	BRE 4 mg vs BRE 2 mg	940	0.01	–0.12, 0.14	0.90	0
CGI-S	BRE 4 mg vs placebo	942	–0.25	–0.42, –0.08	0.004	43
	BRE 2 mg vs placebo	947	–0.22	–0.35, –0.10	0.0006	0
	BRE 4 mg vs BRE 2 mg	941	–0.02	–0.22, 0.18	0.83	58
CGI-I	BRE 4 mg vs placebo	942	–0.28	–0.49, –0.07	0.008	61
	BRE 2 mg vs placebo	947	–0.29	–0.42, –0.16	<0.0001	0
	BRE 4 mg vs BRE 2 mg	941	0.01	–0.20, 0.21	0.96	60
Outcome	**Comparison**	**n**	**RR**	**95% CI**	***P*-value**	**I^2 (%)**
Response rate	BRE 4 mg vs placebo	939	0.82	0.70, 0.96	0.02[e]	67[f]
	BRE 2 mg vs placebo	943	0.86	0.76, 0.98	0.03[g]	52[h]
	BRE 4 mg vs BRE 2 mg	940	0.95	0.83, 1.10	0.50	49
Discontinuation rate due to inefficacy	BRE 4 mg vs placebo	961	0.72	0.39, 1.32	0.29	42
	BRE 2 mg vs placebo	967	1.00	0.68, 1.47	0.99	0
	BRE 4 mg vs BRE 2 mg	960	0.72	0.44, 1.15	0.17	13

Notes: [a]After excluding Kane study data, considerable heterogeneity disappeared (I^2 =0%). 4 mg was similar to 2 mg (SMD =–0.09, 95% CI =–0.07, 0.26, $P=0.26$). [b]After excluding Ishigooka study data, considerable heterogeneity disappeared (I^2 =0%). 4 mg was superior to placebo (SMD =–0.30, 95% CI =–0.44, –0.15, $P<0.0001$). [c]After excluding Ishigooka study data, considerable heterogeneity disappeared (I^2 =4%). 4 mg was similar to 2 mg (SMD =–0.11, 95% CI =–0.26, 0.04, $P=0.16$). [d]After excluding Kane 2015 study data, considerable heterogeneity disappeared (I^2 =0%), 2 mg was superior to placebo (SMD =–0.41, 95% CI =–0.57, –0.25, $P<0.00001$). [e]NNT =8. [f]After excluding Ishigooka study data, considerable heterogeneity disappeared (I^2 =0%). 4 mg was superior to placebo (RR =0.76, 95% CI =0.67, 0.85, $P<0.00001$, NNT =6). [g]NNT =10. [h]After excluding Correll et al study data, considerable heterogeneity disappeared (I^2 =0%). 2 mg was not superior to placebo (RR =0.92, 95% CI =0.83, 1.02, $P=0.11$).

Abbreviations: 95% CI, 95% confidence interval; BRE, brexpiprazole; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity; NNT, number needed to treat; PANSS, Positive and Negative Syndrome Scale; RR, risk ratio; SMD, standardized mean difference.

Table 3 A further meta-analysis with respect to PANSS scores, including only the patients who were not on high-dose antipsychotic prescriptions before participating in the study (with at least 6 weeks at a dose equivalent to 1,000 mg/day chlorpromazine)

Outcome	Comparison	n	SMD	95% CI	*P*-value	I^2 (%)
PANSS total score	BRE 4 mg vs placebo	904	–0.34	–0.47, –0.20	<0.00001	0
	BRE 2 mg vs placebo	913	–0.29	–0.45, –0.12	0.0005	34
	BRE 4 mg vs BRE 2 mg	905	–0.05	–0.19, 0.09	0.51	13
PANSS positive score	BRE 4 mg vs placebo	904	–0.22	–0.40, –0.03	0.02	49
	BRE 2 mg vs placebo	913	–0.15	–0.33, 0.02	0.08	42
	BRE 4 mg vs BRE 2 mg	905	–0.07	–0.20, 0.06	0.27	0
PANSS negative score	BRE 4 mg vs placebo	904	–0.30	–0.43, –0.17	<0.00001	0
	BRE 2 mg vs placebo	913	–0.28	–0.42, –0.13	0.0001	16
	BRE 4 mg vs BRE 2 mg	905	–0.02	–0.15, 0.11	0.71	0

Abbreviations: 95% CI, 95% confidence interval; BRE, brexpiprazole; PANSS, Positive and Negative Syndrome Scale; SMD, standardized mean difference.

the Kane study from the 2 mg/day meta-analysis, the heterogeneity disappeared (I^2 =0%), and brexpiprazole 2 mg/day was observed to be superior to placebo (SMD =–0.41, 95% CI =–0.57, –0.25, P<0.00001) (Table 2).

Although brexpiprazole 4 and 2 mg/day were both superior to placebo in the response rate, these meta-analyses involved considerable heterogeneity (4 mg/day, I^2 =67%; 2 mg/day, I^2 =52%). After excluding the Ishigooka study from the 4 mg/day meta-analysis, the heterogeneity disappeared (I^2 =0%), and the effect size increased (RR =0.76, 95% CI =0.67, 0.85, P<0.00001, NNT =6). Similarly, after excluding the Correll study from the 2 mg/day meta-analysis, the heterogeneity disappeared (I^2 =0%); however, the superiority of brexpiprazole 2 mg/day over placebo also disappeared (RR =0.92, 95% CI =0.83, 1.02, P=0.11).

Our meta-analysis produced no significant differences in any efficacy outcomes between brexpiprazole 4 and 2 mg/day (Table 2). However, we detected considerable heterogeneity in the PANSS total (I^2 =53%) and positive subscale scores (I^2 =63%). After excluding the Kane study data from the meta-analysis of PANSS total score, the heterogeneity disappeared (I^2 =0%) and there was no difference in PANSS total score between 4 and 2 mg/day. After excluding the Ishigooka study data from the meta-analysis of the PANSS positive subscale score, its heterogeneity disappeared (I^2 =4%). There was also no difference in the PANSS positive subscale score between 4 and 2 mg/day (Table 2).

Additional meta-analysis

The Ishigooka study included more patients on high-dose antipsychotics before the trial than the other studies, especially in the brexpiprazole 4 mg/day arm. Because we thought that the data from those patients might have influenced the efficacy results of the Ishigooka study, we performed a further meta-analysis using data from only the patients who were not on high-dose antipsychotic prescriptions before participating in the trials; this resulted in no change in the data from the Correll and Kane studies. In this meta-analysis, brexpiprazole 4 and 2 mg/day were both superior to placebo for the PANSS total and negative subscale scores (Table 3). Furthermore, brexpiprazole 4 mg/day was superior to placebo for the PANSS positive score without the considerable heterogeneity seen in the earlier meta-analysis (Table 3). There was also a marginal difference between brexpiprazole 2 mg/day and placebo in improvements in the PANSS positive subscale score (Table 3). There were no significant differences in PANSS total, positive, and negative scores between brexpiprazole 4 and 2 mg/day (Table 3).

Safety outcomes

Brexpiprazole 2 mg/day, but not 4 mg/day, was associated with a lower all-cause discontinuation than placebo (Table 4). Compared with placebo, both brexpiprazole 4 and 2 mg/day were associated with lower discontinuation rates resulting from adverse events and schizophrenia; however, both the treatment groups were associated with a higher incidence of weight gain than observed in the placebo group (Table 4).

There were no significant differences between brexpiprazole 4 or 2 mg/day and placebo in the meta-analysis results for any of the safety outcomes other than the Simpson-Angus Scale/Drug Induced Extra-Pyramidal Symptoms Scale (SAS/DIEPSS) score, for which brexpiprazole 2 mg/day, but not 4 mg/day, was marginally superior to placebo (Table 4). Finally, there was a significant difference in SAS/DIEPSS score between brexpiprazole 4 and 2 mg/day (Table 4).

Discussion

We performed meta-analyses of the efficacy and safety of brexpiprazole 4 and 2 mg/day for the treatment of schizophrenia

Table 4 Safety outcomes

Outcome	Comparison	n	RR	95% CI	*P*-value	I^2 (%)
Discontinuation rate due to all cause	BRE 4 mg vs placebo	961	0.87	0.73, 1.03	0.10	0
	BRE 2 mg vs placebo	967	0.80	0.67, 0.96	0.01[a]	0
	BRE 4 mg vs BRE 2 mg	960	1.08	0.89, 1.30	0.44	5
Discontinuation rate due to adverse events	BRE 4 mg vs placebo	961	0.66	0.47, 0.92	0.02[b]	0
	BRE 2 mg vs placebo	967	0.51	0.35, 0.74	0.0003[c]	0
	BRE 4 mg vs BRE 2 mg	960	1.28	0.85, 1.92	0.23	0
Serious adverse event	BRE 4 mg vs placebo	961	0.47	0.22, 1.00	0.05	0
	BRE 2 mg vs placebo	966	0.60	0.30, 1.20	0.15	0
	BRE 4 mg vs BRE 2 mg	959	0.78	0.34, 1.78	0.56	0
Death	BRE 4 mg vs placebo	961	3.08	0.13, 74.80	0.49	NA
	BRE 2 mg vs placebo	No death was reported in both the groups				
	BRE 4 mg vs BRE 2 mg	960	3.05	0.13, 74.15	0.49	NA
At least one adverse event	BRE 4 mg vs placebo	961	0.96	0.81, 1.14	0.64	67
	BRE 2 mg vs placebo	966	0.95	0.86, 1.05	0.31	1
	BRE 4 mg vs BRE 2 mg	959	1.01	0.91, 1.12	0.84	0
Schizophrenia	BRE 4 mg vs placebo	961	0.71	0.51, 0.99	0.04[d]	0
	BRE 2 mg vs placebo	966	0.50	0.35, 0.73	0.0003[e]	0
	BRE 4 mg vs BRE 2 mg	959	1.39	0.93, 2.09	0.11	0
Agitation	BRE 4 mg vs placebo	961	0.82	0.50, 1.35	0.44	0
	BRE 2 mg vs placebo	966	0.85	0.41, 1.74	0.65	51
	BRE 4 mg vs BRE 2 mg	959	0.97	0.58, 1.64	0.92	0
Headache	BRE 4 mg vs placebo	961	0.94	0.53, 1.68	0.83	44
	BRE 2 mg vs placebo	966	1.00	0.63, 1.60	0.99	25
	BRE 4 mg vs BRE 2 mg	959	0.92	0.52, 1.65	0.79	44
Insomnia	BRE 4 mg vs placebo	961	0.97	0.66, 1.42	0.87	0
	BRE 2 mg vs placebo	966	0.88	0.60, 1.30	0.53	0
	BRE 4 mg vs BRE 2 mg	959	1.10	0.74, 1.63	0.64	0
Somnolence	BRE 4 mg vs placebo	961	1.12	0.50, 2.50	0.78	0
	BRE 2 mg vs placebo	966	0.79	0.31, 1.96	0.61	0
	BRE 4 mg vs BRE 2 mg	959	1.38	0.42, 4.58	0.60	33
Suicidal thought/suicidal behavior and serious active suicidal ideation	BRE 4 mg vs placebo	961	0.73	0.14, 3.78	0.71	0
	BRE 2 mg vs placebo	966	0.78	0.08, 7.27	0.82	28
	BRE 4 mg vs BRE 2 mg	959	1.15	0.19, 7.04	0.88	0
Akathisia	BRE 4 mg vs placebo	961	1.26	0.55, 2.89	0.58	56
	BRE 2 mg vs placebo	966	0.85	0.40, 1.79	0.67	35
	BRE 4 mg vs BRE 2 mg	959	1.49	0.87, 2.56	0.15	0
Weight gain (≥7%)	BRE 4 mg vs placebo	961	2.51	1.42, 4.42	0.001[f]	0
	BRE 2 mg vs placebo	966	2.73	1.56, 4.78	0.0004[g]	0
	BRE 4 mg vs BRE 2 mg	959	0.91	0.60, 1.36	0.63	0
Outcome	**Comparison**	**n**	**RR**	**95% CI**	***P*-value**	**I^2 (%)**
BARS score	BRE 4 mg vs placebo	950	0.06	–0.07, 0.18	0.38	0
	BRE 2 mg vs placebo	952	–0.07	–0.19, 0.06	0.31	0
	BRE 4 mg vs BRE 2 mg	948	0.12	–0.00, 0.25	0.06	0
SAS/DIEPSS score	BRE 4 mg vs placebo	927	0.08	–0.05, 0.21	0.20	0
	BRE 2 mg vs placebo	926	–0.13	–0.25, 0.00	0.06	0
	BRE 4 mg vs BRE 2 mg	925	0.20	0.07, 0.33	0.002	0
AIMS score	BRE 4 mg vs placebo	949	–0.04	–0.17, 0.09	0.54	0
	BRE 2 mg vs placebo	951	–0.07	–0.19, 0.06	0.30	0
	BRE 4 mg vs BRE 2 mg	948	0.02	–0.10, 0.15	0.71	0
QTcF	BRE 4 mg vs placebo	906	–0.10	–0.29, 0.09	0.32	54
	BRE 2 mg vs placebo	920	–0.05	–0.18, 0.08	0.48	0
	BRE 4 mg vs BRE 2 mg	920	–0.04	–0.31, 0.23	0.79	76

Notes: [a]NNH =13. [b]NNH =20. [c]NNH =14. [d]NNH =20. [e]NNH =17. [f]NNH =25. [g]NNH =17.

Abbreviations: 95% CI, 95% confidence interval; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; BRE, brexpiprazole; DIEPSS, Drug Induced Extra-Pyramidal Symptoms Scale; NA, not applicable; NNH, number needed to harm; QTcF, Fridericia's corrected QT; RR, risk ratio; SAS, Simpson-Angus Scale; SMD, standardized mean difference.

based on three DBRCTs. We performed three sets of meta-analyses comparing brexpiprazole 4 or 2 mg/day with placebo and comparing brexpiprazole 4 mg/day with brexpiprazole 2 mg/day. The meta-analyses showed that both brexpiprazole 4 and 2 mg/day were superior to placebo for improving the patients' PANSS total scores, response rates, and CGI-S and CGI-I scores. However, there was considerable heterogeneity in the meta-analysis of response rates for both brexpiprazole 4 and 2 mg/day. After excluding the data from the Ishigooka study (ie, the Japanese study) from the 4 mg/day meta-analysis, brexpiprazole 4 mg/day was observed to be superior to placebo for the response rate, without considerable heterogeneity. In this case, the Ishigooka study may have been the cause of the considerable heterogeneity initially observed. However, when the Correll study data were excluded from the 2 mg/day meta-analysis for the response rate, brexpiprazole 2 mg/day was no longer superior to placebo, with no heterogeneity. Given these findings, both brexpiprazole 4 and 2 mg/day were considered to be beneficial for the treatment of overall symptoms in patients with schizophrenia. Furthermore, there may be a difference in response rates between brexpiprazole 4 and 2 mg/day, with brexpiprazole 4 mg/day potentially providing greater benefit for improvements in overall psychopathology for acute schizophrenia than brexpiprazole 2 mg/day.

Brexpiprazole 2 mg/day, but not 4 mg/day, was superior for improving the patients' PANSS positive subscale scores. However, there was considerable heterogeneity in the brexpiprazole 4 mg/day meta-analysis. When the Ishigooka study data were excluded, brexpiprazole 4 mg was superior to placebo without heterogeneity, so the Ishigooka study was considered to be the cause of the considerable heterogeneity in this outcome. The brexpiprazole 4 mg arm of the Ishigooka study included more patients who had been on high-dose antipsychotics prior to participating in the trial compared with patients in the other treatment arms. Because there is the potential for a psychosis rebound when switching to a drug such as a dopamine D_2 receptor partial agonist,[8,9] we considered that data from patients who had been on high-dose antipsychotics prior to the trial could influence the efficacy results. In a meta-analysis that excluded such patients (who were all part of the Ishigooka study), brexpiprazole 4 mg/day was found to be superior to placebo for the PANSS positive subscale score, with little heterogeneity. We therefore considered brexpiprazole 4 mg/day to be effective for positive symptoms in patients who had not been prescribed high-dose antipsychotics before switching to this treatment. Conversely, there was only a marginal difference in the PANSS positive subscale scores between brexpiprazole 2 mg/day and placebo in this additional meta-analysis. It is possible that this marginal result may have been a type II error due to the small sample size.

Both brexpiprazole 4 and 2 mg/day were superior to placebo for improving the patients' PANSS negative subscale scores. However, there was considerable heterogeneity in the 2 mg/day meta-analysis, which disappeared after excluding the Kane study data, with brexpiprazole 2 mg/day remaining superior to placebo. It is not known why improvements in the PANSS negative subscale score were similar between brexpiprazole 2 mg/day and placebo only in the Kane study.

The discontinuation rate in the brexpiprazole 4 mg/day arm of the Ishigooka study was high, perhaps affected by the large number of patients who had previously been on high-dose antipsychotics, who may have discontinued the trial because of deterioration in their psychosis (shown by a worse psychopathology scale score). Thus, the mean psychopathology scale score at the endpoint (especially for positive symptoms) for the brexpiprazole 4 mg/day arm may not have shown a sufficient decrease. Conversely, antipsychotic dose reduction and/or placebo treatment may have been effective for some patients with dopamine supersensitivity psychosis in the placebo arm.[10] This could account for the lack of significant differences in the PANSS total and positive scores in the Japanese study between brexpiprazole 4 mg/day and placebo.

Both brexpiprazole 4 and 2 mg/day were well tolerated. However, both brought a risk of body weight gain, with a small effect size and no significant difference between the two doses. Clinicians should closely monitor the patient's body weight when administering brexpiprazole. Brexpiprazole 4 mg/day was also associated with a higher risk of extrapyramidal symptoms than was brexpiprazole 2 mg/day. Although brexpiprazole 4 and 2 mg/day were both associated with a lower incidence of the discontinuation rate due to adverse events when compared with placebo, it was noted that the most common reasons for discontinuation due to adverse events were related to psychiatric problems such as schizophrenia.[4,5,7]

There were several limitations to this study. First, the sample sizes of the studies included in the meta-analysis were small. Second, patient characteristics differed between the studies, including the patients' geographical region, race, and ethnicity. Third, all studies included in our study were industry sponsored, so the possibility of sponsorship bias[17] should be considered when interpreting our results. Fourth, the small number of included studies prevented us from

using a funnel plot to explore potential publication bias; this method is generally used only when ≥10 studies are included in a meta-analysis. Fifth, we obtained unpublished data from Otsuka Pharmaceutical Co., Ltd. and used these data in our meta-analysis. However, we did not receive permission to present the original data in this manuscript since these results were obtained in an unplanned analysis that was not presented in their Clinical Study Report or approval application.

Conclusion

The findings of these meta-analyses suggested that both brexpiprazole 4 and 2 mg/day are beneficial for the treatment of overall symptoms in patients with acute schizophrenia. The patients who responded to brexpiprazole may have been those who had not been prescribed high-dose antipsychotics before switching to brexpiprazole. Although both brexpiprazole 4 and 2 mg/day were well tolerated, clinicians should consider the possibility of body weight gain when prescribing brexpiprazole. In addition, brexpiprazole 4 mg/day had a higher risk of extrapyramidal symptoms than did brexpiprazole 2 mg/day. However, our study had some limitations (the numbers of studies and patients included in our study were small). Also, because our study suggested that the higher dosages of previous medications might have influenced the effects found in the Japanese brexpiprazole 4 mg study, further research is needed to determine the role that dopaminergic supersensitivity induced by antipsychotics may have in outcomes and treatment strategies.

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Supplementary materials

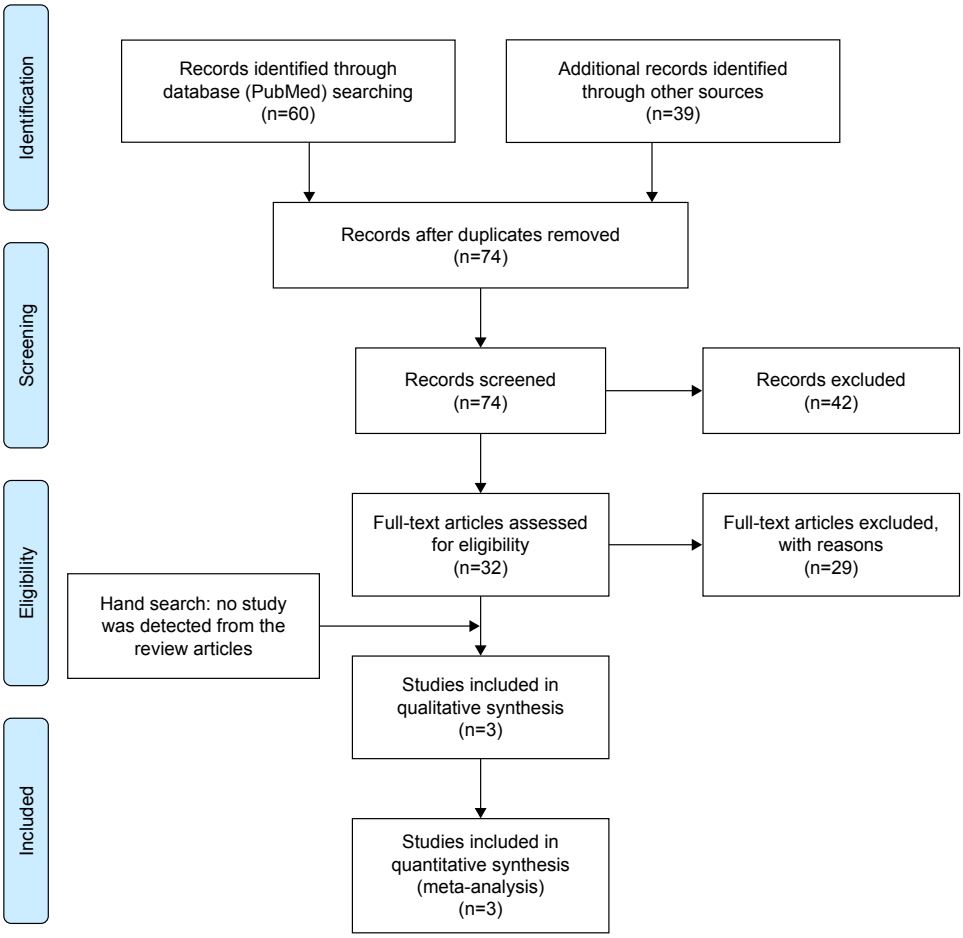

Figure S1 PRISMA flow diagram.
Notes: From Moher et al.[1] For more information, visit www.prisma-statment.org.

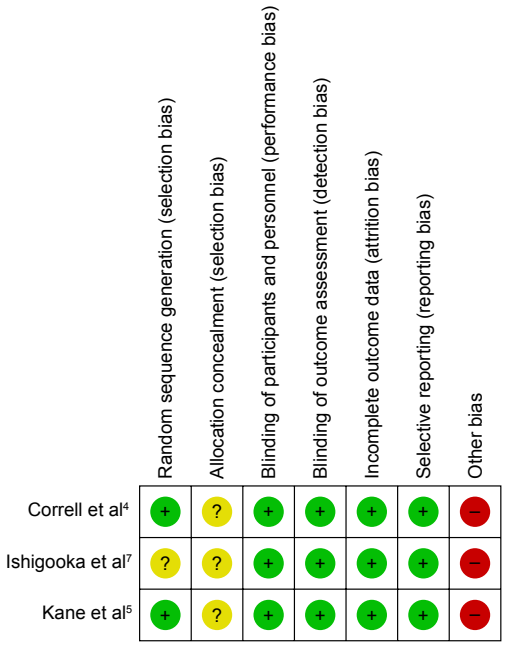

Figure S2 Risk of bias.

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