Adjunctive Brexpiprazole as a Novel Effective Strategy for Treating Major Depressive Disorder

A Systematic Review and Meta-Analysis

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Abstract:

Purpose/Background: Brexpiprazole was approved for adjunctive treatment of major depressive disorder (MDD) in 2015. Because only a small number of randomized controlled trials have investigated the use of brexpiprazole in MDD, we performed a meta-analysis.

Methods/Procedures: We systematically searched literatures in PubMed, Cochrane Library database, EMBASE, Google Scholar, and clinicaltrials.gov up to January 2016. The primary efficacy measure was the mean change in total Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline. Secondary efficacy measures were the mean change in total Hamilton Rating Scale for Depression (17 items) score from baseline and the response (≥50% reduction in MADRS total score) and remission (MADRS total score ≤ 10 with ≥50% reduction) rates.

Findings/Results: Four studies fulfilled the inclusion criteria and were included in the analysis. Brexpiprazole showed superior efficacy over placebo with effect sizes (mean differences) of −1.76 (95% confidence interval [CI], −2.45 to −1.07) for MADRS and −1.21 (95% CI, −1.71 to −0.72) for the 17-item Hamilton Rating Scale for Depression. The risk ratios for response and remission were 1.57 (95% CI, 1.29–1.91) and 1.55 (95% CI, 1.22–1.96), respectively. The incidences of discontinuation due to adverse events, akathisia, and weight increase were higher in the brexpiprazole group than in the placebo group, with risk ratios of 3.44 (95% CI, 1.52–7.80), 3.39 (95% CI, 2.08–5.51), and 4.36 (95% CI, 2.45–7.77), respectively, and the incidence of akathisia was related to the brexpiprazole dose.

Implications/Conclusions: Although our results suggest that brexpiprazole could be an effective adjunctive agent for MDD, they should be cautiously translated into clinical practice because the meta-analysis was based on only a handful of randomized controlled trials.

Key Words: brexpiprazole, OPC-34712, major depressive disorder, efficacy, tolerability, meta-analysis

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Remission of symptoms and functional recovery toward the premorbid state are difficult to achieve when treating a major depressive disorder, despite the plethora of antidepressants available. Only one third of the patients who receive an antidepressant achieve remission during their first treatment trial. Treatment options after the failure of first-line antidepressants include augmentation with agents other than antidepressants (eg, lithium, triiodothyronine, atypical antipsychotics, buspirone, and psychostimulants) and switching or combining antidepressants.[1]

Current reviews and meta-analyses suggest that augmentation with atypical antipsychotics is the best evidenced choice among the strategies suggested for patients with treatment-resistant depression.[2,3] The US Food and Drug Administration–approved atypical antipsychotics for augmentation in major depressive disorder are quetiapine and aripiprazole. Augmentation with those atypical antipsychotics improves treatment outcomes but also increases the risk of adverse events and lowers tolerability.[3–5] In particular, quetiapine is related to changes in metabolic profile and weight gain. Problematic sedation is also a reason for discontinuation.[6] Aripiprazole can increase body weight but does not seem to change metabolic profile.[7] Maybe because of its safety profile, aripiprazole is the most favored atypical antipsychotic in clinical practice (72%, 95% confidence interval [CI], 64%–80%),[8] but frequent akathisia is a major problem.[5,9,10]

In July 2015, the novel atypical antipsychotic brexpiprazole was approved for the adjunctive treatment of major depressive disorder.[11] The major adverse effects of aripiprazole, namely, nausea, restlessness, and akathisia, are thought to be related to its high intrinsic D_2 activity. Brexpiprazole was therefore developed as a novel D_2 partial agonist with significant but lower intrinsic activity (K_i = 0.30 nM) than aripiprazole by the same drug discovery program that developed aripiprazole.[12,13] Brexpiprazole has 10-fold higher affinity for 5-HT_{1A} (K_i = 0.12 nM, partial agonist) and 5-HT_{2A} (K_i = 0.47 nM, antagonist) than aripiprazole and also acts as an antagonist of the noradrenergic $\alpha_{1/2}$ receptor with very high affinity and as a partial agonist for D_3 (K_i = 1.1) or antagonist for 5-HT_{2B} (K_i = 1.9) and 5-HT_7 (K_i = 3.7) with high affinity.[14] These differences in pharmacodynamic profiles between brexpiprazole and aripiprazole can potentially increase tolerability of brexpiprazole over aripiprazole by reducing extrapyramidal symptoms. These differences in pharmacodynamic profiles can also result in different efficacy profiles in the management of major depressive disorders.

Assessing the efficacy and safety profile of newly approved drugs is important. However, few clinical studies have examined the effect of brexpiprazole augmentation of patients with major depressive disorder taking an antidepressant. Only 2 randomized controlled trials (RCTs)[11,15] have been published, although data from other unpublished RCTs and open-label studies are available. Systematic reviews and meta-analyses can help overcome the limitations of small sample sizes and increase the generalizability and statistical power for group comparisons.[16] In this study, we performed a systematic review and meta-analysis of short-term RCTs to synthesize the available quantitative trial evidence. In so doing, we aimed to evaluate the efficacy and tolerability of brexpiprazole as an adjunctive agent in the treatment of depression.

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MATERIALS AND METHODS

Data Sources

We searched for articles in PubMed, the Cochrane Library database, EMBASE, Google Scholar, and clinicaltrials.gov, limiting our searches to studies completed by January 14, 2016, using the search terms "depression" or "depressive" (to include depressive illness or major depressive disorder) and "brexpiprazole" or "OPC-34712." We included RCTs but excluded differently designed clinical studies, as well as review and preclinical articles. We also cross-checked the reference lists of the identified articles to discover additional clinical trial reports. We then reviewed the abstracts identified from article searching and reevaluated potentially eligible articles to ensure that they met the inclusion criteria.

Inclusion Criteria

Inclusion criteria were as follows: sample of patients given a diagnosis of major depressive disorder with history of inadequate response to current antidepressant management, short-term (6–12 weeks) RCTs comparing antidepressant with adjunctive brexpiprazole and antidepressant with placebo, the use of validated assessment tools for depression rated by a clinician for a meta-analysis of efficacy, and reported number of patients experiencing adverse events. We included articles in peer-reviewed journals, abstracts submitted to conferences, and available results at clinicaltrials.gov. We imposed no restrictions regarding depression severity, demographic factors, or study location.

Data Extraction

The characteristics of all clinical trials are summarized in Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JCP/A400. Among those articles, we included RCTs that met the inclusion criteria in our meta-analysis. Because data from publications that were used per protocol can be a source of bias,[11,15] we extracted data for the results of the efficacy outcome measures from clinicaltrials.gov, which used the intent-to-treat with last observation carried forward method to impute missing data. Demographic data and selected outcomes from the chosen RCTs are presented in Table 1.

Efficacy Measures

Montgomery-Åsberg Depression Rating Scale (MADRS) is sensitive to change and can be used both as a categorical outcome (response rate or remission rate) and a continuous outcome (difference to mean change).[17] Because of concern regarding the arbitrary nature of definitions used to define categorical outcomes, we decided to use the changes in the total MADRS score from baseline to end point as the primary efficacy measure.[18] Secondary efficacy measures were changes in the total 17-item Hamilton Rating Scale for Depression (HAM-D-17) score[19] and the response and remission rates, defined as 50% or greater reduction in the total MADRS score and a total MADRS score of 10 or less with 50% or greater reduction, respectively, as indicated by previous studies.[20,21]

Safety and Tolerability Measures

The total number of patients who discontinued treatment because of treatment-emergent adverse events was the primary outcome measure. Secondary outcome measures were the number of patients who experienced specific adverse events, such as akathisia and weight gain.

TABLE 1. Demographics and Selected Outcomes of Randomized Controlled Studies With Results Available

Registry Identifier	Brexpiprazole Dose, mg/d	N	Age, Mean (SD)	Male, n	Completed, n	MADRS LS Mean Diff (SE)	*P*	Responder, %	*P*	Remitter, %	*P*	HAM-D-17 LS Mean Diff (SE)	*P*
NCT01360645	2	188	44.1 (11.6)	58	174	−8.27 (0.61)	<0.001*	23.5	0.02†	14.4	0.06†	−5.89 (0.48)	<0.001‡
	Placebo	191	45.2 (11.3)	54	178	−5.15 (0.60)		14.7		8.38		−3.55 (0.47)	
NCT01360632	1	226	45.7 (11.6)	68	216	−7.65 (0.5)	0.09*	23.1	0.02†	15.1	0.28†	−5.47 (0.36)	0.17‡
	3	230	44.5 (11.2)	74	210	−7.98 (0.51)	0.03*	22.1	0.03†	13.7	0.46†	−6.14 (0.36)	0.007‡
	Placebo	221	46.6 (11.0)	75	208	−6.45 (0.51)		15.1		11.9		−4.8 (0.37)	
NCT00797966	0.15	62	43.9 (10.8)	21	51	−6.62 (0.99)	0.66‡	27.4	0.33†	22.6	0.13†	−5.77 (0.86)	0.60‡
	0.5 ± 0.25	120	44.0 (11.8)	34	102	−6.46 (0.73)	0.7‡	20.2	0.95†	15.1	0.67†	−5.28 (0.63)	0.95‡
	1.5 ± 0.5	121	43.7 (11.6)	41	100	−8.23 (0.74)	0.03‡	34.7	<0.01†	23.7	0.05†	−6.59 (0.62)	0.10‡
	Placebo	126	43.3 (11.5)	44	110	−6.09 (0.72)		19.8		13.5		−5.23 (0.59)	
NCT01052077	1–3	185	44.7 (11.7)	62	167	−8.20 (0.62)	0.14‡	29.9	0.03†	26.1	<0.01†	−5.98 (0.45)	0.32‡
	Placebo	187	42.4 (11.7)	57	171	−7.02 (0.62)		19.9		14.9		−5.40 (0.45)	

Statistical analysis was performed as follows: *mixed model analysis, †Cochran-Mantel-Haenszel, and ‡analysis of covariance with the placebo group.

N indicates number of subjects; SD, standard deviation; LS mean diff, least squares mean difference from baseline to the end of phase; responder, number of subjects with ≥50% reduction in MADRS total score from baseline to the end of phase/total number of subjects × 100; remitter, number of subjects with MADRS total score ≤ 10 and ≥50% reduction in MADRS total score from baseline to the end of phase/total number of subjects × 100.

Data Synthesis and Statistical Analysis

We performed the meta-analysis using Review Manager (RevMan) 5.3 (Cochrane Collaboration,[22] 2014). Changes in MADRS and HAM-D from baseline to end point were calculated as the mean differences between the intervention and placebo groups, with 95% CIs provided. Thus, we used the mean differences and standard errors (SEs) computed by RevMan using 95% CIs in the meta-analysis. We used generic inverse variance for the analysis and obtained summary estimates of the mean differences with 95% CI. When comparing the prevalence of responders, remitters, and those who discontinued treatment because of adverse events, akathisia, and weight increase between the adjunctive brexpiprazole and adjunctive placebo groups, we used the risk ratio (RR) calculated by the Mantel-Haenszel statistical method using the total number of patients and the number of patients with specific events. We obtained summary estimates of RR with 95% CI. We applied a fixed-effect model because the heterogeneity among studies is low in a meta-analysis.[23]

Heterogeneity Analysis, Sensitivity Analysis, and Meta-Regression

We tested the heterogeneity between studies with the I^2 statistic, which evaluates how much of the variance between studies can be attributed to actual differences between the studies rather than to chance. An I^2 value higher than 50% is considered to indicate meaningful heterogeneity. We performed sensitivity analyses to test the robustness of the effects of a single study on the overall estimate by eliminating 1 study at a time.

We also performed a meta-regression to assess the influence of the following moderators on the overall estimate: publication status (published vs unpublished), study location (United States only vs outside the United States/mixed location), phase of the study (phase II or III), and the doses of brexpiprazole under investigation (>2 mg vs others [1–3, 1, or 1.5 ± 0.5 mg]). In this meta-analysis, all published studies were phase III and of mixed locations, and all nonpublished studies were restricted to the United States and phase II. We performed the meta-regression using Comprehensive Meta-Analysis version 2.0 software (Englewood, NJ).

Risk of Bias

We assessed the risk of bias according to the recommendations of the Cochrane Review, and the table was generated using RevMan 5.3. As the number of included studies was less than 10, we did not assess reporting bias using a funnel plot. To reduce reporting biases, we searched and evaluated unpublished literature and accessed online trial registries.

RESULTS

Search Results

Our initial search identified 147 articles. After removing duplicated and nonclinical studies, 13 articles describing clinical trials of the adjunctive use of brexpiprazole in depression remained. In our initial search, we identified conference abstracts from the 2015 annual meetings of the American Psychiatric Association and the American Society of Clinical Psychopharmacology. Our review of those 2 conferences yielded 14 abstracts (4 from the American Psychiatric Association and 10 from American Society of Clinical Psychopharmacology) about clinical trials on adjunctive brexpiprazole for the treatment of major depressive disorder, among which two were nonduplicated, yielding 15 clinical study articles. Searching clinicaltrials.gov yielded 11 relevant completed trials. We were able to match all articles with clinical trials, and the following 9 clinical trials were compatible with previously searched articles: NCT01942733,[24] NCT02012218,[25] NCT01942785,[26] NCT02013531,[27] NCT02013609,[28] NCT01360645,[11,29–34] NCT01360632,[15,29,30,32–34] NCT00797966,[35] and NCT01447576.[32,36] Results were available for another trial, NCT01052077, in clinicaltrials.gov, but no results or compatible articles were available for the phase I clinical trial, NCT01670279, which assessed safety and tolerability in the older adults. Some articles were associated with multiple clinical trials, and some clinical trials were associated with multiple articles. Eventually, we selected 4 RCTs for our meta-analysis. A flow diagram of our study selection process is shown in Supplementary Figure 1, Supplemental Digital Content 2, http://links.lww.com/JCP/A401.

Description of Studies Included in the Meta-Analysis

The 4 identified double-blind placebo-controlled studies (NCT01360645, NCT01360632, NCT00797966, and NCT01052077) examined the efficacy and safety of adjunctive brexpiprazole with antidepressant treatment. The risk of bias was considered low or unclear in all domains, and no study scored high for risk of bias in any domain (Supplementary Figure 2, Supplemental Digital Content 3, http://links.lww.com/JCP/A402). Extracted demographic data and results of interest are listed in Table 1. In total, 3988 patients were enrolled, 1857 patients entered randomization, and 1687 completed the RCT. All subjects underwent an 8-week period of placebo plus an antidepressant. Subjects with an inadequate response after week 8 were randomly assigned to the placebo plus antidepressant group or the brexpiprazole plus antidepressant group for another 6 weeks, for a total of 14 weeks. Brexpiprazole dosage differed by study and assigned arm. All of these studies were financially supported by the manufacturer.

Low- and flexible-dose brexpiprazole (1, 0.15, 0.5 ± 0.25, 1–3 mg) failed to show superiority over placebo when used as an adjunct to antidepressants, but higher dosages (1.5 ± 0.5, 2, and 3 mg) did show superiority to placebo as measured by the change in MADRS total score.[11,35] When considering other depressive outcome measures, HAM-D-17, and the proportion of responders and remitters, the very low doses of 0.15 and 0.5 ± 0.25 mg of brexpiprazole showed consistent negative results, but findings for brexpiprazole groups treated with 1, 1.5 ± 0.5, 2, 3, and 1 to 3 mg of flexible doses were heterogeneous depending on outcome measures (Table 1). Therefore, we performed the meta-analysis using extracted data for the following dosages: 1, 1.5 ± 0.5, 2, 3, and 1 to 3 mg.

Efficacy

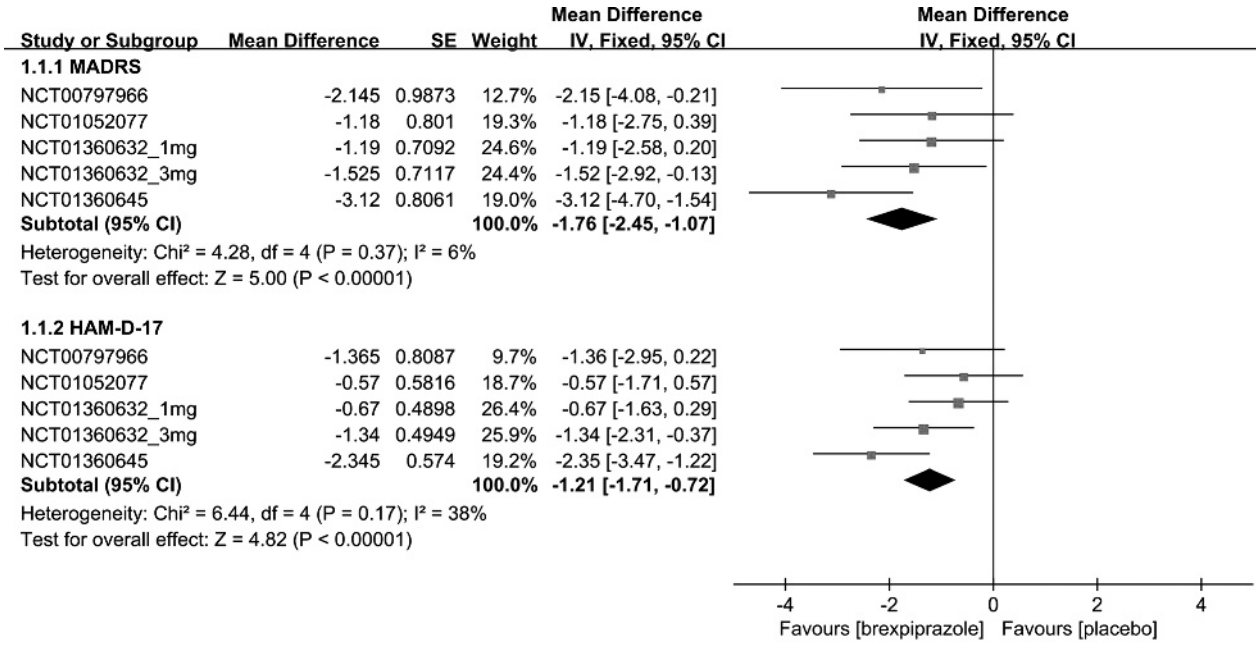
Overall Efficacy

Primary End Point

The pooled mean difference of change in the total MADRS score between brexpiprazole and placebo was −1.76 (95% CI, −2.45 to −1.07, $P < 0.00001$), favoring brexpiprazole over placebo (Fig. 1). Interestingly, the meta-analysis of previously negative studies (brexpiprazole 1 mg and 1-3 mg) also yielded positive results (pooled mean difference, −1.19, 95% CI, −2.23 to -0.14, $P = 0.03$).

Secondary End Point

The pooled mean difference of change in total HAM-D-17 score between brexpiprazole and placebo was −1.21 (95% CI, −1.71 to −0.72; $P < 0.00001$) (Fig. 1). The mean difference of change for previously negative studies (brexpiprazole of 1, 1.5 ± 0.5, and 1–3 mg) was also significant (mean difference, −0.76; 95% CI, −1.42 to −0.09; $P = 0.03$). Meta-analysis results for the frequency



SE= Standard error, 95% CI= 95% Confidence interval, MADRS=Montgomery-Åsberg Depression Rating Scale, HAM-D-17=Hamilton Rating Scale for Depression (17-items)
NCT 01360632_1 mg: difference between placebo arm in NCT 01360632 and 2 mg brexpiprazole arm.
NCT 01360632_3 mg: difference between placebo arm in NCT 01360632 and 3 mg brexpiprazole arm.

FIGURE 1. Meta-analysis of depression rating scale changes from baseline to the end of the trial in the adjunctive brexpiprazole and placebo groups.

of responders and remitters were also positive, with pooled RRs of 1.57 (95% CI, 1.29–1.91; $P < 0.00001$) and 1.55 (95% CI, 1.22–1.96; $P = 0.0004$), respectively (Fig. 2).

Heterogeneity and Sensitivity Analyses

Heterogeneity among studies was not significant with regard to efficacy outcome measures. No study robustly affected the end point results for any of the outcome measures in our sensitivity analysis.

Meta-Regression

Neither publication status, study location, phase of the study ($Z = 0.32$ and $P = 0.7488$ for end point change in MADRS score, $Z = 0.25$ and $P = 0.8055$ for end point change in HAM-D-17 score, $Z = -0.36$ and $P = 0.7202$ for response rate, $Z = -1.21$ and $P = 0.2271$ for remission rate), nor brexpiprazole dose ($Z = -0.99$ and $P = 0.3224$ for end point change in MADRS score, $Z = -1.58$ and $P = 0.1130$ for end point change in HAM-D-17 score, $Z = -0.01$ and $P = 0.9944$ in response rate, $Z = 0.22$ and $P = 0.8270$ in remission rate) had any moderating effect on the end point results for any of the outcome measures.

Safety and Tolerance

Incidence of Discontinuation Due to Adverse Events and Specific Treatment-Emergent Adverse Events

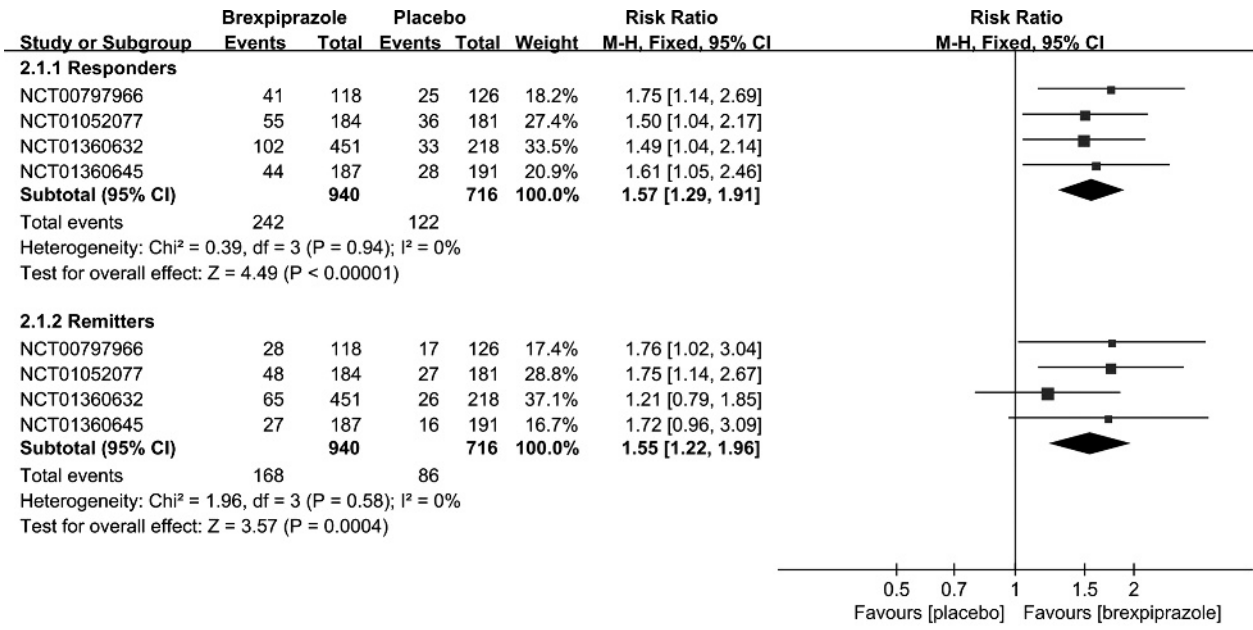
The incidence of discontinuation due to adverse events was significantly higher in the adjunctive brexpiprazole group than in the placebo group, with a pooled RR of 3.44 (95%CI, 1.52–7.80; $P < 0.003$) (Fig. 3). The specific adverse events collected in each study are described in Supplementary Table 2, Supplemental Digital Content 4, http://links.lww.com/JCP/A403. The risks of akathisia and weight increase were higher in the brexpiprazole group than in the placebo group, with pooled RRs of 3.39 (95% CI, 2.08–5.51; $P < 0.00001$) and 4.36 (95% CI, 2.45–7.77; $P < 0.00001$), respectively (Fig. 3). The percentage of discontinuation due to adverse events in all 4 of the 6-week RCTs was 3.1%, and those of emerging akathisia and weight increase were 9.2% and 7.7%, respectively.

Heterogeneity and Sensitivity Analysis

There was no significant heterogeneity among the included studies with regard to safety outcome measures. No study robustly affected the primary end point with regard to tolerability or safety outcome measures.

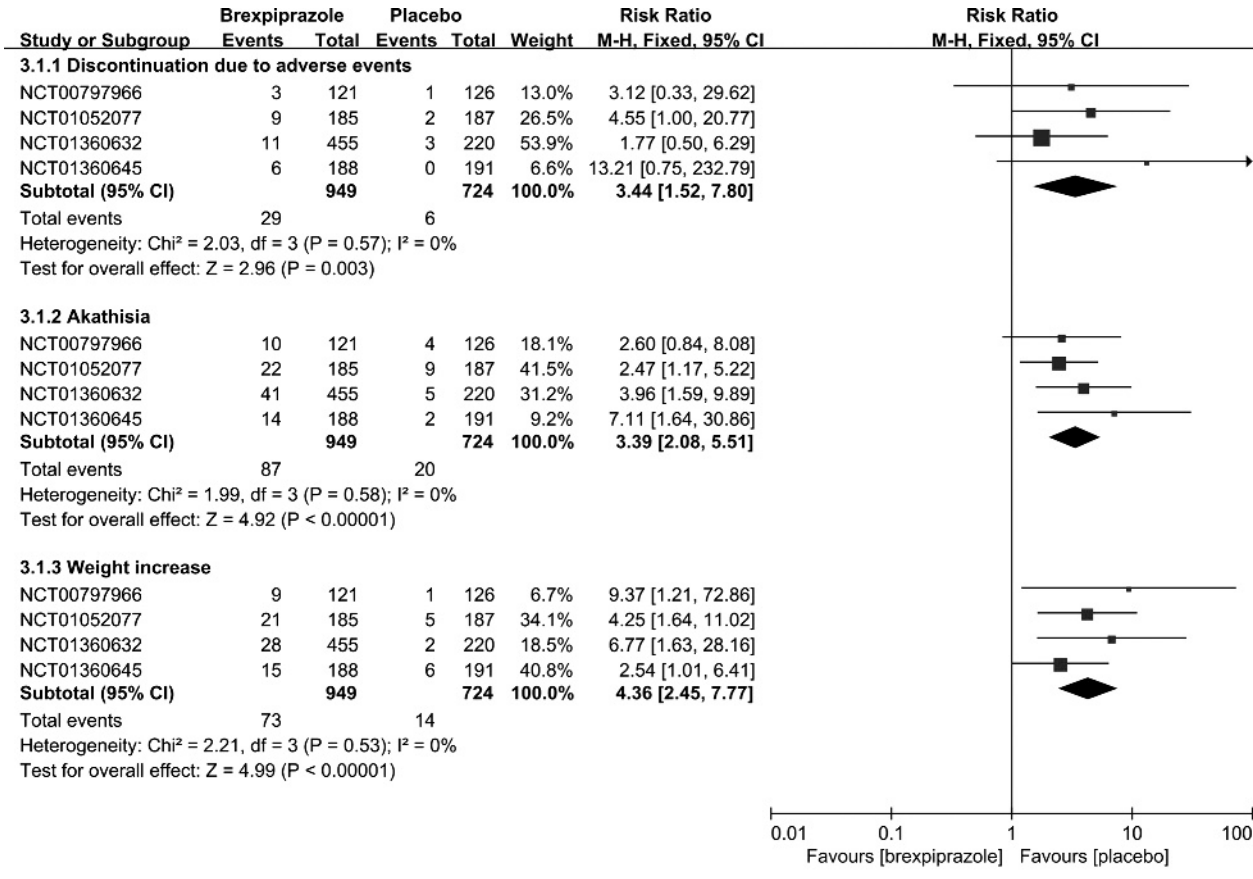
Meta-Regression

Publication status, study location, and phase of the study had no moderating effect on the end point of incidence in discontinuation due to adverse events ($Z = -1.38$, $P = 0.1686$) or specific adverse events, akathisia ($Z = -1.22$, $P = 0.2222$), or weight increase ($Z = 0.61$, $P = 0.5392$). Brexpiprazole dose significantly influenced the incidence of akathisia ($Z = 2.02$, $P = 0.00432$); studies with a restricted dose of more than 2 mg were associated with a higher incidence of akathisia. A subgroup analysis of the studies in which dose was unrestricted to more than 2 mg found a decreased RR of akathisia, which was significantly greater than placebo (RR, 2.35; 95% CI, 1.37–4.02; $P = 0.002$). However, brexpiprazole dose did not significantly affect discontinuation



M-H= Mantel-Haenszel, 95% CI= 95% Confidence interval

FIGURE 2. Meta-analysis of RR for responders and remitters defined by the MADRS in the adjunctive brexpiprazole and placebo groups.



M-H= Mantel-Haenszel, 95% CI= 95% Confidence interval

FIGURE 3. Meta-analysis of RR for discontinuation due to adverse events and specific adverse events in the adjunctive brexpiprazole and placebo groups.

due to adverse events ($Z = 1.23$, $P = 0.2172$) or weight increase ($Z = -0.92$, $P = 0.3600$).

DISCUSSION

The present meta-analysis demonstrated the superiority of adjunctive brexpiprazole 1 to 3 mg to antidepressant monotherapy in patients with inadequate response to current antidepressant management. The quality of evidence was high according to GRADEpro.[37] Although the exact mechanism of brexpiprazole's efficacy against depression is largely unknown, its superiority over antidepressant monotherapy might largely be due to its multimodal action on monoaminergic systems; 5-HT_{1A} and D_2 partial agonists and 5-HT_7 and α_2 antagonists might have antidepressant effects,[38–43] and brexpiprazole has these characteristics.

The overall efficacy of adjunctive brexpiprazole in major depressive disorder seems to be comparable but not superior to that of previously approved atypical antipsychotics. The summary of efficacy results from a previous meta-analysis of 6- to 8-week RCTs of adjunctive atypical antipsychotics in the treatment of depression and from our meta-analysis are described hereinafter (Supplementary Table 3, Supplemental Digital Content 5, http://links.lww.com/JCP/A404).[5] Continuous effect sizes converted to Hedges *g* were 0.23 (95% CI, 0.14–0.32; using MADRS) for brexpiprazole, 0.35 (95% CI, 0.23–0.48) for aripiprazole, 0.26 (95% CI, 0.04–0.45) for olanzapine-fluoxetine combination, and 0.40 (95% CI, 0.26–0.53) for quetiapine. Pooled odds ratios (ORs) for response rates compared with adjunctive placebo were 1.57 (95% CI, 1.29–1.91) for brexpiprazole, 2.07 (95% CI, 1.58–2.72) for aripiprazole, and 1.53 (95% CI, 1.33–2.42) for quetiapine. Remission rate pooled ORs were 1.55 (95% CI, 1.30–2.33) for brexpiprazole, 2.01 (95% CI, 1.48–2.73) for aripiprazole, and 1.79 (95% CI, 1.33–2.42) for quetiapine. All of the RCTs with adjunctive atypical antipsychotics involved subjects with insufficient response to an antidepressant. However, study design did differ among studies; some studies used an additional previous single-blind period (eg, brexpiprazole studies) to confirm treatment resistance, but others (eg, the quetiapine study[44]) did not, and this difference could have resulted in a larger effect size in the latter study. Therefore, a direct comparison of the efficacy of adjunctive brexpiprazole versus previous adjunctive atypical antipsychotics is needed. One open-label single-arm study evaluated treatment outcomes after switching to adjunctive brexpiprazole from a previous adjunctive treatment for which there was an inadequate response. This study included aripiprazole and quetiapine as previous adjunctive agents and reported that the MADRS total score decreased overall (-17.3, $P < 0.0001$).[25] This study implies that brexpiprazole can be the appropriate choice when remission is not achieved with previous adjunctive medications.

Two previously published studies concluded that treatment with adjunctive brexpiprazole of 2 and 3 mg and an antidepressant improved MADRS significantly over placebo with antidepressant, but 1-mg brexpiprazole did not. Therefore, the label indicates 2 mg as the target dose and 3 mg as the maximum dose.[11] However, in our sensitivity analysis, which included 1- to 3-mg dosages, no single study was identified to robustly affect the overall outcome. Furthermore, in the meta-regression, dosage was not a significant moderator of any efficacy outcome measure. These heterogeneous findings might have resulted from the limitations of a single study with a relatively small sample size. Among the placebo group, 1-mg brexpiprazole group, and 3-mg brexpiprazole group, the 1-mg brexpiprazole group had the longest duration of current episodes, highest prevalence of recurrent episodes, and highest baseline MADRS and HAM-D scores. When using a pooled placebo group from the 2 clinical trials described in these 2 publications, 1-mg brexpiprazole also showed significant superiority over placebo with regard to change in MADRS total score from baseline.[31]

In addition to the overall assessment of depression, specific symptoms and comorbid conditions are also important, and many clinicians choose medication based on symptom profiles. Brexpiprazole has similar pharmacodynamic properties to aripiprazole but higher affinity for serotonin 5-$HT1_A$, 5-HT_{2A}, and 5-HT_7.[8] Postsynaptic 5-HT_{1A} agonists have anxiolytic and antidepressant effects, with a potential role in the induction of hippocampal neurogenesis and functional remodeling of the corticolimbic circuits, enhancing catecholamine release in the forebrain.[40] There is some preclinical evidence that 5-HT_7 receptor antagonists have favorable effects on sleep architecture and procognitive effects and can enhance 5-HT release in the prefrontal cortex, leading to anxiolytic and antidepressant effects.[41,42,45–48] The 5-HT_{2A} receptor also seems to be related to a favorable sleep architecture.[49,50] Preclinical studies of brexpiprazole have indicated that adjunctive brexpiprazole has antidepressant, anxiolytic,[12] and procognitive effects superior to those of aripiprazole based on direct comparisons.[51–53] According to these pharmacodynamic profiles, brexpiprazole possibly has a greater anxiolytic effect and effects on sleep and cognition than aripiprazole.[54] In 2 phase III studies, adjunctive brexpiprazole dosages of 2 and 3 mg significantly reduced the total HAM-A score (difference in least squares mean from placebo, -1.09 [$P = 0.0376$] and -0.88 [$P = 0.443$], respectively).[11] The efficacy of brexpiprazole on sleep quality and architecture, anxiety, and irritability has been studied in single-arm open-label studies, which suggested that brexpiprazole had a positive effect, although those studies have the limitations of short follow-up duration and a small number of participants.[24,26,27]

Adjunctive brexpiprazole was related to a higher rate of discontinuation due to treatment-emergent adverse events than placebo. The most frequent and clinically important adverse events were weight gain and akathisia. In our meta-analysis, the pooled RR of discontinuation due to adverse events with brexpiprazole of 1 to 3 mg was 3.44. For akathisia, the pooled OR was 3.65, and the incidence was 9.2%. Considering that the pooled RR of aripiprazole for akathisia was 6.82 and the incidence was 22.5% in a previous meta-analysis,[5] brexpiprazole results in substantially less akathisia than aripiprazole (Supplementary Table 3, Supplemental Digital Content 5, http://links.lww.com/JCP/A404). This finding confirms the expectation that brexpiprazole would be associated with a lower prevalence of akathisia than aripiprazole because of its lower affinity for dopaminergic receptors and higher affinity for serotonergic receptors. These values are greater than those reported for brexpiprazole use in patients with schizophrenia: a 4.4% incidence of akathisia with 2-mg brexpiprazole and a 7.2% incidence with 4-mg brexpiprazole.[55] A similar discrepancy between depressive patients and patients with schizophrenia has also been reported in aripiprazole studies; this suggests that a more cautious approach is needed for patients with a mood disorder.[56] Akathisia was related to brexpiprazole dose ($Z = 2.02$, $P = 0.00432$), and this finding is consistent with previous studies with patients with schizophrenia.[32,55]

Weight increase was more frequent in the brexpiprazole group than in the placebo group, with a pooled RR of 4.36 and an incidence of 7.7%. The incidence of weight gain exceeding 7% of the initial body weight was only reported in studies NCT01360632 and NCT01360645, with a pooled OR of 2.53 (95% CI, 1.05–6.08) and an incidence of 3.7%.[11,15] This incidence rate is similar but somewhat less than those of aripiprazole (4.9%) and quetiapine (4.8%), as found in a previous meta-analysis of short-term studies (Supplementary Table 3, Supplemental Digital Content 5, http://links.lww.com/JCP/A404).[5] Weight increase

seems to occur more often after long-term use of brexpiprazole. In a 52-week long-term study of adjunctive brexpiprazole, 29.5% of patients demonstrated a 7% or greater weight increase, with a mean change of 3.1 kg from baseline. Otherwise, this long-term study found no clinically relevant change in metabolic laboratory measurements: mean change in fasting glucose, 4.61 mg/dL; total cholesterol level, 0.12 mg/dL; high-density lipoprotein cholesterol, −3.21 mg/dL; low-density lipoprotein cholesterol, 0.26 mg/dL; and triglycerides, 16.91 mg/dL.[32]

The present review has some limitations. First, the duration of the included studies was relatively short—6 weeks. The usual time to assess treatment response and make a decision to treat major depression is 4 to 8 weeks; however, considering that all subjects had a history of treatment failure and relatively long current episodes, a postponed treatment response could be expected. Second, all of the included studies were conducted in either North American or European countries. Because treatment response can differ by nationality and race, our results will be difficult to generalize worldwide.[57] Third, currently available data are limited to phase II and III studies that were supported by manufacturers and used highly selective inclusion and exclusion criteria.

Future research would be beneficial. Because brexpiprazole is currently approved by the Food and Drug Administration, postmarket observational studies will provide more information. For now, the available long-term follow-up data are limited to 52 weeks, which might be insufficient to evaluate certain adverse effects, such as tardive dyskinesia, which has been reported in some aripiprazole studies.[58] Furthermore, actual clinical situations can be complex, with unexpected physical and psychiatric comorbidities, as well as idiosyncratic reactions. Studies comparing brexpiprazole with aripiprazole focusing on specific symptoms, such as cognition, sleep, and anxiety, would be helpful. Because lower-price generic versions of aripiprazole are available, it is important to demonstrate the superiority of brexpiprazole over aripiprazole. After such information becomes available, it will become possible to establish the most effective and precise strategy for using adjunctive brexpiprazole with antidepressants.

In conclusion, 1 to 3 mg of adjunctive brexpiprazole with an antidepressant would be beneficial in managing treatment-resistant depression with less risk of akathisia, sedation, and metabolic perturbations. Brexpiprazole might be particularly useful in treating depressive patients with anxiety, lowered cognitive function, and poor sleep architecture based on its pharmacodynamic properties. Brexpiprazole product labeling recommends 2 to 3 mg as the target dose for adjunctive use in depression, but the results of our present meta-analysis suggest that, when encountering dose-related adverse events, such as akathisia, lowering the dosage to 1 or 1.5 mg can also be beneficial. Postmarket observational studies and direct comparison between aripiprazole and brexpiprazole focusing on specific symptom profiles would help clearly differentiate these 2 drugs.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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