Brexpiprazole

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 24. Medicines for mental and behavioural disorders > 24.2. Medicines for mood disorders > 24.2.1. Medicines for depressive disorders

ATC codes: N05AX16

Indication	Depressive disorders ICD11 code: 6A7Z
INN	Brexpiprazole
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid > tablet:** 0.25 mg ; 0.5 mg ; 1 mg ; 2 mg ; 3 mg ; 4 mg
EML status history	Application rejected in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Brexpiprazole
DrugBank	Brexpiprazole

Expert Committee recommendation

The Expert Committee acknowledged the substantial global burden of major depressive disorder and noted that the EML did not currently include any medicines for adjunctive therapy to antidepressant treatments. From the evidence presented in the application, the Committee noted that most studies were short-term and showed only modest incremental benefit for brexpiprazole compared with placebo, Furthermore, the Committee noted that other second-generation antipsychotics and lithium showed similar or superior gains. In terms of safety, brexpiprazole appears to be less well tolerated than many other second-generation antipsychotics. Based on these considerations, the Expert Committee did not recommend the inclusion of brexpiprazole on the EML for adjunctive treatment of major depressive disorder. The Committee recommended that any future application for medicines for adjunctive treatment of major depressive disorder should present a comprehensive evaluation of the evidence for all relevant treatment options for this indication, in preference to an application that focuses on a single medicine.

Background

Brexpiprazole has not previously been evaluated for addition to the EML.

Public health relevance

According to the 2021 Global Burden of Disease study, the global prevalence of major depressive disorder is 3%, affecting almost 230 million people. It was responsible for about 46 million disability-adjusted life years (DALYs), equivalent to 1.6% of global DALYs. The prevalence of major depressive disorders varies by WHO region and World Bank income level, with the highest rates observed in the American, European and the Eastern Mediterranean regions, and in high-income and low-income countries (1). The overall mortality rate of depressive episodes (indicative of major depressive disorder) was 0.20 per 100 000 from 1999 to 2020 in the United States, with females generally showing higher mortality rates than men (0.25 per 100 000 versus 0.12 per 100 000) (2).

Benefits

Systematic reviews The application identified 11 systematic reviews and/or meta-analyses on the comparative effectiveness and safety of brexpiprazole versus other adjunct antipsychotics to antidepressant treatments in major depressive disorder (3–13). Those studies prioritized in the application are summarized in the following paragraphs. A 2023 systematic review and network meta-analysis of 56 randomized controlled trials (11 448 participants) compared and ranked the efficacy and safety of four antipsychotics (aripiprazole, brexpiprazole, olanzapine and quetiapine) in the adjuvant treatment of major depressive disorder in adults (3). The studies were short term, ranging from 4 to 12 weeks duration. The quality of studies in the network meta-analysis was generally low. The primary efficacy outcome was the mean change in Montgomery–Asberg Depression Rating Scale (MADRS) total score from baseline to endpoint. A total of 23 studies were included in the primary efficacy analysis. Compared with placebo, all antipsychotics were significantly more effective: quetiapine, standardized mean difference (SMD) −0.40 (95% confidence interval (CI) −0.68 to −0.12); olanzapine, SMD −0.35 (95% CI −0.59 to −0.11); aripiprazole, SMD −0.28 (95% CI −0.47 to −0.09); and brexpiprazole, SMD −0.25 (95% CI −0.42 to −0.07). No significant differences were seen between the different antipsychotics. For the primary efficacy outcome, the surface under the cumulative ranking curve (SUCRA) rankings from highest to lowest were quetiapine, olanzapine, aripiprazole, brexpiprazole and placebo. All antipsychotics were associated with significantly greater response rates compared with placebo. Aripiprazole was associated with significantly greater response rates than olanzapine and quetiapine. No significant difference was seen in response rate between brexpiprazole and the other antipsychotics. The SUCRA rankings for response rate from highest to lowest were aripiprazole, brexpiprazole, olanzapine, quetiapine and placebo. A 2023 systematic review and meta-analysis of 45 randomized controlled trials (12 725 participants) evaluated the efficacy and safety of antipsychotics as monotherapy and adjunctive therapy for the treatment of adults with major depressive disorder (4). Thirty-two studies involved adjunctive antipsychotic therapy. The primary efficacy outcome was study-defined treatment response, mainly the percentage of patients with at least 50% improvement in depressive symptom scale scores from baseline. Pooled analysis found that, collectively, all antipsychotics were significantly superior to placebo plus antidepressant therapy for treatment response: relative risk (RR) 1.35 (95% CI 1.26 to 1.45); 28 randomized controlled trials, 7366 participants. Individually, ziprasidone (RR 1.80, 95% CI 1.07 to 3.04; two randomized controlled trials, 199 participants), risperidone (RR 1.59, 95% CI 1.19 to 2.14; two randomized controlled trials, 313 participants), aripiprazole (RR 1.54, 95% CI 1.35 to 1.76; eight randomized controlled trials, 2416 participants), brexpiprazole (RR 1.41, 95% CI 1.21 to 1.66; six randomized controlled trials, 2167 participants), cariprazine (RR 1.27, 95% CI 1.07 to 1.52; one randomized controlled trial, 808 participants) and quetiapine (RR 1.23, 95% CI 1.08 to 1.41; six randomized controlled trials, 1339 participants) were significantly superior to placebo plus antidepressant therapy. A 2022 meta-analysis of 15 randomized controlled trials (6570 participants) evaluated the efficacy of adjunctive aripiprazole (eight randomized controlled trials, 2671 participants) and brexpiprazole (seven randomized controlled trials, 3899 participants) in adults with major depressive disorder (5). The primary outcome measure was remission rate, where remission was defined as a MADRS total score of ≤ 10 and a ≥ 50% reduction from baseline at the follow-up visit. Overall, the study found high-certainty evidence that antipsychotic therapy was associated with significant benefit compared with placebo for remission rate (odds ratio (OR) 1.55, 95% CI 1.32 to 1.84). Individually, both aripiprazole (OR 1.82, 95% CI 1.52 to 2.19) and brexpiprazole (OR 1.37, 95% CI 1.09 to 1.73) were associated with significantly better regression rates (high-certainty evidence). For the secondary outcome of response rate (at least 50% reduction in MADRS score), there was high-certainty evidence of significant benefit over placebo for antipsychotic therapy (OR 1.62, 95% CI .44 to 1.82), aripiprazole (OR 1.84, 95%

CI 1.54 to 2.19) and brexpiprazole (OR 1.46, 95% CI 1.24 to 1.71). Significant benefits were also reported for change in MADRS score from baseline and change in clinical global impression of severity scores from baseline. A 2021 systematic review and meta-analysis of 49 randomized controlled trials (10 031 participants) evaluated the efficacy and tolerability of adding second-generation antipsychotics, esketamine, or lithium as adjunctive treatment to antidepressant therapy for major depressive disorder in adults (6). The trials were of up to 12 weeks in duration. From the results of the random-effects meta-analysis, efficacy of all adjunctive treatments was significantly superior to placebo: lithium (OR 2.22, 95% CI 1.44 to 3.43; 14 randomized controlled trials, 640 participants); intranasal esketamine (OR 1.94, 95% CI 1.52 to 2.46; seven randomized controlled trials, 1287 participants); and second-generation antipsychotics (OR 1.59, 95% CI 1.44 to 1.75; 28 randomized controlled trials, 8077 participants). Numbers needed to treat for response were five, seven and 11 for lithium, intranasal esketamine and second-generation antipsychotics, respectively. Among second-generation antipsychotics, numbers needed to treat ranged from six for risperidone to 16 for brexpiprazole. Randomized trials The application included details of four company-funded randomized studies conducted in the clinical development programme for brexpiprazole to evaluate efficacy and safety in the adjunctive treatment of major depressive disorder: Pyxis (14), Polaris (15), Sirius (16) and Delphinus (17). Only the Delphinus trial, prioritized in the application, is summarized below. The Delphinus trial was a multicentre, randomized, double-blind, active-referenced, placebo-controlled study of the efficacy and safety of brexpiprazole (2–3 mg/day) as adjunctive treatment for major depressive disorder (17). Patients (n = 2174) with a major depressive episode after an inadequate response to previous antidepressant treatment entered an 8- or 10-week prospective treatment phase and received double-blind placebo adjunct to open-label antidepressant. Following the prospective phase, participants with an inadequate response (n = 503) continued the same antidepressant therapy and were randomized (2:2:1) to receive adjunctive brexpiprazole 2−3 mg/day (n = 197), placebo (n = 206) or extended-release quetiapine 150−300 mg/day (n = 100) for 6 weeks. The primary efficacy endpoint was the change in the MADRS total score from randomization to week 6. After 6 weeks, brexpiprazole was associated with a significantly greater change from baseline in MADRS total score compared with placebo (−6.0 versus −4.6; least squares mean difference (LSMD) −1.48, 95% CI −2.566 to −0.39). No significant difference was seen between quetiapine and placebo for this outcome (−4.9 versus −4.6; LSMD −0.30, 95% CI −1.63 to 1.04). For the secondary efficacy endpoint of change from randomization to week 6 in mean score in the Sheehan Disability Scale, no significant difference was seen between brexpiprazole and placebo (−1.0 versus −0.7; LSMD −0.23, 95% CI −0.52 to 0.07). Significant differences were observed between brexpiprazole and placebo for other secondary efficacy outcomes including on the Clinical Global Impressions – Severity scale and Sheehan Disability Scale social life and family life items. No significant differences were seen for MADRS response, MADRS remission and Sheehan Disability Scale work/studies item.

Harms

Systematic reviews From the 2023 systematic review and network meta-analysis of aripiprazole, brexpiprazole, olanzapine and quetiapine in the adjuvant treatment of major depressive disorder in adults (3), no significant differences were found between the four antipsychotics and placebo for acceptability (all cause discontinuation, 20 randomized controlled trials, 7524 participants). For tolerability (discontinuation due to adverse events, 20 randomized controlled trials, 6524 participants) compared with placebo, quetiapine (RR 0.24, 95% CI 0.11 to 0.53), olanzapine (RR 0.30, 95% CI 0.10 to 0.55), brexpiprazole (RR 0.37, 95% CI 0.18 to 0.75) and aripiprazole (RR 0.39, 95% CI 0.22 to 0.69) were significantly less well tolerated. No significant differences were seen between the individual antipsychotics for either safety outcome. From the 2022 systematic review and meta-analysis of the efficacy and safety of antipsychotics as monotherapy and adjunctive therapy (4), adjunctive antipsychotic therapy was significantly less well tolerated than placebo with higher intolerability-related discontinuation compared with placebo (RR 2.39, 95% CI 1.69 to 3.38; 26 randomized controlled trials, 7553 participants). Among individual antipsychotics, ziprasidone (RR 18.2, 95% CI 2.53 to 131; two randomized controlled trials, 200 participants), quetiapine (RR 4.19, 95% CI 2.22 to 7.90; five randomized controlled trials, 1326 participants), cariprazine (RR 3.30, 95% CI 1.59 to 6.84; one randomized controlled trial, 819 participants), brexpiprazole (RR 3.24, 95% CI 1.54 to 6.79; six randomized controlled trials, 2246 participants) and aripiprazole (RR 2.08, 95% CI 1.23 to 3.51; seven

randomized controlled trials, 2308 participants) were associated with significantly higher discontinuation due to intolerability. From the 2022 meta-analysis of adjunctive aripiprazole and brexpiprazole (5), the pooled ORs for any adverse events compared to placebo were 1.58 (95% CI 1.37 to 1.83) for antipsychotics, 1.37 (95% CI 1.21 to 1.56) for brexpiprazole and 1.95 (95% CI 1.52 to 2.51) for aripiprazole. For serious adverse events, the pooled ORs compared to placebo were not statistically significant for antipsychotics (OR 0.72, 95% CI 0.48 to 1.08), brexpiprazole (OR 0.65, 95% CI 0.40 to 1.05), or aripiprazole (OR 0.94, 95% CI 0.43 to 0.03). The most commonly reported serious adverse events were arterial occlusive disease, cellulitis and suicidal ideation. From the 2021 systematic review and meta-analysis of adding the adjunctive second-generation antipsychotics, esketamine or lithium (6), the numbers needed to harm were nine, five and five for lithium, intranasal esketamine and second-generation antipsychotics, respectively. Among individual antipsychotics, the number needed to harm ranged from 19 with brexpiprazole to three with quetiapine. Randomized trials In the Delphinus trial (17), the most frequently reported treatment-emergent adverse events occurring in ≥ 5% of patients receiving brexpiprazole were akathisia (6.1%), somnolence (5.6%), headache (5.6%), increased appetite (2.5%) and dry mouth (1.0%). Body weight increase ≥ 7% at any post-baseline visit was reported by 5.7%, 5.1% and 2.4% in the brexpiprazole, aripiprazole and placebo groups, respectively. No consistent differences were observed between treatment groups for electrocardiogram assessment, vital signs and laboratory measurements. Non-randomized studies The company-funded Orion study was a 52-week (amended to 26-week), multicentre, open-label study to assess long-term safety and tolerability of brexpiprazole (0.5–3 mg/day) as adjunctive therapy to antidepressant treatment in adults with major depressive disorder (18). Of 2944 enrolled participants, 1895 (64.4%) completed the study. Almost three quarters of participants had at least 6 months exposure to brexpiprazole. A total of 2123/2938 (72.3%) participants experienced at least one treatment-emergent adverse event. The most frequently reported such events, occurring in ≥ 5% of participants, were weight increase (17.7%), somnolence (8.0%), headache (7.2%), akathisia (6.7%), increased appetite (6.3%) and insomnia (6.3%). Severe treatment-emergent adverse events were experienced by 215/2938 (7.3%) participants. Discontinuation due to treatment-emergent adverse events was reported in 253/2938 (8.6%) participants. Mean weight gain from baseline was 2.7 kg and 3.2 kg at weeks 26 and 52, respectively. The percentage of participants with weight increase ≥ 7% from baseline was 25.8%. During the open-label treatment phase, suicidal ideation and suicidal behaviour were reported in 5.5% and 0.2% of participants, respectively. Treatment-emergent suicidal ideation occurred in 0.4% of patients. Four deaths occurred during the study, of which two were suicides. One suicide death was considered by the investigator to be possibly related to adjunctive brexpiprazole treatment. The company-funded Aquila study was a 26-week, multicentre, open-label study of the safety and tolerability of brexpiprazole (1–3 mg/day) as adjunctive therapy to antidepressant treatment in elderly patients (≥ 65 years) with major depressive disorder (19). Of 132 treated participants, 44 (33.3%) withdrew from the study, including 24 (18.2%) due to adverse events. At least one treatment-emergent adverse effect was experienced by 102 (77.3%) participants. The most frequently reported treatment-emergent adverse events occurring in ≥ 5% of patients were fatigue (15.2%), restlessness (12.9%), increased appetite (9.8%), akathisia (8.3%) and weight gain (8.3%). The treatment-emergent adverse events most frequently responsible for study withdrawal were fatigue, akathisia, tremor, anxiety and depression. With respect to weight gain, the mean change in body weight from baseline to week 26 was 0.9 kg. Weight gain of ≥ 7% from baseline was reported in four participants. Small mean increases in prolactin levels were reported in some participants. One participant without suicidal ideation at baseline experienced treatment-emergent suicidal ideation. No deaths occurred during the open-label treatment period.

Cost / cost effectiveness

The application reported ranges of lowest list prices for brexpiprazole by tablet strength in high- income countries and low- and middle-income countries. The lowest price in high-income countries ranges from 0.82 United States dollars (US$) to US$ 6.17 per unit, while the lowest price in low- and middle-income countries ranges from US$ 0.89 to US$ 5.09 per unit. Comparative prices of other antipsychotic medicines were not presented. A 2017 company-funded modelled economic analysis evaluated the cost–effectiveness of adjunctive brexpiprazole versus alternative adjunctive treatments and antidepressant monotherapy for major depressive disorder from a United States payer perspective over a 48-week time horizon (28). Brexpiprazole was associated with higher clinical

response and remission rates after 6 weeks compared with alternative adjunctive antipsychotics and antidepressant monotherapy, as well as higher total costs per patient. Overall, despite higher total costs, medical care cost-savings were observed with the use of brexpiprazole compared with alternatives. A 2019 company-funded retrospective study compared real-world health-care utilization and costs of brexpiprazole and extended-release quetiapine as adjunctive treatment in patients with major depressive disorder using data from IQVIA Real World Data– US Adjudicated Claims database between July 2014 and September 2016 (29). Resource use and health-care costs in the 6 months after the start of treatment were compared between non-matched populations and between propensity score-matched groups. Significant differences were found between brexpiprazole and quetiapine in the non-matched cohorts for the following variables: proportion of patients with all-cause hospital stay (6.6% versus 12.5%); proportion of patients with emergency department visit for any reason (16.9% versus 27.5%); mean number of all-cause hospitalizations (0.10 versus 0.21) and number of emergency department visits (0.30 versus 0.55) per patient; mean number of all-cause physician office visits per patient (14.89 versus 12.57); and mean medical costs (US$ 6421 versus US$ 8545) and pharmacy costs (US$ 7401 versus US$ 4691) per patient. No significant difference was seen between treatments for mean total health-care costs per patient (US$ 13 821 versus US$ 13 235). Differences in these parameters between the matched cohorts were not statistically significantly different. A 2018 study compared health-care use and costs in 1380 patients with major depressive disorder using data from IQVIA's PharMetrics Plus Adjudicated Claims database before and after starting adjunctive atypical antipsychotic treatment with aripiprazole, brexpiprazole, lurasidone or quetiapine between 1 October 2014 and 30 September 2015 (30). Starting adjunctive antipsychotic treatment reduced all-cause and major depressive disorder-related hospitalizations by 12.2% and 10.4%, respectively, compared with antidepressant monotherapy. Starting antipsychotic treatment was associated with significant decreases in mean hospital costs (US$ 6217 and US$ 1166 per patient) compared with antidepressant monotherapy. Mean all-cause medical costs were significantly reduced by US$ 4513 per patient. Pharmacy costs were significantly increased by US$ 4236 per patient, the majority of which was attributed to psychotropic drug use. A 2023 study investigated the use of health-care resources and costs associated with use of atypical antipsychotics as first- versus later-line adjunctive treatment of major depressive disorder in 508 830 patients using data from the Merative MarketScan Commercial Database between 1 January 2014 and 30 June 2019 (31). Use of health-care resources was significantly higher in patients starting adjunctive antipsychotics as later-line treatment than those starting as first-line treatment, largely attributable to outpatient visits. Later-line initiation was also associated with significantly higher health-care costs per patient than first-line initiation for all-cause health-care costs (mean difference US$ 2441) and mental health-related health-care costs (mean difference US$ 1762).

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders does not currently include any recommendations on adjunctive therapy to antidepressants for major depressive disorder (20). A number of national and professional society guidelines recommend the use of adjunctive antipsychotics in patients with major depressive disorder who do not respond, or have limited response to, antidepressant treatment (21–27).

Availability

Brexpiprazole has been approved by the United States Food and Drug Administration for use as adjunctive therapy to antidepressants for the treatment of major depressive disorder in adults. It has not been approved by the European Medicines agency for this indication. The application reported that brexpiprazole has market availability in 67 countries globally. It has regulatory approval for adjunctive treatment of major depressive disorder in 29 countries globally. Brexpiprazole is under patent protection until 2033. Generic brands of brexpiprazole are not currently available.

Other considerations

The Department of Mental Health, Brain Health and Substance Use reviewed and provided comments on the application. The technical department thought it was difficult to justify the inclusion of brexpiprazole on the EML at

this time, based on the available evidence for clinical efficacy and harms, low availability in low- and middle-income countries, high cost and patent status.

1. Global Burden of Disease database [online database]. Seattle, WA: Institute for Health Metrics and Evaluation; 2021 (https://vizhub.healthdata.org/gbd-results/).
2. Patel R, Arisoyin AE, Okoronkwo OU, Aruoture S, Okobi OE, Nwankwo M et al. Trends and factors associated with the mortality rate of depressive episodes: an analysis of the CDC wide-ranging online data for epidemiological research (WONDER) database. Cureus. 2023;15(7):e41627 (https://doi.org/10.7759/cureus.41627).
3. Wang J, Li W, Li M, Wu H, Qiu Z. Comparative efficacy and safety of 4 atypical antipsychotics augmentation treatment for major depressive disorder in adults: a systematic review and network meta-analysis. Medicine (Baltimore). 2023;102(38):e34670 (https://doi.org/10.1097/md.0000000000034670).
4. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Efficacy and safety/tolerability of antipsychotics in the treatment of adult patients with major depressive disorder: a systematic review and meta-analysis. Psychol Med. 2023;53(9):4064–82 (https://doi.org/10.1017/s0033291722000745).
5. Mishra A, Sarangi SC, Maiti R, Sood M, Reeta K. Efficacy and safety of adjunctive serotonin-dopamine activity modulators in major depression: a meta-analysis of randomized controlled trials. J Clin Pharmacol. 2022;62(6):721–32 (https://doi.org/https://doi.org/10.1002/jcph.2022).
6. Vázquez GH, Bahji A, Undurraga J, Tondo L, Baldessarini RJ. Efficacy and tolerability of combination treatments for major depression: antidepressants plus second-generation antipsychotics vs. esketamine vs. lithium. J Psychopharmacol. 2021;35(8):890–900 (https://doi.org/10.1177/02698811211013579).
7. Kishi T, Sakuma K, Saito T, Nakagawa A, Kato M, Iwata N. Comparison of brexpiprazole, aripiprazole, and placebo for Japanese major depressive disorder: a systematic review and network meta-analysis. Neuropsychopharmacol Rep. 2024;44(1):165–75 (https://doi.org/10.1002/npr2.12414).
8. Scott F, Hampsey E, Gnanapragasam S, Carter B, Marwood L, Taylor RW et al. Systematic review and meta-analysis of augmentation and combination treatments for early-stage treatment-resistant depression. J Psychopharmacol. 2023;37(3):268–78 (https://doi.org/10.1177/02698811221104058).
9. Yan Y, Yang X, Wang M, Chen B, Yin L, Ma X. Efficacy and acceptability of second-generation antipsychotics with antidepressants in unipolar depression augmentation: a systematic review and network meta-analysis. Psychol Med. 2022;52(12):2224–31 (https://doi.org/10.1017/S0033291722001246).
10. Furukawa Y, Oguro S, Obata S, Hamza T, Ostinelli EG, Kasai K. Optimal dose of brexpiprazole for augmentation therapy of antidepressant-refractory depression: a systematic review and dose-effect meta-analysis. Psychiatry Clin Neurosci. 2022;76(9):416-22 (https://doi.org/10.1111/pcn.13438).
11. Antoun Reyad A, Girgis E, Mishriky R. Efficacy and safety of brexpiprazole in acute management of psychiatric disorders: a meta-analysis of randomized controlled trials. Int Clin Psychopharmacol. 2020;35(3):119–28 (https://doi.org/10.1097/yic.0000000000000308).
12. Kishi T, Sakuma K, Nomura I, Matsuda Y, Mishima K, Iwata N. 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. Int J Neuropsychopharmacol. 2019;22(11):698–709 (https://doi.org/10.1093/ijnp/pyz040).
13. Demyttenaere K, Detraux J, Racagni G, Vansteelandt K. Medication-induced akathisia with newly approved antipsychotics in patients with a severe mental illness: a systematic review and meta-analysis. CNS Drugs. 2019;33(6):549–66 (https://doi.org/10.1007/s40263-019-00625-3).
14. Thase ME, Youakim JM, Skuban A, Hobart M, Augustine C, Zhang P et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry. 2015;76(9):1224–31 (https://doi.org/10.4088/JCP.14m09688).
15. Thase ME, Youakim JM, Skuban A, Hobart M, Zhang P, McQuade RD et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. J Clin Psychiatry. 2015;76(9):1232–40 (https://doi.org/10.4088/JCP.14m09689).
16. Hobart M, Skuban A, Zhang P, Augustine C, Brewer C, Hefting N et al. A randomized, placebo-controlled study of the efficacy and safety of fixed-dose brexpiprazole 2 mg/d as adjunctive treatment of adults with major depressive disorder. J Clin Psychiatry. 2018;79(4):17m12058 (https://doi.org/10.4088/JCP.17m12058).
17. Hobart M, Skuban A, Zhang P, Josiassen MK, Hefting N, Augustine C et al. Efficacy and safety of flexibly dosed brexpiprazole for the adjunctive treatment of major depressive disorder: a randomized, active-referenced, placebo-controlled study. Curr Med Res Opin. 2018;34(4):633–42 (https://doi.org/10.1080/03007995.2018.1430220).
18. Hobart M, Zhang P, Skuban A, Brewer C, Hefting N, Sanchez R et al. A long-term, open-label study to evaluate the safety and tolerability of brexpiprazole as adjunctive therapy in adults with major depressive disorder. J Clin Psychopharmacol. 2019;39(3):203–9 (https://doi.org/10.1097/jcp.0000000000001034).
19. Lepola U, Hefting N, Zhang D, Hobart M. Adjunctive brexpiprazole for elderly patients with major depressive disorder: an open-label, long-term safety and tolerability study. Int J Geriatr Psychiatry. 2018;33(10):1403–10 (https://doi.org/10.1002/gps.4952).
20. Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Geneva, World Health Organization; 2023 (https://iris.who.int/handle/10665/374250). Licence: CC BY-NC-SA 3.0 IGO.
21. Practice guideline for the treatment of patients with major depressive disorder, third edition. Washington, DC: American Psychiatric Association; 2010. (http://www.psychiatryonline.com).
22. Lam RW, Kennedy SH, Adams C, Bahji A, Beaulieu S, Bhat V et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 update on clinical guidelines for management of major depressive disorder in adults. Can J Psychiatry. 2024;69(9):641–87 (https://doi.org/10.1177/07067437241245384).
23. Depression in adults: treatment and management. NICE guideline [NG222]. London: National Institute for Health and Care Excellence; 2022 (https://www.nice.org.uk/guidance/ng222).
24. Cleare A, Pariante CM, Young AH, Anderson IM, Christmas D, Cowen PJ et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology gui

delines. J Psychopharmacol. 2015;29(5):459–525 (https://doi.org/10.1177/0269881115581093).
25. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Möller H-J. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry. 2013;14(5):334–85 (https://doi.org/10.3109/15622975.2013.804195).
26. Qaseem A, Owens DK, Etxeandia-Ikobaltzeta I, Tufte J, Cross JT, Jr., Wilt TJ et al. Nonpharmacologic and pharmacologic treatments of adults in the acute phase of major depressive disorder: a living clinical guideline from the American College of Physicians. Ann Intern Med. 2023;176(2):239–52 (https://doi.org/10.7326/m22-2056).
27. Malhi GS, Bell E, Bassett D, Boyce P, Bryant R, Hazell P et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2021;55(1):7–117 (https://doi.org/10.1177/0004867420979353).
28. Sussman M, Yu J, Kamat SA, Hartry A, Legacy S, Duffy R et al. Cost–effectiveness of brexpiprazole adjunctive treatment for major depressive disorder. J Affect Disord. 2017;207:54–62 (https://doi.org/10.1016/j.jad.2016.09.006).
29. Seetasith A, Greene M, Hartry A, Burudpakdee C. Real-world economic outcomes of brexpiprazole and extended-release quetiapine adjunctive use in major depressive disorder. Clinicoecon Outcomes Res. 2019;11:741–55 (https://doi.org/10.2147/CEOR.S220007).
30. Seetasith A, Greene M, Hartry A, Burudpakdee C. Changes in healthcare resource use and costs associated with the use of adjunctive atypical antipsychotics in major depressive disorder. Value Health. 2018;21:S186 (https://doi.org/10.1016/j.jval.2018.04.1265).
31. Jain R, Laliberté F, Germain G, Mahendran M, Higa S, Harrington A et al. Treatment patterns, health care resource utilization, and costs associated with use of atypical antipsychotics as first vs subsequent adjunctive treatment in major depressive disorder. J Manag Care Spec Pharm. 2023;29(8):896–906 (https://doi.org/10.18553/jmcp.2023.29.8.896).

