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Brexpiprazole as Adjunctive Treatment for Major Depressive Disorder Following Treatment Failure With at Least One Antidepressant in the Current Episode: a Systematic Review and Meta-Analysis

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Abstract

Background: This systematic review and meta-analysis included double-blind, randomized, placebo-controlled trials of brexpiprazole adjunctive treatment (0.5–3 mg/d) for major depressive disorder where antidepressant treatment had failed.
Methods: The outcomes were the response rate (primary), remission rate (secondary), Montgomery Åsberg Depression Rating Scale score (secondary), Sheehan Disability Scale scores (secondary), Clinical Global Impression–Improvement/Severity scores, discontinuation rate, and individual adverse events. A subgroup meta-analysis of the data at week 6 compared outcomes by dose >2 mg/d or ≤2 mg/d (2 mg/d is the recommended dose).
Results: We identified 9 studies (n = 3391). Compared with placebo, brexpiprazole (any dose) was superior for response rate (risk ratio [RR] = 0.93, 95% confidence interval [95% CI] = 0.89–0.97, number needed to treat = 17), remission rate (RR = 0.95, 95% CI = 0.93–0.98, number needed to treat = 25), Montgomery Åsberg Depression Rating Scale score (standardized mean difference = −0.20, 95% CI = −0.29, −0.11), Sheehan Disability Scale score (standardized mean difference = −0.12, 95% CI = −0.21, −0.04), and Clinical Global Impression–Improvement/Severity scores but was associated with a higher discontinuation rate, akathisia, insomnia, restlessness, somnolence, and weight increase. Doses >2 mg/d had a significantly higher RR for response rate than ≤2 mg/d (0.96 vs 0.89); moreover, compared with placebo, doses >2 mg/d were associated with higher incidences of akathisia (RR = 4.58) and somnolence (RR = 7.56) as well as were marginally associated with a higher incidence of weight increase (RR = 3.14, *P* = .06). Compared with placebo, doses ≤2 mg/d were associated with higher incidences of akathisia (RR = 2.28) and weight increase (RR = 4.50).
Conclusions: Brexpiprazole adjunctive treatment is effective for major depressive disorder when antidepressant treatment fails. At 6 weeks, doses ≤2 mg/d presented a better risk/benefit balance than >2 mg/d.

Keywords: major depressive disorder, brexpiprazole, response rate, systematic review, meta-analysis

Significance Statement

This systematic review and meta-analysis included 9 double-blind, randomized, placebo-controlled trials (n = 3391) of brexpiprazole (0.5–3 mg/d) for major depressive disorder (MDD) for patients whose antidepressant treatment had failed. Compared with placebo, brexpiprazole adjunctive treatment showed superior response and remission rates and Montgomery Åsberg Depression Rating Scale and Sheehan Disability Scale scores but was associated with a higher discontinuation rate, akathisia, insomnia, restlessness, somnolence, and weight increase. The risk ratio for response rate was lower with doses ≤2 mg/d than with those >2 mg/d. Compared with placebo, doses >2 mg/d were associated with higher incidences of akathisia and somnolence as well as were marginally associated with a higher incidence of weight increase. Doses ≤2 mg/d were associated with higher incidences of akathisia and weight increase compared with placebo. In conclusion, although brexpiprazole was effective for these MDD patients, clinicians should be careful about the adverse events associated with brexpiprazole.

Introduction

Major depressive disorder (MDD) is a common, serious mood condition with a lifetime prevalence of 20.6% (Hasin et al., 2018). A recent Bayesian meta-regression study, which included 328 diseases and injuries and 2982 sequelae across 195 countries, reported that, in 2016, MDD was among the top 10 conditions for the years lived with disability in 191 of the countries (GBD, 2017).

The recent Canadian Network for Mood and Anxiety Treatments guideline for the treatment of MDD differentiated between depression of mild severity and depression of moderate or greater severity, as determined by symptom scales and/or functional impairment (Kennedy et al., 2016). For mild severity, first-line treatments include psychoeducation, self-management, and psychological treatments. For patients with a major depressive episode of moderate or greater severity, the first-line treatments include most second-generation antidepressants, such as serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors. The guideline recommends the following 3 treatment strategies for managing patients whose response to an antidepressant was inadequate: (1) switch to another first-line drug with superior efficacy, (2) add an adjunctive medication, or (3) after the failure of 1 or more first-line drugs, consider switching to a second-line or third-line drug. The guideline recommends that the decision between switching or adjunctive strategies should be based on clinical factors individual to the patient. The adjunctive treatment can include some newer dopamine D_2 antagonists and D_2 partial agonists, according to the neuroscience-based nomenclature (Zohar et al., 2015; Uchida, 2018) (these were previously known as "atypical antipsychotics"), triiodothyronine, and lithium (Kennedy et al., 2016). The guideline recommends aripiprazole, quetiapine, and risperidone as first-line adjunctive drugs for patients who are nonresponsive or partially responsive to antidepressant treatment (Kennedy et al., 2016).

Brexpiprazole was approved by the US Food and Drug Administration (FDA) on July 10, 2015 as an adjunctive treatment for patients with MDD. The efficacy of brexpiprazole is thought to be mediated by a combination of partial agonist activity on serotonin 5-HT_{1A} and dopamine D_2 receptors and antagonist activity on serotonin 5-HT_{2A} receptors (FDA, 2015). Aripiprazole is also a partial agonist of serotonin 5-HT_{1A} and dopamine D_2 receptors, but it has lower serotonin 5-HT_{2A} receptor occupancy (Maeda et al., 2014). Because serotonin 5-HT_{2A} receptor antagonism is thought to contribute to antidepressant activity, reducing the incidence of akathisia and improving of sleep patterns (Maeda et al., 2014), brexpiprazole would be expected to be more effective and safer than aripiprazole. The package insert for brexpiprazole designates the starting, recommended, and maximum doses as 0.5 to 1 mg/d, 2 mg/d, and 3 mg/d, respectively (FDA, 2015).

A previous systematic review and meta-analysis of brexpiprazole (1–3 mg/d) as an adjunctive treatment for MDD (Yoon et al., 2017) included 4 double-blind, randomized, placebo-controlled trials (NCT00797966; NCT01052077; Thase et al., 2015a, 2015b). This compared brexpiprazole with placebo for Montgomery Åsberg Depression Rating Scale score (MADRS; Montgomery and Asberg, 1979), 17-item Hamilton Depression Rating Scale score (HAM-D17; Hamilton, 1960), response rate, remission rate, and adverse effects, calculating the risk ratios (RRs) or mean differences (MDs) with 95% confidence intervals (CIs). This reported that brexpiprazole was superior to placebo for MADRS score (MD = −1.76, 95% CI = −2.45 to −1.07), HAM-D17 score (MD = −1.21, 95% CI = −1.71 to −0.72), response rate (RR = 1.57, 95% CI = 1.29–1.91), and remission rate (RR = 1.55, 95% CI = 1.22–1.96) (Yoon et al., 2017). However, compared with placebo, brexpiprazole was associated with a higher incidence of discontinuation due to adverse events (RR = 3.44, 95% CI = 1.52–7.80), akathisia (RR = 3.39, 95% CI = 2.08–5.51), and weight increase (RR = 4.36, 95% CI = 2.45–7.77) (Yoon et al., 2017). The efficacy outcomes, risk of discontinuation, and weight increase were not associated with brexpiprazole dose; however, the risk of akathisia was higher with >2 mg/d than with ≤2 mg/d brexpiprazole (Yoon et al., 2017). The authors concluded that the concomitant administration of antidepressants with 1 to 3 mg of adjunctive brexpiprazole was beneficial in managing treatment-resistant MDD, with a lower risk of akathisia, sedation, and metabolic syndrome (Yoon et al., 2017).

Since the report of Yoon et al., 4 new double-blind, randomized, placebo-controlled trials of adjunctive brexpiprazole treatment for MDD have been published (NCT01837797; Bauer et al., 2019; Hobart et al., 2018a, 2018b). We have therefore performed an updated systematic review and meta-analysis of double-blind, randomized, placebo-controlled trials with the aim of obtaining more conclusive evidence on the usefulness of treatment with antidepressants combined with adjunctive brexpiprazole for patients with MDD (Yoon et al., 2017). Our analysis included some additional efficacy and safety outcomes that were not considered in the previous study, for example, the Sheehan Disability Scale (SDS), which evaluates the functional impact of psychiatric disorders by assessing disability during work/school activities, in family relationships, and in social functioning (Sheehan et al., 1996); the mortality rate; and neuropsychiatric adverse events, such as suicide-related symptoms, insomnia, restlessness, and somnolence (Yoon et al., 2017). We also tested for associations between the meta-analysis results for the efficacy and safety outcomes and the dose of brexpiprazole by performing a subgroup analysis that compared doses of ≤2 mg/d with doses >2 mg/d and a meta-regression analysis that used the dose of brexpiprazole as a moderator. Moreover, we examined whether

the meta-analysis results for efficacy outcomes were associated with other clinical moderators by performing additional subgroup analyses (published studies vs unpublished studies and fixed-dose studies vs flexible-dose studies) and meta-regression analyses (percentage of placebo responders and sample size). In addition, the time to treatment response in patients with MDD was evaluated through a meta-analysis of 3 efficacy outcomes (response rate, remission rate, and improvement in the MADRS score) at weeks 1, 2, 3, 4, 5, and 6 after the start of brexpiprazole adjunctive therapy.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009) and was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) (Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist).

Search Strategy and Inclusion Criteria

A systematic literature review was performed following the "PICO" strategy, which considers the participants/population, interventions, comparator/control, and outcomes, as follows. The participants were MDD patients with a history of depression and at least 1 antidepressant treatment failure in the current episode. The intervention was the administration of adjuvant brexpiprazole concomitantly with an antidepressant treatment. The control was placebo, and the outcomes were efficacy and safety, as described in detail in the following section.

The analysis included only double-blind, randomized, placebo-controlled trials that investigated brexpiprazole treatment in patients with MDD and that lasted ≥4 weeks. Relevant studies were identified by 4 authors (T.K., I.N., K.S., and Y.M.) through independent searches of Scopus, MEDLINE, and the Cochrane Library with no language restrictions. The search time frame was from inception to January 6, 2019, and the search terms used were (brexpiprazole) AND (major depressive disorder) AND (random*). The authors also searched ClinicalTrials. gov (http://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, thus minimizing the possibility of publication bias. The identified studies were independently assessed for inclusion by 4 authors (T.K., I.N., K.S., and Y.M.) based on the inclusion and exclusion criteria. In addition, the reference lists of the selected articles and reviews were searched manually to identify further relevant published and unpublished studies, including conference abstracts.

Data Synthesis and Outcome Measures

The primary efficacy outcome was response (which was defined as a ≥50% reduction from baseline in MADRS score) rate at week 6. The secondary efficacy outcomes, which were considered to be as important as the primary outcome, were remission (which was defined as a MADRS total score ≤10 and a ≥50% reduction from baseline) rate at week 6, an improvement in MADRS score at week 6, and an improvement of the SDS total score at week 6. The following outcomes were also measured: the response rates at weeks 1, 2, 3, 4, and 5; remission rates at weeks 1, 2, 3, 4, and 5; improvements in the MADRS score at weeks 1, 2, 3, 4, and 5; response rate, defined as an improvement in Clinical Global Impression–Improvement (CGI-I) score (Guy and Bonato,

1970) of 1 or 2 at week 6; improvement in the CGI–Severity (CGI-S) score (Guy and Bonato, 1970) at week 6; improvement in CGI-I score at week 6; improvement in HAM-D17 score at week 6; improvement in the Inventory of Depressive Symptomatology–Self-Report score (Rush et al., 1996) at week 6; improvements in SDS subscale scores for work/school, social life, and family life at week 6; the all-cause discontinuation rate; discontinuation rate due to adverse events or inefficacy; and the incidence of individual adverse events.

Data Extraction

Data were independently extracted from the selected studies by 4 of the authors (T.K., N.I., K.S., and Y.M.). Only studies that performed intention-to-treat analyses or used full analysis set populations were included. In cases where relevant data for the meta-analysis were missing, the authors of those studies were contacted and unpublished data were requested (personal communication to Otsuka Pharmaceutical Co., Ltd., Tokyo, 101–8535 Japan; https://www.otsuka.co.jp/en/).

Although 9 double-blind, randomized, placebo-controlled trials were finally selected for inclusion, data from a phase I study that evaluated safety and tolerability in elderly patients (NCT01670279) were not used in the present meta-analysis because the observational period differed between the treatment arms (Table 1). Therefore, 8 studies were included in our meta-analysis (NCT00797966; NCT01052077; NCT01837797; Thase et al., 2015a, 2015b; Bauer et al., 2019; Hobart et al., 2018a, 2018b). However, the observational periods for these studies were not consistent (Table 1). In 6 of the studies, the observational period was 6 weeks; the observational periods for the other 2 studies were 20 weeks (NCT01837797) and 24 weeks (Bauer et al., 2019). So that the meta-analysis for efficacy outcomes used data with consistent observational periods, we used the efficacy outcomes at week 6 of the 24-week study (Bauer et al., 2019). However, no information pertaining to efficacy outcomes was available for the 20-week study (NCT01837797). The safety outcomes (the discontinuation rate and the incidence of individual adverse events) were reported only for the end of each of the 2 longer duration studies, so our primary meta-analysis for safety outcomes included data for which the observational periods were not consistent (i.e., 6 weeks for 6 studies, 20 weeks for 1 study, and 24 weeks for 1 study).

The NCT00797966 study was a 4-arm study that compared brexpiprazole doses of 0.15 mg/d, 0.5±0.25 mg/d, and 1.5±0.5 mg/d with placebo (NCT00797966). However, the dose of brexpiprazole approved by the FDA for the treatment of MDD is 0.5 to 3 mg/d (FDA, 2015), so only the data pertaining to the brexpiprazole 1.5±0.5 mg/d arm were used in our meta-analysis. The study of Thase et al. (2015a) was a 3-arm study that compared brexpiprazole doses of 1 mg/d and 3 mg/d with placebo (Thase et al., 2015a); the data from the 2 brexpiprazole arms (1 mg/d and 3 mg/d) were combined for our primary meta-analysis to avoid a unit of analysis error (Higgins and Green, 2011). However, these doses were considered separately in the subgroup meta-analysis to compare brexpiprazole doses ≤2 mg/d and >2 mg/d.

Meta-Analysis Methods

Our primary meta-analysis compared brexpiprazole at all doses with placebo for all outcomes. It was performed using Review Manager software (RevMan, 2014). Given the potential heterogeneity across the included studies, a random effects model was

Table 1. Characteristics of the included double-blind, randomized, placebo-controlled trials of brexpiprazole

(1) NCT number, (2) country, (3) study duration and study design, (4) sponsorship	Patient inclusion criteria	Drug (mg/d), n	MADRS at baseline	Mean age (mean ± SD, y)/ male (%)	Race (%)	Combined AD (dose, mg/d)
(1) NCT01670279, (2) USA, (3) up to 45 d, DBRPCT [a], (4) industry	Elderly pt (age 70~85 y) with MDD who received AD tx	BRE3 [b] (fixed), 6 BRE3 [c] (fixed), 7 PBO, 5	NR	73.2 ± 4.0/33.3 76.0 ± 5.3/28.6 72.6 ± 1.5/20.0	NR	NR
(1) NCT01837797 [d], (2) USA, (3) 20 wk, DBRPCT, (4) industry	Elderly out-pt (age ≥65 y) with moderate to severe (insufficient response to 1~2 AD tx) MDD (DSM-IV-TR, MINI) who received AD tx	BRE3 (fixed), 6 BRE1 (fixed), 3 PBO, 6	NR	NR/0.0% NR/33.3% NR/50.0%	NR	NR
(1) Bauer 2019 (NCT01838681) [d], (2) international, (3) 24 wk, DBRPCT, (4) industry	Adult out-pt (age 18~75 y) with MDD (DSM-IV-TR, MINI) who had an inadequate response to 1~3 AD tx (ATRQ <50% improvement), current depressive episode ≥8 wk, MADRS≥26 and CGI-S≥4	BRE1~3 (flexible, mean dose 2.69), 444 PBO, 442	25.9 ± 4.1 25.8 ± 4.1	47.1 ± 12.1/30.9 46.4 ± 12.1/31.5	Caucasian 95.5 Caucasian 96.1	DUL60, ESC10~20, FLU20~40, PAR-IR20~40, SER50~200, VEN-XR75~225
(1) Hobart 2018b (NCT01727726) [d], (2) international, (3) 6 wk, DBRPCT, (4) industry	Adult out-pt (age 18~65 y) with MDD (DSM-IV-TR) who had an inadequate response to 1~3 AD tx (MGHATRQ<50% improvement), current depressive episode ≥8 wk, MADRS≥26	BRE2~3 (flexible, mean dose 2.2), 197 PBO, 206	25.4 ± 5.1 25.4 ± 5.2	43.6 ± 11.5/35.0 41.8 ± 11.7/27.7	Caucasian 90.4 Caucasian 90.3	DUL30~60, ESC10~20, FLU20~40, PAR-CR25~50, SER50~200, VEN-XR37.5~225
(1) Hobart 2018a (NCT02196506) [d], (2) international, (3) 6 wk, DBRPCT, (4) industry	Adult out-pt (age 18~65 y) with MDD (DSM-IV-TR) who had an inadequate response to 1~3 AD tx (MGHATRQ<50% improvement), current depressive episode≥8 wk, HDRS17≥18	BRE2 (fixed), 202 PBO, 192	27.1 ± 5.7 26.2 ± 6.2	43.0 ± 12.7/23.4 42.7 ± 12.5/28.7	Caucasian 85.4 Caucasian 84.7	DUL40~60, ESC10~20, FLU20~40, PAR-CR37.5~50, SER100~200, VEN-XR75~225
(1) NCT00797966, (2) USA, (3) 6 wk, DBRPCT, (4) industry	Adult pt (age 18~65 y) with MDD (DSM-IV-TR), current depressive episode (insufficient response to 1~2 AD tx) ≥8 wk	BRE 1.5 ± 0.5,121 PBO, 126	NR	43.7 ± 11.6/33.9 43.3 ± 11.5/34.9	NR	DES, ESC, FLU, PAR-CR, SER, VEN-XR
(1) Thase 2015b (NCT01360645), (2) international, (3) 6 wk, DBRPCT, (4) industry	Adult out-pt (age 18~65 y) with MDD (DSM-IV-TR) who had an inadequate response to 1~3 AD tx (MGHATRQ<50% improvement), current depressive episode ≥8 wk, HDRS17≥18	BRE2 (fixed), 188 PBO, 191	26.6 ± 5.8 27.1 ± 5.6	44.1 ± 11.6/30.9 45.2 ± 11.3/28.3	Caucasian 86.7 Caucasian 86.9	DUL40~60, ESC10~20, FLU20~40, PAR-CR37.5~50, SER100~200, VEN-XR75~225
(1) Thase 2015a (NCT01360632), (2) international, (3) 6 wk, DBRPCT, (4) industry	Adult out-pt (age 18~65 y) with MDD (DSM-IV-TR) who had an inadequate response to 1~3 AD tx (MGHATRQ<50% improvement), current depressive episode≥8 wk, HDRS17≥18	BRE3 (fixed), 230 BRE1 (fixed), 226 PBO, 221	26.4 ± 5.2 26.7 ± 5.6 26.3 ± 5.3	44.5 ± 11.2/32.2 45.7 ± 11.6/30.1 46.6 ± 11.0/33.9	Caucasian 87.4 Caucasian 81.0 Caucasian 85.1	DUL40~60, ESC10~20, FLU20~40, PAR-CR37.5~50, SER100~200, VEN-XR75~225

Table 1. Continued

(1) NCT number, (2) country, (3) study duration and study design, (4) sponsorship	Patient inclusion criteria	Drug (mg/d), n	MADRS at baseline	Mean age (mean ± SD, y)/ male (%)	Race (%)	Combined AD (dose, mg/d)
(1) NCT01052077, (2) USA, (3) 6 wk, DBRPCT, (4) industry	Adult out-pt (age 18~65 y) with MDD (DSM-IV-TR) who had an inadequate response to 1~3 AD tx (MGHATRQ<50% improvement), current depressive episode≥8 w, HDRS17≥18	BRE1~3, 185 PBO, 187	NR	44.7 ± 11.7/33.5 42.4 ± 11.7/30.5	NR	FDA approved AD

Abbreviations: AD, antidepressant; ATRQ, Antidepressant Treatment Response Questionnaire; CGI-S, Clinical Global Impression-Severity; d, day; DBRPCT, double-blind; randomized; placebo-controlled trial; DES, desvenlafaxine; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders; Fourth Edition Text Revision; DUL, duloxetine; ESC, escitalopram; FDA, Food and Drug Administration; FLU, fluoxetine; HDRS17; 17-item Hamilton Depression Rating Scale of depression; MADRS, Montgomery Åsberg Depression Rating Scale; MDD, major depressive disorder; MGHATRQ, Massachusetts General Hospital Antidepressant Treatment History Questionnaire; MINI, Mini-International Neuropsychiatric Interview; NR, not report; PAR-IR(CR), paroxetine-immediate release (controlled release); PBO, placebo; SER, sertraline; tx, treatment; VEN, venlafaxine XR.

aTotal individual subject duration is expected to be no more than 119 days (a 30-day screening period, a 14-day washout period, up to 45-day in-clinic treatment period, and a 30-day follow-up after the last dose of trial medication).

bIn the titration phase, participants received 0.5 mg brexpiprazole for 7 days, followed by 1 mg brexpiprazole for 7 days. In the fixed-dose phase, participants received 2 mg brexpiprazole for 14 days, followed by 3 mg brexpiprazole for 14 days.

cIn the titration phase, participants received 0.5 mg brexpiprazole for 7 days, followed by 1 mg brexpiprazole for 7 days. In the fixed-dose phase, participants received 3 mg brexpiprazole for 14 days.

dA new DBRCT was conducted after reporting the previous meta-analysis (Yoon et al., 2017).

used. Continuous outcomes were analyzed by calculating standardized mean differences (SMDs) with 95% confidence intervals (CIs). Dichotomous outcomes were analyzed by calculating RRs with 95% CIs. For cases where the RRs showed statistically significant between-group differences with respect to treatment efficacy, discontinuation rates, or the incidence of individual adverse events based on RRs were significant, either the number needed to treat (NNT) or the number needed to harm (NNH) was calculated from the risk difference (RD), using the formula NNT or NNH=1/RD.

Heterogeneity was tested using the I^2 statistic, with $I^2 \geq 50\%$ considered to indicate considerable heterogeneity (Higgins and Green, 2011). The study protocol specified that a sensitivity analysis would be performed if considerable heterogeneity were detected in a primary or secondary outcome; however, considerable heterogeneity was not detected in any primary or secondary outcome.

We performed the following subgroup and meta-regression analyses. The first subgroup analysis compared the primary and secondary efficacy outcomes between subgroups of patients across the studies who were administered doses of brexpiprazole ≤2 mg/d and those administered doses >2 mg/d. The threshold of 2 mg/d was chosen because it is the FDA's recommended dose of brexpiprazole for MDD (FDA, 2015). One study (NCT01052077) was excluded from the subgroup analysis, because no information on the mean dose of brexpiprazole was reported (Table 1). The second subgroup analysis compared the efficacy outcomes between the published and unpublished studies to check for a gray literature bias, in which published trials possibly have a greater overall intervention effect than gray trials (Higgins and Green, 2011). The third subgroup analysis compared the efficacy outcomes between the fixed-dose and flexible-dose studies. A meta-regression analysis was performed to evaluate the associations between the meta-analysis results for efficacy outcomes and the following clinical modulators: brexpiprazole

dose, percentage of placebo responders, and sample size. The percentage of placebo responders was included in the meta-regression analysis because a previous meta-analysis showed that the superiority of a drug over placebo would be less pronounced in an analysis that included adjunctive trials with high placebo response rates (e.g., ≥40%) (Iovieno and Papakostas, 2012). Sample size was included in the analysis because forest plots for the primary and secondary outcomes suggested that, compared with smaller trials, larger trials seemed to be associated with smaller brexpiprazole treatment effects compared with placebo. The meta-regression analysis was performed using Comprehensive Meta-Analysis software version 2 (Biostat Inc., Englewood, NJ).

The studies included in the meta-analysis of safety outcomes (i.e., discontinuation rates and the incidence of individual adverse event) had different durations (6, 20, and 24 weeks). It was thought that the study duration might influence the meta-analysis, so a second subgroup analysis was performed for safety outcomes that included only the 6-week studies, excluding the 2 studies with longer duration (NCT01837797; Bauer et al., 2019). The sample size of the 20-week study (NCT01837797) was very small (n=15), so no subgroup analysis was performed for the long-duration studies. Moreover, when the subgroup analysis including only the 6-week studies revealed significant differences between brexpiprazole and placebo in terms of safety outcomes, an additional subgroup analysis of safety outcomes was performed based on the dose of brexpiprazole (i.e., brexpiprazole ≤2 mg/d or >2 mg/d). In addition, a meta-regression analysis was performed to evaluate the association between the results of the meta-analysis for these safety outcomes and the dose of brexpiprazole. The Cochrane Handbook suggests the use of a funnel plot only when ≥10 studies are included in a meta-analysis (Higgins and Green, 2011), so Egger's regression was used to detect publication bias. Again, Comprehensive Meta-Analysis software version 2 was

used. 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 82 studies initially identified by searching the literature, 35 were excluded after reviewing the titles and abstracts. Reviews of the full text resulted in the exclusion of 8 further studies: 4 (systematic) review articles (Beyer and Weisler, 2016; Yoon et al., 2017; Romeo et al., 2018; Weiller et al., 2018) and 4 post-hoc analysis studies (McIntyre et al., 2016; Hobart et al., 2018c; Nelson et al., 2018; Thase et al., 2019) (Supplementary Figure 1). Four more studies were retrieved from the clinical trial registries (Supplementary Figure 1), and 9 double-blind, randomized, placebo-controlled trials) were finally selected for inclusion. These included a total of 3391 patients (brexpiprazole, n = 1815; placebo, n = 1576). A summary of the included studies is presented in Table 1. Two of the 9 studies (NCT01670279; NCT01837797) included elderly patients with MDD and had very small sample sizes (total n < 20). Seven of the 9 studies included adult patients with MDD and had large sample sizes (total n > 200). One study did not report the number of ineffective antidepressant treatments that had been attempted prior to the study (NCT01670279), whereas the other 8 studies included only

patients who had experienced an inadequate response to at least 1 course of antidepressant treatment prior to enrollment in the study. All the studies were sponsored by pharmaceutical companies. All were double-blind, randomized, placebo-controlled trials published in English, using either intention-to-treat analysis or full analysis set populations. As noted earlier, the observational periods were inconsistent among the included studies (Table 1): 6 weeks for 6 of the studies, 20 weeks for 1 study (NCT01837797) and 24 weeks for 1 study (Bauer et al., 2019). The remaining study had different observational periods for each treatment arm (NCT01670279). Four unpublished studies (NCT00797966, NCT01052077, NCT01670279, and NCT01837797) did not report the mean baseline MADRS scores; we contacted Otsuka Pharmaceutical Co., Ltd. (Tokyo, 101–8535 Japan; https://www.otsuka.co.jp/en/), but they were unable to provide the missing information because the studies had not been published. Supplementary Figure 2 summarizes the assessment of the methodological quality of the included studies according to the Cochrane Risk of Bias criteria.

Efficacy Outcomes

Compared with placebo, brexpiprazole (at any of the included doses) showed the following: higher response rates at all the time points except week 1 (week 6: RR = 0.93, 95% CI = 0.89–0.97, P = .0005, I^2 = 34%, NNT = 17, 95% CI = 11–33; Supplementary Figure 3); higher remission rates at weeks 3, 4, and 6 (week

Table 2. Efficacy outcomes

	N	n	RR (95% CI)	P	I^2 (%)	NNT (95% CI)
Response rate (MADRS) at wk 1	3	1267	1.00 (0.96–1.05)	.89	72	
Response rate (MADRS) at wk 2	3	1278	0.96 (0.93–0.99)	.02	0	25 (14–100)
Response rate (MADRS) at wk 3	3	1278	0.95 (0.91–0.99)	.02	0	20 (13–100)
Response rate (MADRS) at wk 4	3	1278	0.88 (0.80–0.96)	.004	60	9 (6–25)
Response rate (MADRS) at wk 5	3	1278	0.92 (0.86–0.99)	.03	37	17 (8–100)
Response rate (MADRS) at wk 6	7	3327	0.93 (0.89–0.97)	.0005	34	17 (11–33)
Response rate (CGI-I) at wk 6	6	2445	0.83 (0.78–0.90)	<.00001	0	10 (7–17)
Remission rate (MADRS) at wk 1	3	1255	1.00 (0.98–1.03)	.81	40	
Remission rate (MADRS) at wk 2	3	1266	0.99 (0.95–1.02)	.50	36	
Remission rate (MADRS) at wk 3	3	1266	0.96 (0.93–1.00)	.03	0	25 (14–∞)
Remission rate (MADRS) at wk 4	3	1266	0.91 (0.85–0.98)	.02	61	13 (8–50)
Remission rate (MADRS) at wk 5	3	1266	0.95 (0.88–1.02)	.17	56	
Remission rate (MADRS) at wk 6	7	3315	0.95 (0.93–0.98)	.003	24	25 (14–50)
Discontinuation due to inefficacy	8	3373	0.88 (0.44–1.75)	.71	0	

	N	n	SMD (95% CI)	P	I^2 (%)	
MADRS score at wk 1	5	2038	−0.16 (−0.25, −0.07)	.0005	0	
MADRS score at wk 2	6	2440	−0.23 (−0.32, −0.15)	<.00001	0	
MADRS score at wk 3	5	2049	−0.24 (−0.32, −0.15)	<.00001	0	
MADRS score at wk 4	6	2419	−0.26 (−0.34, −0.18)	<.00001	0	
MADRS score at wk 5	5	2049	−0.26 (−0.35, −0.17)	<.00001	0	
MADRS score at wk 6	7	3289	−0.20 (−0.29, −0.11)	<.00001	33	
HAM-D17 score at 6 wk	5	1967	−0.20 (−0.30, −0.11)	<.00001	0	
IDS-SR score at 6 wk	4	1656	−0.17 (−0.31, −0.03)	.02	48	
CGI-S score at 6 wk	7	3289	−0.14 (−0.24, −0.05)	.003	44	
CGI-I score at 6 wk	6	2445	−0.21 (−0.29, −0.13)	<.00001	0	
SDS total score at 6 wk	7	3252	−0.12 (−0.21, −0.04)	.003	25	
SDS work/school subscale score at 6 wk	4	1612	−0.04 (−0.14, 0.06)	.45	0	
SDS social life subscale score at 6 wk	4	1830	−0.17 (−0.27, −0.08)	.0003	0	
SDS family life subscale score at 6 wk	4	1830	−0.19 (−0.29, −0.10)	<.0001	0	

Abbreviations: 95% CI, 95% confidence interval; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity; HAM-D17, 17-item Hamilton depression rating scale; IDS-SR, Inventory of Depressive Symptomatology–Self-Report; MADRS, Montgomery Åsberg Depression Rating Scale; NNT, number needed to treat; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standardized mean difference; wk, week.

6: RR = 0.95, 95% CI = 0.93–0.98, P = .003, I^2 = 24%, NNT = 25, 95% CI = 14–50; Supplementary Figure 4); greater improvements in the MADRS total score at all time points (week 6: SMD = −0.20, 95% CI = −0.29 to −0.11, P < .00001, I^2 = 33%; Supplementary Figure 5); and greater improvement in SDS total score at week 6 (SMD = −0.12, 95% CI = −0.21 to −0.04, P = .003, I^2 = 25%; Supplementary Figure 6) (Table 2). Publication bias was found for the primary outcome in each treatment group (Egger's test P values = .00690). At week 6, brexpiprazole was superior to placebo in terms of HAM-D17 score, Inventory of Depressive Symptomatology–Self-Report score, CGI-S score, CGI-I score, SDS social life subscale score, and SDS family life subscale score (Table 2).

Subgroup Analysis: Efficacy Outcomes

Brexpiprazole at doses of >2 mg/d and ≤2 mg/d was superior to placebo in the improvement in the MADRS score at 6 weeks; however, only brexpiprazole ≤2 mg/d was superior to placebo in terms of the 6-week response rates, remission rates, and SDS total scores (Table 3). A significant subgroup difference was found regarding the 6-week response rate (Table 3).

In both the published and unpublished studies subgroups, brexpiprazole was superior to placebo for the 6-week response rate, remission rate, and MADRS score. However, for the 6-week SDS total score, it was superior to placebo only in the published studies subgroup (Table 4). Significant subgroup differences were found for the response and remission rates (Table 4).

Table 3. Subgroup analysis for efficacy outcomes

	Subgroup	N	n	RR (95% CI)	P	I^2 (%)	NNT (95% CI)	Test for subgroup difference, P
Response rate (MADRS) at wk 6	BRE > 2 mg/d	3	1722	0.96 (0.93–1.00)	0.05	0		0.04
	BRE ≤ 2 mg/d	4	1458	0.89 (0.84–0.95)	<0.0001	0	11 (8–25)	
Remission rate (MADRS) at wk 6	BRE > 2 mg/d	3	1713	0.98 (0.95–1.01)	0.17	0		0.12
	BRE ≤ 2 mg/d	4	1451	0.94 (0.90–0.98)	0.005	0	20 (11–50)	

	Subgroup	N	n	SMD (95% CI)	P	I^2 (%)		Test for subgroup difference, p
MADRS score at wk 6	BRE > 2 mg/d	3	1684	−0.15 (−0.28, −0.02)	0.02	40		0.17
	BRE ≤ 2 mg/d	4	1458	−0.26 (−0.37, −0.16)	<0.00001	0		
SDS total score at 6 wk	BRE > 2 mg/d	3	1683	−0.09 (−0.22, 0.04)	0.18	46		0.24
	BRE ≤ 2 mg/d	4	1441	−0.19 (−0.30, −0.09)	0.0003	0		

Brexpiprazole >2 mg/d vs ≤2 mg/d studies.
Abbreviations: 95% CI, 95% confidence interval; BRE: brexpiprazole; MADRS, Montgomery Åsberg Depression Rating Scale; NNT, number needed to treat; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standardized mean difference; wk: week.

Table 4. Subgroup analysis for efficacy outcomes. Published vs unpublished studies

	Subgroup	N	n	RR (95% CI)	P	I^2 (%)	NNT (95% CI)	Test for subgroup difference, P
Response rate (MADRS) at wk 6	Published studies	5	2718	0.95 (0.92–0.98)	.002	2	20 (14–50)	.04
	Unpublished studies	2	609	0.85 (0.78–0.94)	.001	0	8 (5–20)	
Remission rate (MADRS) at wk 6	Published studies	5	2706	0.97 (0.94–1.00)	.02	0	33 (25–∞)	.02
	Unpublished studies	2	609	0.87 (0.81–0.95)	.0009	0	9 (6–50)	

	Subgroup	N	n	SMD	P	I^2 (%)		Test for subgroup difference, P
MADRS score at wk 6	Published studies	5	2680	−0.21 (−0.32, −0.10)	.0003	52		.84
	Unpublished studies	2	609	−0.19 (−0.35, −0.03)	.02	0		
SDS total score at 6 wk	Published studies	5	2673	−0.11 (−0.20, −0.02)	.02	31		.54
	Unpublished studies	2	579	−0.18 (−0.39, 0.03)	.09	38		

Abbreviations: 95% CI, 95% confidence interval; MADRS, Montgomery Åsberg Depression Rating Scale; NNT, number needed to treat; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standardized mean difference; wk: week.

In both the fixed-dose and flexible-dose studies subgroups, brexpiprazole was superior to placebo for the 6-week response rate and MADRS score; however, brexpiprazole was superior to placebo for the 6-week remission rate and SDS total score in only the fixed-dose studies subgroup (Table 5). There were no significant subgroup differences in the subgroup analyses (Table 5).

Meta-Regression Analysis: Efficacy Outcomes

The meta-regression analysis did not reveal any associations between the effect size with respect to the primary and secondary efficacy outcomes and either the dose of brexpiprazole or the percentage of placebo responders (Supplementary Tables 1 and 2). However, the third meta-regression analysis showed that sample size was associated with the SMDs for MADRS score and SDS total score (Supplementary Table 3; Supplementary Figures 7 and 8).

Safety Outcomes

Compared with placebo, brexpiprazole (at all the doses) was associated with higher all-cause discontinuation and discontinuation due to adverse events as well as with higher incidences of akathisia, insomnia, restlessness, somnolence, and weight increase (Table 6).

Subgroup Analysis: Safety Outcomes

When data from the 2 long-duration studies were excluded from the primary meta-analysis so that the subgroup analysis included only the 6-week-long studies, brexpiprazole was again found to be associated with higher incidences than placebo of discontinuation due to adverse events, akathisia, insomnia, somnolence, and weight increase (Supplementary Table 4). A further subgroup meta-analysis compared brexpiprazole

Table 5. Subgroup analysis for efficacy outcomes. Fixed dose vs flexible dose studies

	Subgroup	N	n	RR (95% CI)	P	I² (%)	NNT (95% CI)	Test for subgroup difference, P
Response rate (MADRS) at wk 6	Fixed dose studies	3	1440	0.91 (0.86–0.96)	.0007	0	14 (8–33)	.61
	Flexible dose studies	4	1887	0.93 (0.87–1.00)	.04	59	17 (9–100)	
Remission rate (MADRS) at wk 6	Fixed dose studies	3	1428	0.95 (0.91–1.00)	.03	0	25 (13–∞)	.79
	Flexible dose studies	4	1887	0.94 (0.89–1.00)	.05	61		
	Subgroup	N	n	SMD (95% CI)	P	I² (%)		Test for subgroup difference, P
MADRS score at wk 6	Fixed dose studies	3	1440	−0.26 (−0.37, −0.15)	<.00001	8		.15
	Flexible dose studies	4	1849	−0.15 (−0.25, −0.04)	.007	22		
SDS total score at 6 wk	Fixed dose studies	3	1434	−0.17 (−0.27, −0.06)	.002	0		.44
	Flexible dose studies	4	1818	−0.10 (−0.23, 0.03)	.12	43		

Abbreviations: 95% CI, 95% confidence interval; MADRS, Montgomery Åsberg Depression Rating Scale; NNT, number needed to treat; RR, risk ratio; SDS, Sheehan Disability Scale; SMD, standardized mean difference; wk: week.

Table 6. Safety outcomes

Outcome	N	n	RR (95% CI)	P	I² (%)	NNH (95% CI)
Discontinuation due to all cause	8	3373	1.34 (1.11–1.60)	.002	0	33 (20–100)
Discontinuation due to adverse events	8	3373	2.36 (1.46–3.82)	.0004	0	50 (33–50)
Death	4	1851	No death was reported in both the groups.			
Suicide attempt	6	2751	1.63 (0.28–9.66)	.59	0	
Suicidal ideation	6	2751	0.61 (0.33–1.11)	.10	0	
Serious adverse events	8	3370	0.80 (0.41–1.55)	.50	0	
Akathisia	7	3355	2.93 (2.04–4.21)	<.00001	0	20 (17–25)
Dizziness	3	1303	1.63 (0.60–4.47)	.34	0	
Headache	6	2976	0.85 (0.64–1.14)	.27	8	
Insomnia	6	2316	2.12 (1.25–3.59)	.005	0	50 (25–∞)
Restlessness	4	1929	2.93 (1.07–8.02)	.04	58	33 (20–100)
Somnolence	4	2357	2.87 (1.33–6.19)	.007	32	33 (20–100)
Weight increase	8	3370	2.88 (1.87–4.42)	<.00001	16	20 (17–33)
Diarrhea	3	998	1.02 (0.49–2.16)	.95	42	
Nasopharyngitis	6	2976	1.29 (0.82–2.03)	.27	35	

Abbreviations: 95% CI, 95% confidence interval; NNH, number needed to harm; RR, risk ratio.

Table 7. Subgroup analysis for safety outcomes, excluding long-duration studies: brexpiprazole >2 mg/d vs ≤2 mg/d studies

	Subgroup	N	n	RR (95% CI)	P	I^2 (%)	NNH (95% CI)	Test for subgroup difference, P
Discontinuation due to adverse events	BRE >2 mg/d	2	854	2.11 (0.72–6.21)	.17	0		.84
	BRE ≤ 2 mg/d	4	1467	2.47 (0.87–7.07)	.09	3		
Akathisia	BRE >2 mg/d	2	852	4.58 (2.25–9.35)	<.0001	0	13 (7–∞)	.12
	BRE ≤ 2 mg/d	4	1466	2.28 (1.35–3.86)	.002	4	25 (17–50)	
Insomnia	BRE >2 mg/d	1	403	1.31 (0.36–4.80)	.69	na		.63
	BRE ≤ 2 mg/d	2	641	2.14 (0.48–9.54)	.32	54		
Somnolence	BRE >2 mg/d	2	852	7.56 (2.27–25.15)	.001	0	20 (14–33)	.37
	BRE ≤ 2 mg/d	2	840	2.96 (0.55–15.81)	.20	56		
Weight increase	BRE >2 mg/d	2	852	3.14 (0.93–10.58)	.06	39		.62
	BRE ≤ 2 mg/d	4	1466	4.50 (2.18–9.26)	<.0001	0	25 (14–33)	

Abbreviations: BRE, brexpiprazole; 95% CI, 95% confidence interval; NNH, number needed to harm; RR, risk ratio.

doses >2 mg/d and ≤2 mg/d to investigate the dose dependency of these safety outcomes (Table 7). Both dose levels were associated with a higher incidence of akathisia compared with placebo (Table 7), but only doses >2 mg/d were associated with a higher incidence of somnolence compared with placebo (Table 7). The difference compared with placebo in weight increase was marginal for doses >2 mg/d but significant for doses ≤2 mg (Table 7).

Meta-Regression Analysis: Safety Outcomes

The meta-regression analysis found no associations between the effect size of safety outcomes and the dose of brexpiprazole (Supplementary Table 1).

Discussion

This study provided an updated systematic review and meta-analyses that included 9 double-blind, randomized, placebo-controlled trials (including a total of 3391 patients) and evaluated the efficacy and safety of adjunctive brexpiprazole administered with antidepressants in patients with MDD. Compared with placebo, brexpiprazole at any of the analyzed doses produced more responders and remitters and was also superior for the other efficacy outcomes evaluated at 6 weeks, with the exception of the SDS work/school subscale score. The subgroup meta-analysis of response rates at week 6 showed that brexpiprazole at doses ≤2 mg/d had a significantly lower RR for response rate than brexpiprazole at doses >2 mg/d, that is, the response rate at 6 weeks was higher with doses ≤2 mg/d than with doses >2 mg/d. In addition, brexpiprazole at doses ≤2 mg/d but not >2 mg/d was superior to placebo for 6-week remission rate and MADRS score, although there were no significant subgroup differences in these outcomes between the >2 mg/d and ≤2 mg/d subgroups. Thus, doses ≤2 mg/d seemed to have been more effective than doses >2 mg/d for patients with MDD. Our meta-analysis showed that brexpiprazole at doses >2 mg/d was associated with the risk of acute adverse events, such as akathisia and somnolence; it is therefore possible that the negative results for efficacy outcomes with doses >2 mg/d may have been the result of the patients' intolerance of brexpiprazole at this dosage level.

We discussed the effect size of response rate and remission rate of brexpiprazole compared with other newer dopamine D_2 antagonists and D_2 partial agonists. A recent random effects model meta-analysis of adjunctive treatment for MDD with these drugs, which included only double-blind, randomized, placebo-controlled trials of 4–12 weeks duration, reported the

NNT (95% CI) for the response and remission rates as follows: aripiprazole 7 (5–12) and 9 (6–18), respectively; olanzapine/fluoxetine combination, 17 (7–34) and 19 (9–713); quetiapine, 10 (6–26) and 9 (6–19); and risperidone, 8 (5–33) and 9 (5–35) (Spielmans et al., 2013). Although the definitions of response and remission used in that study differed from those in the present study, the NNT for these outcomes seemed to appear higher at 17 (11–33) and 25 (14–50) for brexpiprazole (at all doses) compared with other newer dopamine D_2 antagonists and D_2 partial agonists other than the olanzapine/fluoxetine combination.

Brexpiprazole at all doses was associated with the risk of akathisia, insomnia, restlessness, somnolence, and weight increase. Even when the long-duration studies were excluded from the primary meta-analysis of safety outcomes, the risks of these outcomes were still present, with the exception of restlessness. The subgroup analysis based on the dose of brexpiprazole revealed a risk of somnolence for doses >2 mg/d but not for doses ≤2 mg/d. Although both brexpiprazole at doses >2 mg/d and ≤2 mg/d were associated with a risk of akathisia (NNH=13 [7–∞] and 25 [17–50], respectively), the NNH for doses ≤2 mg/d was about one-half of that of doses >2 mg/d. The meta-analysis by Spielmans et al. mentioned earlier reported the following NNHs for other newer dopamine D_2 antagonists and D_2 partial agonists compared with placebo for the incidence of adverse events: aripiprazole: akathisia, 4 (3–6); sedation, 14 (8–33); weight gain of ≥7%, 29 (10–119); olanzapine/fluoxetine combination: akathisia, 28 (11–321); sedation, 5 (3–12); elevated metabolic laboratory results, 10 (5–29); weight gain of ≥10%, 9 (5–20); elevated prolactin, 6 (4–11); quetiapine: sedation, 3 (2–3); elevated metabolic laboratory results, 6 (4–9); weight gain of ≥7%, 37 (12–594) (Spielmans et al., 2013). Although the present study made no direct comparisons between brexpiprazole and other newer dopamine D_2 antagonists and D_2 partial agonists regarding the risk of individual adverse events (which would have involved performing a network meta-analysis), brexpiprazole appeared to have a lower risk than those other drugs for these drug-induced adverse events, with higher NNHs for the safety outcomes. Given these findings, we consider brexpiprazole ≤2 mg/d to be an appropriate dose for MDD, in line with the recommendation by the FDA (FDA, 2015). It is noteworthy that a recent network meta-analysis showed that a very low dose (less than one-half the defined dose by the FDA-approved indications) of newer dopamine D_2 antagonists and D_2 partial agonists did not effectively improve depressive symptoms in patients with MDD (Zhou et al., 2015).

Brexpiprazole and aripiprazole are serotonin 5-HT_{1A} and dopamine D_2 receptor partial agonists. Brexpiprazole has a

higher antagonist activity on serotonin 5-HT$_{2A}$ receptors than aripiprazole, so it would be expected to have a stronger anti-depressant effect and to carry less risk of adverse events (such as akathisia) for patients with MDD (Maeda et al., 2014). Although all-dose brexpiprazole has been reported to have higher NNTs than aripiprazole for response rate and remission rate in MDD patients (Spielmans et al., 2013), brexpiprazole ≤2 mg/d had a similar NNT for response rate compared with aripiprazole. However, although the risk of weight gain was similar between brexpiprazole and aripiprazole, brexpiprazole (especially at doses ≤2 mg/d) seemed to have a lower risk of akathisia and somnolence compared with aripiprazole (Spielmans et al., 2013).

In the present study, the time to treatment response in patients with MDD was investigated by performing a meta-analysis of the efficacy outcomes (response rate, remission rate, and improvement in the MADRS total score) at weeks 1, 2, 3, 4, 5, and 6 after starting the adjunctive brexpiprazole therapy. From the first week after the start of the treatment with brexpiprazole, the MADRS score improved. From the second week, there was a significant difference in response rates between the treatment groups, and at week 3, a significant difference in the remission rates as well. Thus, brexpiprazole was shown to ameliorate the symptoms of MDD patients brexpiprazole improved the symptoms in patients with MDD early. However, no significant differences were found between groups in terms of remission rate at week 5. This meta-analysis result had considerable heterogeneity (I^2=56%). Because the RRs for the remission rate were similar for weeks 5 and 6 (RR=0.95), the negative result at week 5 may have been caused by a type II error related to the small sample size. Indeed, more patients were in remission at week 6 (n=3315) than at week 5 (n=1266).

Our meta-regression analysis showed that sample size was associated with the SMDs for MADRS and SDS total scores. It is possible that the larger trials had looser inclusion criteria, which might have resulted in greater heterogeneity in response to the treatment. The inclusion criterion differed for patient age between Bauer's 2018 study (18–75 years) and the other studies (18–65 years). It might be expected that trials that included individuals who had experienced more failed courses of treatment would show a reduced estimated efficacy.

The present study had several limitations. First, although the publication bias was minimized in the search of clinical trial registries, it was still detected for the primary outcome. The present study included 4 unpublished studies (i.e., gray literature) with publicly available data on the clinical trial registries. The Cochrane Handbook refers to the possibility that published trials may have an overall greater intervention effect than gray trials (Higgins and Green, 2011); however, our subgroup analysis showed that the unpublished studies had larger effect sizes than the published studies for both response and remission rates. Although the present study included fixed-dose and flexible-dose studies, there were no significant subgroup differences in the primary and secondary outcomes between the fixed-dose and flexible-dose studies subgroups. Second, the patients' characteristics, such as geographical region, race, and ethnicity, differed among the included studies. Third, the present study did not investigate which antidepressants were compatible with brexpiprazole. Fourth, all the studies included in this review were industry sponsored, so the possibility of sponsorship bias (Naci et al., 2014) should be considered when interpreting the results.

In conclusion, the results of this analysis suggest that brexpiprazole is a useful adjuvant treatment for patients with MDD who have experienced at least 1 failure of antidepressant treatment. Brexpiprazole at doses ≤2 mg/d seemed to provide a better risk/benefit balance than >2 mg/d. However, although brexpiprazole was shown to be generally well tolerated, clinicians should be aware of possible akathisia, somnolence, and weight increase when prescribing it.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology* (IJNPPY) online.
Supplementary Figure 1. PRISMA flow diagram.
Supplementary Figure 2. Risk of bias summary.
Supplementary Figure 3. Response rate at week 6.
Supplementary Figure 4. Remission rate at week 6.
Supplementary Figure 5. MADRS total score at week 6.
Supplementary Figure 6. SDS total score at week 6.
Supplementary Figure 7. Meta-regression analysis: MADRS score at week 6 vs sample size.
Supplementary Figure 8. Meta-regression analysis: SDS total score at week 6 vs sample size.
Supplementary Table 1. Meta-regression analysis: brexpiprazole dose.
Supplementary Table 2. Meta-regression analysis: percentage of placebo responders (remitters).
Supplementary Table 3. Meta-regression analysis: sample size.
Supplementary Table 4. Subgroup analysis for safety outcomes, excluding the long-duration studies.

Statement of Interest

Drs Kishi, Oya, Matsui, Nomura, Sakuma, Okuya, Matsuda, Fujita, Yoshimura, and Iwata declare that they have no direct conflicts of interest relevant to this study. No grant support or other sources of funding were used to conduct this study or prepare this manuscript. Dr Kishi has received speaker's honoraria from Daiichi Sankyo, Dainippon Sumitomo, Eisai, Janssen, Otsuka, Meiji, MSD, Yoshitomi, and Tanabe-Mitsubishi and has received a Health and Labour Sciences Research Grant and a Fujita Health University School of Medicine research grant. Dr Sakuma has received speaker's honoraria from Eisai, Kissei, Meiji, Otsuka and Torii and has received a grant-in-aid for Young Scientists (B). Dr Nomura has received speaker's honoraria from Meiji, MSD, Torii, Janssen, and Otsuka. Dr Matsuda has received speaker's honoraria from Dainippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Otsuka, Tanabe-Mitsubishi, and Pfizer

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