PROPOSAL FOR THE ADDITION OF BREXPIPRAZOLE TABLETS FOR THE ADJUNCTIVE TREATMENT OF ADULTS WITH MAJOR DEPRESSIVE DISORDER (MDD) TO THE WORLD HEALTH ORGANIZATION (WHO) MODEL LIST OF ESSENTIAL MEDICINES (EML)

Applicant:
Otsuka Pharmaceutical Inc.

Contact:
Heidi Waters, MBA, PhD,
Senior Director Policy Research, GVRWE, Otsuka
Email: heidi.waters@otsuka-us.com

Date of development: October 30, 2024

Table of Contents

List of Abbreviations

Abbreviations	
5-HT2A	Serotonin 2A Receptor
5HT1A	Serotonin 1A Receptor
AAP	Atypical Antipsychotics
ACP	American College of Physicians
ADT	Antidepressant Therapy
AE	Adverse Event
AOR	Adjusted Odds Ratio
APA	American Psychiatric Association
ARI	Aripiprazole
ATRQ	Antidepressant Treatment Response Questionnaire
BAP	British Association for Psychopharmacology
BARS	Barnes Akathisia Rating Scale
BIA	Budget Impact Analysis
BRE	Brexpiprazole
CANMAT	Canadian Network for Mood and Anxiety Treatments
CAR	Cariprazine
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CI	Confidence Interval
CR	Controlled Release
CrCl	Creatine Clearance
CUA	Cost Utility Analysis
C-SSRS	Columbia Suicide Severity Rating Scale
D2	Dopamine Receptor D2
DALY	Disability-Adjusted Life Year

Abbreviations	
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DT	Delirium Tremens
ECG	Electrocardiogram
ED	Effective Dose
EMA	European Medicines Agency
EPS	Extrapyramidal Symptoms
EML	Model List of Essential Medicines
EMLc	Model List of Essential Medicines for Children
ES	Effect Size
EU	European Union
FDA	Food and Drug Administration
GAD-7	Generalized Anxiety Disorder 7
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HDRS-17	Hamilton Depression Rating Scale-17
HCP	Healthcare Provider
HCRU	Healthcare Resource Utilisation
HDL	High-Density Lipoprotein
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IDS-SR	Inventory of Depressive Symptomatology - Self-Report
LDL	Low-Density Lipoprotein
LMIC	Low- and Middle-Income Countries
LOT	Line of Therapy

Abbreviations	
LSM	Least Squares Mean
LSMD	Least Squares Mean Difference
MADRS	Montgomery-Åsberg Depression Rating Scale
MaHTAS	Malaysian Health Technology Assessment Section
MAOI	Monoamine Oxidase Inhibitors
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
mhGAP	Mental Health Gap Action Programme
MINI	Mini-International Neuropsychiatric Interview
MNHS	Mexican National Health System
MXN	Mexican Peso
NAP	Newly Approved Antipsychotics
NaSSA	Noradrenergic and Specific Serotonergic Antidepressants
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta Analysis
NMDA	N-Methyl-D-Aspartate
NMS	Neuroleptic Malignant Syndrome
NNH	Number Needed to Harm
NNT	Number Needed to Treat
OFC	Olanzapine + Fluoxetine Combination
OLA	Olanzapine
OR	Odds Ratio
P	Probability
PBO	Placebo
PHQ-9	Patient Health Questionnaire-9
PI	Prescribing Information

Abbreviations	
PICO	Patient Intervention Comparator Outcome
PIP	Pipamperone
PKR	Pakistani Rupee
PPPY	Per Person Per Year
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QUE	Quetiapine
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RCT	Randomised Controlled Trial
RG	Recommendation Grade
RIS	Risperidone
RR	Relative Risk
RSP	Risperidone
SAE	Serious Adverse Event
SAS	Simpson-Angus Scale
SDAM	Serotonin-Dopamine Activity Modulator
SDS	Sheehan Disability Scale
SE	Standard Error
SGA	Second-Generation Antipsychotics
SLR	Systematic Literature Review
SMD	Standardised Mean Difference
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
SUCRA	Surface Under the Cumulative Ranking Curve
TCA	Tricyclic Antidepressant
TEAE	Treatment-Emergent Adverse Event

Abbreviations	
THI	Thioridazine
TRD	Treatment-Resistant Depression
UI	Uncertainty Interval
US	United States
USD	United States Dollars
WFSBP	World Federation of Societies of Biological Psychiatry
WHO	World Health Organization
WLQ	Work Limitations Questionnaire
WTP	Willingness to Pay
XR	Extended Release
YLD	Years Lived with Disability
ZIP	Ziprasidone
ZPS	Ziprasidone

1. Summary Statement of the Proposal

- Major depressive disorder (MDD) is a chronic, debilitating, and heterogenous disease that is characterised by depressed mood, diminished interests, and impaired cognitive function. Affecting over 185 million people, MDD significantly reduces life expectancy, largely due to suicide, and doubling all-cause mortality risk. It accounts for 37.3% of mental disorder-related disability adjusted life years (DALYs), with the highest burden in low- and middle-income countries (LMICs) (section 6.1).
- Approximately 50% of patients with MDD experience inadequate response to antidepressant treatments (ADTs), which are frequently associated with worse clinical, economic, and societal outcomes which worsens with each subsequent inadequate therapy. The large treatment gap in LMICs exacerbates the economic burden, impacting not only patients and families but also employers and governments due to reduced productivity, lower labour participation, and increased welfare expenditures (section 6.2).
- The World Health Organization (WHO) Model List of Essential Medicines (EML) - 23rd list, 2023 currently recommends ADTs including, amitriptyline tablets and fluoxetine with a square box warning with citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline as therapeutic alternatives for the treatment of major depression (section 9.1). Currently there are no adjunctive therapy to ADTs included in the WHO EML for the treatment of MDD in adults. However, adjunctive treatments for MDD are recommended in various national guidelines due to the significant burden of MDD (section 9.2).
- Given the high clinical and economic burden of MDD, particularly in LMICs, there is a pressing need for additional effective treatment options to improve clinical outcomes and quality of life (QoL; section 9.1). For patients with inadequate response to ADTs, early augmentation with antipsychotics may improve patient well-being beyond the core symptoms of depression (section 6.3).
- Otsuka is proposing the addition of brexpiprazole tablets as a new listing as an adjunctive treatment to ADTs for the treatment of adult patients with MDD. Adjunctive brexpiprazole is a safe and effective treatment option for patients with MDD who have an inadequate response to traditional ADTs.
    - Brexpiprazole demonstrates efficacy and is generally well tolerated (section 6.3.1).
    - Adjunctive brexpiprazole improves symptoms of depression in patients with or without symptoms of anxiety, and may have unique clinical benefits, including potentially improving anxiety, irritability, and sleep (section 6.3.1).
    - Brexpiprazole is associated with a low risk of activating or sedating side effects (section 6.3.1).
    - Adjunctive brexpiprazole in MDD could potentially reduce the economic burden by lowering relapse rates, improving work productivity, and decreasing healthcare utilisation (section 6.3.2).
    - Adjunctive brexpiprazole improves depressive symptoms and may improve patient well-being and life engagement beyond the core symptoms of depression (section 6.3.3).

- Otsuka is passionate and committed about helping others. We envision a world where everyone can access the healthcare they need. Our promise is to invest in products, programs, policies, and advocacy efforts that help remove stigma and discrimination, increase access to care, and address social determinants of health (section 10.2.1). Otsuka strives to make medications affordable and accessible, particularly in LMICs. By supporting the inclusion of essential medicines, like brexpiprazole, on the WHO EML, we aim to provide vital treatment options for chronic conditions such as MDD. Recognising the financial barriers many patients face, we are committed to responsible pricing strategies (section 10.2).

2. Consultation with WHO Technical Departments

Notification to submit an application for brexpiprazole for the adjunctive treatment of MDD in adults was shared with the WHO EML Secretariat on May 29, 2024, with acknowledgement and referral to the WHO Department of Mental Health and Substance Use.

The Mental Health Unit of the WHO Department of Mental Health, Brain Health and Substance Use provided consultation and considerations for the submission on August 8, 2024.

Description of the correspondence from the WHO Technical Department regarding the submission has been presented in Appendix A.1.

3. Other Organisation(s) Consulted and/or Supporting the Submission

The following experts have provided endorsement for the addition of brexpiprazole to the WHO EML for the adjunctive treatment of MDD in adults:

- **Professor Christoph Correll**, Professor of Psychiatry and Molecular Medicine in The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Hempstead, NY, US.
- **Doctor Muzaffer Kaser**, Consultant Psychiatrist in the National Health Service (NHS) and Affiliate Assistant Professor at the Department of Psychiatry at University of Cambridge, Cambridge, United Kingdom.

Full details of the letters of support can be found in Appendix A.2.

4. Key Information Summary for the Proposed Medicine

International non-proprietary name	Brexpiprazole
ATC code	N05AX16
Indication(s): ICD11 codes	6A71 Recurrent depressive disorder: 6A71.3 Recurrent depressive disorder, current episode severe, without psychotic symptoms
Dosage form	Tablet
Strength	0.25 mg/0.5 mg/1 mg/2 mg/3 mg/4 mg
EML	Yes
EMLc	No

Abbreviations: ATC: Anatomical Therapeutic Chemical; EML: Model List of Essential Medicines; EMLc: Model List of Essential Medicines for Children; ICD: International Classification of Diseases

5. Listing as an Individual Medicine or Representative of a Pharmacological Class/Therapeutic Group

The Company is proposing the addition of brexpiprazole tablets as a new listing as an adjunctive treatment to antidepressants for the treatment of adult patients with MDD. The proposed addition of brexpiprazole on the WHO EML would be to:

- Section 24: Medicines for mental and behavioural disorders.
- Section 24.2: Medicines used in mood disorders.
- Section 24.2.1: Medicines for depressive disorders.

6. Information Supporting the Public Health Relevance, Proposed Indication, and Target Population

- Depression is a widespread, debilitating psychiatric illness with far-reaching clinical and humanistic consequences *(1, 2)*.
- MDD is a chronic, debilitating disease that is characterised by depressed mood, diminished interests, and impaired cognitive function *(3)*. It is multifactorial with both genetic and environmental factors playing a role *(2)*.
- MDD is diagnosed when an individual has a persistently low or depressed mood, anhedonia (the lack of interest, enjoyment, or pleasure from life's experiences) or decreased interest in pleasurable activities, feelings of guilt or worthlessness, lack of energy, poor concentration, appetite changes, psychomotor retardation or agitation, sleep disturbances, or suicidal thoughts. Per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), an individual must have five of the above-mentioned symptoms, of which one must be a depressed mood or anhedonia causing social or occupational impairment, to be diagnosed with MDD. History of a manic or hypomanic episode must be ruled out to make a diagnosis of MDD *(4)*.

6.1 Epidemiology

6.1.1 Incidence

The global incidence of MDD was reported at over 2.7 billion cases in 2019, underscoring the high burden of the disease.

- As per the Global Burden of Disease study (GBD) study, global age standardised incidence rate of depressive disorders was 3,588.25 (95% uncertainty interval [UI]: 3,152.71-4,060.42) in 2019 *(5)*. Higher incidence rate is observed in females compared with males; and in 2019, there were 110,123,422 (95% UI: 96,668,365, 124,305,433) incidence cases in males, and 180,062,320 (95% UI: 159,076,846, 204,131,417) incidence cases in females globally *(5)*.
- The global incidence of MDD was 2,784,803,790 (95% UI: 241,280,545, 312,774,423) in 2019 *(5)*.

6.1.2 Prevalence

MDD is a highly prevalent disorder, affecting 4.6% (over 185 million people) of the population globally, with higher prevalence observed in LMICs.

- According to the GBD study, the global prevalence of depressive disorders in 2019 was 279.6 (95% UI: 251.6, 310.3) million, with an age standardised prevalence of 3,440.1 (95% UI: 3,097.0, 3,817.6) per 100,000 people *(6)*.

- The global prevalence of MDD in 2017 was approximately 4.6% of the global population *(7)*, and in 2019, affected over 185 million people *(6)*. Overall, the prevalence of MDD varies by region, with the highest rates observed in North Africa and the Middle East, and Sub-Saharan Africa *(8)*, highlighting the significant burden of the disease in LMICs. The age standardised prevalence of MDD by location is presented in Table 1.
- The prevalence of MDD was highest in Sub-Saharan Africa (3,265.0 cases per 100,000 people [95% UI: 2,853.5, 3,735.5]) and North Africa and the Middle East (3,322.1 cases per 100,000 people [95% UI: 2,843.8, 3,902.1] and was greater than in high-income regions (Australasia, high-income Asia Pacific, high-income North America, Southern Latin America, Western Europe) *(6)*.
- The prevalence of MDD is 3-times higher in younger adults (18 to 29 years) compared with older adults (above 60 years). Additionally, MDD is more common in females (1.5 to 3-fold higher rates) than in males beginning in early adolescence *(2)*.
- The COVID-19 pandemic has significantly impacted the psychological distress on a global scale especially in females and the younger age group (≤40 years old) *(9)*. A large systematic literature review (SLR) and meta-analysis by the COVID-19 Mental Disorders Collaborators (2021) revealed a 27.6% increase in the global prevalence of MDD following the COVID-19 pandemic outbreak (change from pre-pandemic prevalence, 2013 to 2019). The study estimated an increase of 53.2 million cases of MDD worldwide after the COVID-19 pandemic, with a range of 44.8 to 62.9 million, resulting in a total prevalence of 3,152.9 cases per 100,000 people (range: 2,722.5, 3,654.5) *(10)*.

Table 1: Age-standardised prevalence of MDD per 100,000 people by region in 2019

Location	Age standardised prevalence (95% UI) per 100,000
Global	2,285.6 (2,006.4, 2,591.6)
High-income regions[a]	2,714.6 (2,402.5, 3,063.7)
Central Asia	2,110.9 (1,830.5, 2,446.6)
Central Europe	1,514.9 (1,323.4, 1,736.9)
Eastern Europe	2,259.4 (1,961.0, 2,596.1)
North Africa and Middle East	3,322.1 (2,843.8, 3,902.1)
South Asia	2,683.4 (2,363.1, 3,031.8)
Southeast Asia	2,683.4 (2,363.1, 3,031.8)
Sub-Saharan Africa	3,265.0 (2,853.5, 3,735.5)

Source: *(6)*
Abbreviations: MDD: major depressive disorder; UI: uncertainty interval
Note: [a] Includes Australasia, high-income Asia Pacific, high-income North America, Southern Latin America, Western Europe

6.1.3 Mortality and Survival

MDD increases the risk of premature death, with a 20-fold higher suicide risk and increased all-cause mortality compared to the general population.

- On average, people with severe mental disorders, including MDD, die 10 to 20 years earlier than the general population *(11, 12)*.
    - The overall mortality rate of depressive episodes (indicative of MDD) was 0.20 per 100,000 from 1999 to 2020 in the US *(13)*. Additionally, females generally showed higher mortality rates (0.25 per 100,000) associated with depressive episodes than males (0.12 per 100,000) *(13)*.
    - Patients with depression who are not responding adequately to several treatments are at increased risk for premature death, particularly suicide *(12)*. Individuals with MDD have a 20-fold higher risk of suicide compared with the general population *(14, 15)*.
    - According to a retrospective study in the US, the suicide mortality rates are higher for patients with poor response to treatment, with rates at 0.74/1,000 person-years and 1.87/1,000 person-years for treatment-resistant depression (TRD) in females and males, respectively, and 0.14/1,000 person-years and 0.74/1000 person-years for non-TRD in females and males, respectively *(12)*.
- A recent population wide study showed that all-cause mortality was more than double in patients with MDD compared with a matched population cohort (patients with no recordings of depression, intentional self-harm, or antidepressant therapy) *(16)*. All-cause mortality was more than double in adults with MDD who had a diagnosis of suicidal behaviour compared with those with MDD without records of suicidal behaviour *(17)*. In addition, another study demonstrated that mortality was significantly higher for patients with TRD compared with patients with non-TRD *(12)*.

6.1.4 Disability-Adjusted Life Years

MDD is a leading cause of disability worldwide, responsible for a significant global disease burden, particularly in LMICs, and is projected to become the top cause of global disease burden by 2030.

- In 2018, MDD ranked third in terms of global disease burden according to the WHO, and it is predicted to be first by 2030 *(18, 19)*.
- According to the GBD, depression accounted for the largest proportion (37.3%) of DALYs caused by mental disorders in 2019 globally *(6)*. The age standardised DALYs of mental disorders by region is described in Table 2.
- At the disorder level, depressive disorders were ranked thirteenth among the top 25 leading causes of DALYs, and mental disorders were the second leading cause of years lived with disability (YLD) in 2019 *(6)*.
- The GBD 2019 estimated that MDD and dysthymia were jointly responsible for 46.9 million (1.85%) DALYs globally, with MDD accounting for 1.47% and dysthymia for 0.38% of the DALYs caused by depression *(20, 21)*. Additionally, the global DALY burden of MDD is higher in females than males, with age-standardised DALY rates of 564 vs. 354, respectively in 2019 *(20, 21)*. In 2019, MDD accounted for 30.04 million (95% UI: 20.58, 41.51) DALYs in LMICs, representing 80.76% of the global burden, and the DALYs rate of MDD generally increased with age across all income groups in LMICs, showing an inverse relationship to income level *(19)*.

Table 2: Age-standardised rates and number of DALYs for mental disorders by location in 2019

Location	Age-standardised DALY rates per 100,000 (95% UI)	Total DALYs in 1,000 (95% UI)
Central Asia	1,346.7 (993.7, 1,776.3)	1,254.6 (925.7, 1,655.3)
Central Europe	1,341.6 (992.9, 1,773.0)	1,741.8 (1,289.0, 2,274.4)
Eastern Europe	1,462.2 (1,083.3, 1,926.2)	3,453.8 (2,562.0, 4,531.6)
North Africa and Middle East	1,957.6 (1,445.0, 2,569.8)	12,116.5 (8,906.4, 1,5976.0)
South Asia	1,575.1 (1,162.0, 2,043.7)	28,157.3 (20,742.5, 36,673.5)
Southeast Asia	1,293.4 (964·4, 1,697.1)	9,101.5 (6,759·1, 11,965.0)
Sub-Saharan Africa	1,669.3 (1,226.5, 2,200.0)	15,065.9 (11,006.3, 20,015.8)

Source: *(6)*
Abbreviations: DALY: disability adjusted life years; UI uncertainty interval

6.2 Burden of MDD

MDD is one of the most burdensome illnesses globally, with significant negative impacts on activities of daily living, QoL, cognitive function, employment status, and work productivity *(22)*.

6.2.1 Clinical Burden

MDD is a chronic, debilitating condition and the burden of MDD continues to increase despite current treatment options.

- MDD is a debilitating disease associated with substantial symptom severity *(3)*. The treatment pathway for MDD patients is highly complicated, characterised by variation in disease presentation, uncertainty of diagnoses, and diversity of treatment effects *(22)*.
- MDD is frequently associated with comorbidities with other chronic and acute conditions (physical and psychiatric) *(23-25)*.
    - MDD is significantly associated with increased incidence of many chronic disorders, such as dementia and Alzheimer's disease, and people with MDD are at increased risk of developing other physical diseases such as cancer, arthritis, asthma, diabetes, and cardiovascular disorders *(23, 24)*.
    - Additionally, depression can worsen pre-existing conditions and make chronic disease management more difficult *(23)*.
- Irritability can be a major symptom in patients with MDD, with over a quarter of patients (27.7%) with lifetime MDD reporting the presence of irritability in their worst lifetime depressive episode *(26)*.
- Approximately three quarters (72.1%) of patients with lifetime MDD present with at least one comorbid psychiatric disorder, most commonly anxiety disorders (59.2%) *(25)*.

- Anxiety and irritability can often signal a more severe form of depression, negatively affecting functioning and QoL *(26, 27)*. Anxiety is associated with poorer acute outcomes following ADT treatment compared with individuals without anxious depression *(28)*. Clinicians are more likely to prescribe an adjunctive antipsychotic for patients presenting with anxious depression and irritability *(29)*.
- The COVID-19 pandemic had a profound impact on mental health disorder severity and treatment needs. A retrospective study in Italy reported that post-lockdown hospitalisations showed an increase in the severity of major depressive episodes (MDE), with 34.4% of patients experiencing severe MDE compared to 21.4% pre-lockdown (hospitalisations from January 2018 to December 2021 for an MDE; Italian lockdown 9 March 2020). There were also higher rates of MDE with psychotic features (6.9% vs. 2.0%) and suicidal ideation (41.9% vs. 27.3%). Fewer patients had been receiving psychiatric care before admission (56.3% post-lockdown vs. 68.8% pre-lockdown), but more were receiving psychotherapy (20.0% post-lockdown vs. 11.7% pre-lockdown). Additionally, there was more frequent increase of ADT dosages (20.0% post-lockdown vs. 10.4% pre-lockdown) and increased use of augmentation strategies (16.3% post-lockdown vs. 8.4% pre-lockdown) to treat MDE *(30)*. This demonstrates that the burden of MDD continues to increase despite current treatment options.

Approximately 50% of patients with MDD experience inadequate response to ADTs alone.

- MDD can be managed with pharmacological and psychotherapeutic treatments *(4)*. Goals of treatment change with the phase of a MDE, which can be divided into the acute, continuation, and maintenance phases *(31)*. The overall goal for treatment is the full resolution of symptoms and associated improvements in function and QoL *(32)*.
- Monotherapy ADTs are widely used as the first-line treatment for MDD (e.g., selective serotonin reuptake inhibitors [SSRI], serotonin-norepinephrine reuptake inhibitors [SNRIs], and atypical ADTs) *(4)*. Additionally, adjunctive treatment with atypical antipsychotics (AAP), as recommended by national and international guidelines, may help achieve symptom improvement in patients who have an inadequate response to previous ADT monotherapy (section 9.2). Despite multiple treatment options approved for the treatment of MDD, approximately 50% of patients experience no response to treatment with a first-line ADT *(33)*.
- Multiple definitions have been used to characterise treatment outcomes for depression: remission, response, partial response, and non-response. Response is typically defined as at least 50% improvement in the symptoms of depression (decrease from baseline depression scale scores to trial endpoint), as measured by a clinical rating scale such as Hamilton Rating Scale for Depression (HAM-D) or Montgomery–Åsberg Depression Rating Scale (MADRS) *(34)*.
- While some patients may respond well to ADT monotherapy, the majority of individuals with MDD demonstrate inadequate response to first-line treatments.
    - Inadequate response is typically defined as a failure to achieve response to an ADT at an adequate dose and duration (i.e., at least 6 to 8 weeks) *(34, 35)*.
    - There is a lack of consensus around the definition of TRD *(36, 37)*. However, failure to respond or achieve remission after 2 or more trials (after 2 years) of medication treatment for MDD can be considered TRD *(12, 38)*. The prevalence of TRD in MDD rages from 12% to 55% *(38-41)*.
    - The term TRD has limitations, as it arbitrarily defines treatment responsiveness, overlooks psychological treatments, and often fails to consider factors such as partial response,

treatment intolerance, and illness characteristics. The 2009 National Institute for Health and Care Excellence (NICE) depression guideline shifted away from using TRD, focusing instead on sequenced treatment options for inadequate response *(42)*. Hence TRD can be considered as a subset of patients with MDD who have an inadequate response to ADTs.

Factors such as presence of residual symptoms, multiple unsuccessful ADT trials, anxiety, and irritability, can contribute to poor treatment response, as they are linked to greater severity and impaired functioning.

- Patients with MDD who have responded to or remitted from ADT frequently have persistent residual symptoms (e.g., fatigue, sleep problems, cognitive symptoms) that may interfere with functioning and QoL *(43)*.
- Relapse in MDD is the presence of residual symptoms, not only in those who have responded without full remission but also in those who have achieved a full remission during acute treatment *(43)*. Residual symptoms include both symptoms that have persisted from baseline as well as new onset symptoms *(43)*. Residual MDD symptoms significantly increase the risk of depressive relapse *(32, 43)*. Further, lower response rates are observed with subsequent unsuccessful ADT trials *(39)*.
- The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial assessed treatment outcomes in patients with MDD receiving one (n=3,671) to four (n=123) successive acute treatment lines *(39)*. Those with an acceptable benefit, preferably symptom remission, from any treatment line also entered a 12-month naturalistic follow-up phase.
    - The trial reported response rates of <20% when switching to a third ADT monotherapy after two consecutive unsuccessful ADTs *(39)*. The remission rates were 36.8%, 30.6%, 13.7%, and 13.0% for the first, second, third, and fourth acute treatment lines, respectively. The overall cumulative remission rate was 67% *(39)*.
    - Additionally, those who required more treatment lines had higher relapse rates during the naturalistic follow-up phase *(39)*.
- Factors that may contribute to poor response include the presence of anxiety and/or irritability, which have been associated with greater overall severity and impaired functioning, making it more difficult to treat patients *(26, 44)*. Socioeconomic factors are linked to higher resistance to multiple ADT strategies *(41)*. In the STAR*D trial, there were more patients who were unemployed, had lower monthly household income, and less years in education in the groups that presented with inadequate responses after two sequential ADT regimens compared to the groups treated in the first two lines *(39)*.
- Patients with inadequate response to ADT leading to relapses experience a further reduced QoL, functional status, and wellbeing. Non-adherence and relapses lead to complex and protracted forms of depression, with poor responses to treatment and major effects on work functioning, interpersonal relationships, and QoL (section 6.2.3).
- LMICs have significantly lower treatment rates of MDD compared to high-income regions *(20)*. With up to 75% of individuals with MDD residing in LMICs, this indicates that a substantial proportion of people with MDD globally do not access any health-related services *(20)*. Further, longer duration of untreated illness negatively influences the course and outcome of depression, resulting in an increased need for effective options from initial treatment *(45)*.
    - The treatment coverage for MDD is low in many parts of the world and particularly in LMICs *(20)*. A SLR and Bayesian meta-regression analysis was conducted to determine the

treatment gap in 84 countries from 2000 to 2019. The study reported that treatment coverage for health services varied significantly by income level, with high-income locations having 51% coverage (95% UI: 20, 82) and LMICs having 20% coverage (95% UI: 1, 53). For mental health services, high-income locations had 33% (95% UI: 8, 66) coverage, while LMICs had 8% (95% UI: 1, 36) coverage. Minimally adequate treatment rates were 23% (95% UI: 2, 55) in high-income countries and 3% (95% UI: 1, 25) in LMICs *(20)*.

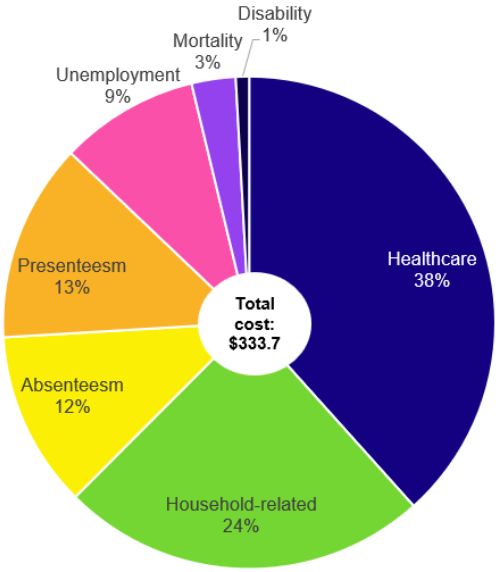
- Despite advancements in treatments a substantial proportion of individuals with MDD residing in LMICs have inadequate response to ADTs *(46, 47)*. Even after recovering from an acute episode, many continue to experience persistent psychological, psychosocial, and functional issues *(46)*. Delaying changes in treatment can prolong the period of depression if symptoms are not responding/going to respond to the current drug/dose. This delayed recovery heightens the risk of residual functional deficits, increasing depression-related morbidity, and even mortality *(4, 48)*.
- MDD is a significant health concern in LMICs, particularly among females, the young, and the elderly (section 6.1.2) *(19)*. It is crucial to prioritise interventions and allocate healthcare resources to effectively reduce the burden of MDD in these vulnerable populations *(19)*.
- Residual symptoms and their contribution to patient functioning/disease progression, together with the lower coverage of treatments and minimally adequate treatment rates demonstrates the importance of finding the right treatment at the onset of MDD in LMICs. It is important that patients with an inadequate response are both promptly identified and prescribed an effective course of treatment as early in the disease course as possible.

6.2.2 Economic Burden

Healthcare costs and productivity losses associated with MDD are high.

- Along with high clinical burden, MDD is also associated with a significant economic and societal burden. Between 2010 and 2018, the economic burden of MDD in the US surged by 37.9%, from $236.6 billion to $326.2 billion (2020 values) *(49)*. Indirect costs (absenteeism or presenteeism) and direct costs (medical costs, prescription drug costs) accounted for 61% and 35% of the total cost for MDDs, respectively, with the remainder of costs (4%) attributable to suicide *(49)*.
- The majority of the indirect costs are driven by work-related expenses such as presenteeism, absenteeism, unemployment, as well as all-cause mortality and disability, and the impact on household members without MDD *(50)*.
    - A study analysed the economic burden of adults with MDD in the US using a prevalence-based and human capital approach and reported the incremental societal economic burden at $333.7 billion or $16,854 per adult (2023 USD) with MDD. The percentage breakdown of cost components are illustrated in Figure 1.
    - Further, the study reported that a hypothetical early treatment response rate of 50.0% (compared to 19.8% with current standard of care [SoC]) could reduce the incremental economic burden of MDD by 7.7% relative to the current SoC *(50)*.

Figure 1: Percentage breakdown of cost components of MDD in the US (USD, billion; 2019 USD)



Source: *(50)*
Abbreviations: MDD: major depressive disorder; US: United States; USD: United States Dollars

- The large treatment gap observed in LMICs (section 6.2.1) affects not just the health, wellbeing, and outcomes of patients and their families, but also has inevitable consequences for employers and governments as a result of diminished productivity at work, reduced rates of labour participation, foregone tax receipts, and increased health and other welfare expenditures *(51)*.
    - Findings from LMICs reported that indirect costs (including the costs of suicide) and direct costs of depression account for 84% and 16% of the total cost of depression, respectively *(49, 52)*. This economic burden is exacerbated by the absence of public health insurance or reimbursement schemes for severe mental diseases *(52)*. Globally, 27% of countries lack such coverage, leading to out-of-pocket expenses for individuals, which constitute 40 to 43% of mental health costs in African and South-East Asian regions *(52)*.
    - A study in Pakistan in 2022 estimated that the total (direct and indirect) costs of depression was 15,978 Pakistani Rupees (PKR; USD $99) per month *(53)*. The estimated direct cost was 11,108 PKR (USD $69) and 4,869 PKR (USD $30) per month for indirect costs. The lower indirect costs could be attributed to the fact that in most developed countries, there is a high employment level, so their loss in terms of income and productivity losses is higher as compared to LMICs *(53)*.

Economic and societal burden are significantly higher among patients with MDD who experience relapse or recurrence.

- Patients with MDD who relapse have a higher resource utilisation with more frequent visits to psychiatrists and psychotherapists *(54)*. A US-based study reported annual healthcare and productivity costs $5,481 and $4,048 higher, respectively, for patients with TRD compared to those with treatment-responsive depression (study based on publications from January 1996 to August 2013; costs reported in 2012 USD) *(55)*.
- Additionally, inadequate response to treatment presents an added economic societal burden. Studies have reported that patients with inadequate response incur higher costs compared to those patients with adequate response *(38, 56)*. A 2006 US based cross-sectional study

analysed the effects of inadequate response to ADTs and reported that partial response and non-response to treatment were associated with greater likelihood of emergency department (ED) utilisation (odds ratios [ORs]: 1.26 and 1.54, respectively; P<0.01 for both) and hospitalisation (OR: 1.23; P=0.05 and OR: 1.39; P<0.01, respectively) *(57)*.

- In patients with MDD, the total general medical healthcare costs show a trend in increased cost with increasing lines of therapies. A retrospective cohort, US-based study examining the economic burden of MDD based on the number of treatment lines reported that patients completing treatment with a single line of ADTs had the lowest costs, with expenses rising significantly with additional treatment lines *(58)*.
    - Patients who completed treatment for their episode with a single line of ADT had the lowest total adjusted direct costs (commercial $9,975; Medicare $14,628) followed by those who completed with two lines (commercial $11,723; Medicare $15,526) and those treated with three or more lines of ADT regimens (commercial $21,259; Medicare $20,964) *(58)*. Delays in symptom resolution, even as early as the second treatment line demonstrates that it is necessary to treat patients with the most effective strategy at the first instance.
- Inadequate response to ADT is also associated with lower likelihood of employment and greater likelihood of work productivity loss among the employed *(57, 59)*. Mean adjusted incremental unemployment rates derived from the 2017 National Health and Wellness Survey data in the US were reported to be 8.0% and 3.9% for adults with treatment-resistant MDD and those with non-treatment-resistant MDD, respectively *(38)*.
- A retrospective study in the US comparing the economic burden of patients with TRD (defined as patients with MDD patients after two ADT courses; including augmentation therapy with anticonvulsant, anxiolytic, antipsychotic, lithium, psychostimulant, and thyroid hormone medications), those with non-treatment-resistant MDD, and those without MDD was conducted, utilising data from the US claims databased of privately insured employees and dependents from January 2010 to March 2015 *(59)*.
    - Patients with TRD had more healthcare resource utilisation than either control cohort (2.0 and 4.7 times the inpatient visit rate vs. controls with non-treatment-resistant MDD or non-MDD controls, respectively) *(59)*.
    - Patients with TRD had higher per patient per year (PPPY) direct healthcare costs: $6,709 more than non-treatment-resistant MDD controls and $9,917 more than controls without MDD after adjustment (all P<0.001) (USD 2015) *(59)*.
    - Higher direct costs among patients with TRD were driven predominantly by higher inpatient and outpatient costs *(59)*.
    - Patients with TRD had 1.7 and 6.2 times more work-days lost than those with non-treatment-resistant MDD and those without MDD, resulting in an additional cost of $1,811 and $3,460 PPPY (P<0.001), respectively *(59)*.
- MDD is associated with a significant economic and societal burden which increases with subsequent inadequate treatment. Increased economic burden associated with delayed episode resolution as early as the second line compared to the first line in MDD demonstrates the need for an effective course of treatment as early in the disease course as possible.

6.2.3 Humanistic Burden

MDD is associated with impairment across multiple domains of functioning and patients with inadequate response to ADT are at higher risk of worse outcomes.

- MDD is associated with impairments across multiple domains of functioning, including social role functioning (e.g., low marital quality, low work performance, low earnings) *(60)* and various adaptive functions, including communication, daily living skills, and socialisation *(61)*.
    - Patients with MDD often have impaired functioning compared to those without MDD; depressive disorders are the second leading cause of YLD globally (section 6.1.4).
    - Patients with MDD have significantly lower QoL than healthy individuals or those with chronic medical conditions like hypertension, cancer, or chronic pain *(62, 63)*.
- Patients with MDD and comorbid medical or psychiatric disorders are at even greater risk for low QoL *(24, 63-65)*. Poor QoL in patients with MDD is linked to high relapse rates, negative impacts on occupational and social activities, impaired future outlook, medical complications such as heart disease, and increased healthcare costs *(24, 63, 65)*.
- Patients with inadequate response to ADT leading to relapses experience a further reduced QoL, functional status, and wellbeing *(66)*. Patients with TRD will go on to suffer more complex and protracted forms of depression, with poor responses to treatment and major effects on work functioning, interpersonal relationships, and QoL *(67)*.

Prolonged inadequate response to ADT leads to significant frustration for both patients and caregivers, impacting treatment adherence, QoL, and psychological wellbeing, especially in LMICs where treatment efficacy is further hindered by self-stigma.

- Multiple courses of ADT over a prolonged period can be highly frustrating for people with MDD. In a survey of patients with inadequate response to ADT:
    - Approximately a third (29.8%) of patients reported feeling frustrated with their medication and 19.2% with their health care practitioner (HCP) *(68)*.
    - More than half (59.3%) of patients indicated that frustration with medication was primarily due to perceived lack of efficacy. The longer the current episode duration and the greater the disruption to daily living, the more likely the respondents experienced feelings of frustration with medication altogether *(68)*.
    - Additionally, feelings of frustration with medication led to a third (33.3%) of patients wanting to quit taking their medication *(68)*.
- Similarly, in LMICs a substantial proportion of individuals with MDD do not respond to ADTs *(69)*. Even after recovering from an acute episode, many continue to experience persistent psychological, psychosocial, and functional issues which hampers QoL *(46)*.
- Self-stigma levels have been reported to have a negative impact on the treatment efficacy and QoL in patients with MDD *(70)*. This impact of stigma on treatment efficacy also affects sustainable employment and wellbeing *(71, 72)* which can strongly influence the onset and exacerbation of their depression *(46)*.
- The QoL of caregivers (family or friends) of individuals with MDD is also seriously impaired, mainly by altered psychological or mental wellbeing and social life resulting from caring for a loved one with MDD *(73)*. Inadequately treated depression can leave patients' families and carers

frustrated. A study reported that caregivers of patients with TRD faced heightened levels of psychological distress and burden, leading to negative psychological and physiological effects *(74)*.

6.3 Proposed Indication and Target Population

MDD is a prevalent, chronic, recurrent, and highly disabling condition with a complex treatment pathway. Approximately 50% of patients with MDD experience inadequate response to ADT, which are frequently associated with worse outcomes. Healthcare costs and productivity losses associated with MDD are high. Economic and societal burden are significantly higher among patients with MDD who experience relapse or recurrence**.** MDD is associated with impairments across multiple domains of functioning and patients with inadequate response to ADT are at risk of worse outcomes.

The efficacy of brexpiprazole in the adjunctive treatment of MDD was evaluated in two 6-week, placebo-controlled, fixed-dose trials of adult patients with MDD, with or without symptoms of anxiety, who had an inadequate response to prior ADT (1 to 3 courses) in the current episode and who had also demonstrated an inadequate response throughout the 8 weeks of prospective ADT, or venlafaxine extended-release) (section 6.3.1).

Including brexpiprazole to the WHO EML as an adjunctive treatment to ADTs for adult patients with MDD can address several unmet needs in LMICs. Brexpiprazole demonstrates efficacy is generally well tolerated and may be a useful treatment alternative for adjunctive therapy in MDD. Further this efficacy is sustained and there is continued improvement (additional to any initial improvement) in all efficacy measures and functional outcomes. Adjunctive brexpiprazole may improve anxiety, irritability and sleep. Brexpiprazole has a favourable tolerability and safety profile with a low risk of activating or sedating side effects. Additionally, brexpiprazole has simple pharmacokinetics and is given in a convenient once-daily oral dose with or without food (section 6.3.1).

6.3.1 Clinical Benefits

For patients with inadequate response to ADT, augmentation with antipsychotics may offer benefits compared with ADT combination therapy or switching treatments.

- Effective treatment is important to prevent the long-term consequences of prolonged MDD (section 6.2.1). Increasing the dose or switching to another ADT may not improve outcomes for patients with inadequate treatment response (section 6.3).
- For patients with inadequate response to ADT, there is a need for a safe and effective treatment option to ensure patients gain the most benefit from their treatment (section 6.3).
    - Among strategies to augment response with non-ADT drugs, adjunctive second-generation antipsychotics have strong evidence supporting their use. A SLR of ADT augmentation, combination, and switching strategies concluded that second-generation antipsychotics are best supported by the evidence as the first-line choice for patients who did not respond to first-line ADT *(75)*.
    - In clinical studies adjunctive treatment with an atypical antipsychotic may enable symptom improvement as early as one week after initiation *(76, 77)*.
    - Even in patients with minimal response to 8 weeks of ADT, 6 weeks of adjunctive AAPs significantly improves response (36% vs. 19%, respectively; P<0.0001) and remission

(24% vs. 12%, respectively; P<0.0001) compared to ADT + adjunctive placebo (based on a study with pooled data from three RCTs in 1,038 patients in a 6-week, double-blind adjunctive phase) *(78)*.

- Treatment augmentation may offer some benefits compared with combination therapy or switching treatments (e.g., maintaining partial response from ADT, synergistic effects from drugs with different pharmacological profiles, and no wash-out period) *(79)*.
- Initiating adjunctive therapy early in treatment increases the likelihood of remission and lowers cost impact (all-cause and MDD-related medical costs) – primarily due to lower rates of healthcare resource utilisation *(80)*.

Brexpiprazole demonstrates efficacy, is generally well tolerated, and may be a useful treatment alternative for adjunctive therapy in MDD

- The serotonergic, dopaminergic and noradrenergic systems appear to play important roles in the pathophysiology of MDD *(18)*. Therapies that target multiple neurologic circuits may have improved efficacy and tolerability in the treatment of MDD *(81)*.
- Brexpiprazole is a dopamine, serotonin, and noradrenaline activity modulator which is a partial agonist at serotonin 5HT1A and dopamine D2 receptors, and an antagonist at serotonin 5-HT2A and noradrenaline α1B/2C receptors, all at similar potency *(82 , 83)*.
- Adjunctive brexpiprazole improves symptoms of depression in patients with inadequate response (patients with 1 to 3 lines of previous treatment) and improves social functioning in patients with MDD as demonstrated in 2 pivotal 6-week trials (Pyxis and Polaris). Adjunctive brexpiprazole significantly improved depressive symptoms compared to adjunctive placebo (see Appendix A.4 for further detail).
- Across both pivotal trials, the observed treatment effect and safety with adjunct brexpiprazole in patients with MDD and inadequate response to ADT were consistent regardless of the ADT used.
    - ADTs used by patients with MDD in the 2 pivotal trials (Pyxis, Polaris) included escitalopram (10 mg or 20 mg/day), fluoxetine (20 mg or 40 mg/day), paroxetine controlled-release (CR; 37.5 mg or 50 mg/day), sertraline (100 mg, 150 mg, or 200 mg/day), duloxetine (40 mg or 60 mg/day), and venlafaxine (75 mg, 150 mg, or 225 mg/day) *(76, 77)*.
- Further, open-label studies of brexpiprazole have demonstrated that patients with MDD who have inadequate response to ADT have continued improvement (additional to any initial improvement) in all efficacy measures and functional outcomes.
    - A multicentre, open-label study demonstrated that by week 52, the modal Clinical Global Impressions-Severity (CGI-S) score shifted from "mildly ill" to "normal, not at all ill." The Clinical Global Impressions-Improvement (CGI-I) scores indicated that patients were "minimally to much improved" on average. Functional improvements were noted in the Sheehan Disability Scale (SDS) scores, with better functioning in work/studies, social life, and family life. Additionally, depressive symptoms, measured by the Inventory of Depressive Symptomatology-Self Report (IDS-SR) total score, showed a reduction *(84)*.
    - Another, open-label, Phase 3b study (n=61) demonstrated that switching to adjunctive brexpiprazole is associated with improvements in depressive symptoms were observed (least squares mean [LSM] change from baseline to week 6 in MADRS total score, −17.3;

P<0.0001) as well as improvements in general and cognitive functioning (mean change from baseline to week 6: SDS, -3.1; P<0.0001; Massachusetts General Hospital–Cognitive and Physical Functioning Questionnaire, −9.2; P<0.0001). Overall, improvements were observed in depressive symptoms, general functioning, cognitive function, and energy/alertness *(85)*.

- The Pyxis trial demonstrated that brexpiprazole leads to a significantly greater mean reduction from baseline to week 6 in the Hamilton Anxiety Rating Scale (HAM-A) total score compared with placebo *(76)* (see Appendix A.4).
- Adjunctive brexpiprazole improves symptoms of depression in patients with or without symptoms of anxiety, and may improve, irritability, and sleep in patients (n=1,120) with anxious distress. ADT + brexpiprazole showed greater improvements than ADT + placebo (P<0.05) in terms of apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, lassitude, inability to feel, and pessimistic thoughts *(86, 87)*. Additionally in an exploratory, 6-week, open-label study of patients with MDD (n=32) and symptoms of anxiety, symptoms of depression in patients with anxiety improved during adjunctive treatment with brexpiprazole. Improvements from baseline were observed at Week 6 for least squares mean change in MADRS total score (P<0.0001 vs. baseline), HAM-A total score (P<0.0001) and mean SDS mean score *(87)*.
- In an exploratory, open-label, 8-week study of patients with inadequate response to ADT (n=44) who received adjunctive brexpiprazole, sleep disturbances, as measured by polysomnography and a Consensus Sleep Diary for Morning, significantly improved (P<0.05). Improvement in sleep disturbance was associated with improvement in daytime sleepiness, and in cognitive and physical functioning (P<0.0001). Additionally, depressive symptoms improved with adjunctive brexpiprazole, as did functioning symptoms. Improvements in depressive symptoms were dependent on sleep (p<0.0001) *(88)*.
- In an open-label, exploratory study including patients with MDD (n=54), irritability and anger symptoms were improved at Week 6 of treatment with adjunctive brexpiprazole. Additionally, irritability symptoms worsened after discontinuation of brexpiprazole at Week 10 (patients discontinued brexpiprazole at Week 6) *(89)*.
- In a 12-week, open-label, exploratory study including patients (n=47) aged 18 to 35 in a work or school environment with MDD and an inadequate response to 1 to 3 ADTs, improvements in depressive symptoms were observed after receiving adjunctive brexpiprazole. Additional significant improvements were observed at Week 12 in other functional measures, including SDS and Work Limitations Questionnaire (WLQ), indicating improvements in the effect of patients' symptoms on functioning (work/school, social life, and home responsibilities) *(90)*.

Brexpiprazole has a favourable tolerability and safety profile with a low risk of activating or sedating side effects.

- Brexpiprazole has a novel mechanism of action due to its pharmacologic profile (high affinity [Ki<1 nM] for 5-HT1A, 5-HT2A, D2, and α1B/2C receptors) and its intrinsic activity at the D2 receptor, which is between those of pure antagonists and the partial agonist aripiprazole *(83, 91)*.
    - Brexpiprazole showed partial agonist activity at the 5-HT1A receptor in cloned receptor systems, which may contribute to antipsychotic activity and result in an improved side effect profile *(83)*.

- Due to activity at 5-HT2A receptors and D2 receptors occurring at similar doses, brexpiprazole may enable potential benefits of 5-HT2A antagonism, including antipsychotic efficacy, lower risk of akathisia, and improvements to cognitive function, sleep, and affective states *(83)*.

- Adjunctive brexpiprazole was associated with a low rate of discontinuation due to adverse events (AEs) in the 2 pivotal 6-week studies (Pyxis and Polaris). The most frequent AEs were akathisia, restlessness, and weight gain. Further, adjunctive brexpiprazole is associated with low rates of sedating and activating effects (see Appendix A.4 for more details).

- Further, open-label studies have consistently demonstrated the safety profile of brexpiprazole as an adjunctive treatment for patients with MDD.
    - During the long-term adjunctive brexpiprazole treatment (in a 52-week study from three RCTs with 2,944 patients), the most common treatment-emergent adverse events (TEAEs) with an incidence of 5% or greater included weight increase (17.7%), somnolence (8.0%), headache (7.2%), akathisia (6.7%), increased appetite (6.3%), insomnia (6.3%), fatigue (6.1%), viral upper respiratory tract infection (5.4%), and anxiety (5.2%). Most TEAEs were mild or moderate in severity, with severe TEAEs occurring in 7.3% of patients. The only TEAE leading to discontinuation in at least 1% of patients was weight increase, affecting 2% of patients. There were no clinically relevant findings for events related to prolactin, lipids, or glucose, including the incidence of shifts to abnormal levels. No clinically meaningful changes were observed on formal extrapyramidal symptom (EPS) rating scales *(84)*.
    - In the 52-week, open-label extension, 14.1% of patients discontinued because of an AE. The most frequently reported TEAEs were akathisia (10.0%) and weight gain (25.5%). Rates of sedation and somnolence were low (sedation: 3.7%; somnolence: 9.4%). In the study, brexpiprazole was associated with small changes in metabolic parameters and moderate weight increase *(92)*.

Brexpiprazole has simple pharmacokinetics and is given in a convenient once-daily oral dose with or without food.

- The peak plasma concentrations occur within 4 hours after brexpiprazole administration and steady-state concentrations were attained within 10 to 12 days of dosing. Brexpiprazole can be administered with or without food *(93)*.

- An exploratory, open-label study explored the impact of adding brexpiprazole to the treatment of patients with MDD who were not responding to adjunctive or combination therapy of their current ADTs. The study included patients who had received prior adjunctive or combination ADT therapy and were as follows: ADT + aripiprazole (augmentation), n=12; ADT + quetiapine (augmentation), n=11; ADT + ADT (combination), n=13; ADT + bupropion (combination), n=19; ADT + stimulant (augmentation with modafinil, methylphenidate, or another psychostimulant), n=6.
    - Improvements were observed in depression, general functioning, cognitive function, energy/alertness, and patient satisfaction *(85)*.

6.3.2 Economic Benefits

Adjunctive brexpiprazole in MDD is effective and well-tolerated, potentially reducing the economic burden by lowering relapse rates, improving work productivity, and decreasing healthcare utilisation.

- MDD imposes a significant economic and societal burden, which worsens with inadequate treatment response. Most indirect costs stem from work-related issues like presenteeism, absenteeism, unemployment, mortality, and disability, as well as the impact on household members. This burden is especially high among patients who relapse, leading to increased healthcare utilisation and visits to psychiatrists and psychotherapists. TRD further adds to the economic burden, with inadequate response to ADT linked to lower employment rates and reduced work productivity (section 6.2.2).
- Earlier initiation of AAPs in patients with MDD is associated with significant reductions in all-cause and MDD-related hospitalisations and ED visits compared to those who have delayed use of AAPs *(94)*. Additionally, early treatment (within the first year of first ADT or within six months of evidence of inadequate therapy) is associated with significantly lower all-cause cost and greater reduction in hospitalisation and overall medical costs compared to delayed treatment *(94, 95)*.
    - A real-world study including patients with MDD showed that the early initiation of adjunctive brexpiprazole is associated with significantly lower outpatient healthcare utilisation and cost compared to late initiation (defined as at least 12 months after first ADT). Patients who received adjunctive brexpiprazole 12 months or more after first ADT were 33% more likely to have overall MDD-specific visits compared to those who received brexpiprazole within 2 months (incidence risk ratio: 1.33; 95% confidence interval [CI]: 1.09, 1.063; p=0.005) *(96)*.
- Some of the antipsychotics indicated as adjunctive treatment for MDD are associated with high rates of AEs (e.g., EPS, akathisia, fatigue, somnolence, sedation, weight gain, sexual dysfunction, and hyperprolactinemia, depending on compound), which contribute to treatment discontinuation and switches (section 6.3) *(97, 98)*.
- Hence unresolved symptoms and tolerability-related effects of adjunctive therapies for patients with MDD are associated with high rates of treatment discontinuation and higher resource use and costs *(84, 97, 99)*.
    - Among the randomised patients in the pivotal MDD of brexpiprazole trials (RCTs: Pyxis, Polaris, Sirius, and Delphinus), more than 90% of patients completed the randomised treatment phase of the trials *(99)*. Further, among 2,944 patients in a long-term (up to 52 weeks), open-label safety study of adjunctive brexpiprazole in MDD, discontinuation due to TEAEs occurred in 8.7% of patients *(84)*.
- Given the detrimental impact of inadequate response to treatment in MDD on QoL and costs to patients, it is crucial to consider both efficacy and the indirect economic burden, including out-of-pocket expenses for additional monitoring due to AEs. For instance, pharmacokinetic factors play a role, as seen with the co-administration of quetiapine with venlafaxine. The addition of venlafaxine may increase the serum levels of venlafaxine's active metabolites which can result in the need of additional monitoring, discontinuation, and raise the risk of AEs *(100)*.

- Adjunctive brexpiprazole is associated with economic benefits including reduced hospital care and all-cause medical costs compared to other adjunctive AAPs *(101)*.
    - In a US real-world study including 4,862 patients treated with adjunctive AAPs (brexpiprazole, quetiapine, and lurasidone), brexpiprazole showed significantly lower risk of discontinuation and hospital care compared to quetiapine (no significant difference compared to lurasidone) and lower risk of hospitalisation or ED visits compared to both quetiapine and lurasidone. Adjunctive brexpiprazole has significantly lower all-cause medical costs compared with adjunctive quetiapine (no significant difference compared to lurasidone) *(101)*. Additional data on the economic benefits of brexpiprazole can be found in section 10.1.
- Overall, adjunctive brexpiprazole is effective and demonstrates a favourable safety profile. It has the potential to reduce relapses and inadequate treatment response.

6.3.3 Humanistic Benefits

Adjunctive brexpiprazole may improve life engagement and social functioning in patients with MDD even in those with inadequate responses to traditional ADTs.

- Patients with MDD often experience impaired functioning compared to those without MDD, and depressive disorders are the second leading cause of YLD globally. Poor QoL in patients with MDD is associated with high relapse rates, negative impacts on work and social activities, a negative outlook, medical complications, and increased healthcare costs. Patients with inadequate ADT response suffer prolonged loss of QoL, functional status, and wellbeing, leading to more complex and chronic depression with significant effects on work, relationships, and overall QoL (section 6.2.3).
- Adjunctive brexpiprazole improves social functioning in patients with MDD:
    - In patients with MDD and inadequate response to ADTs, 6-week adjunctive brexpiprazole improved social functioning as measured by the SDS in the 4 randomised controlled trials (RCTs; two pivotal 6-week trials [Pyxis and Polaris], and two other 6-week trials [Sirius, and Delphinus]) (see Appendix A.4 for trial summaries).
    - In pooled analysis of the three 6-week studies (Pyxis, Polaris, and Delphinus) adjunctive brexpiprazole 2 to 3 mg improved social life, family and work/studies life as measured by the SDS *(84)*.
    - Additionally, in patients with MDD and inadequate response (an inadequate response to previous adjunctive or combination therapy) to ADTs, an open-label, Phase 3b exploratory analysis of 6-week adjunctive brexpiprazole, demonstrated that brexpiprazole lead to improvements were observed in depressive symptoms, general functioning, cognitive function, and energy/alertness *(84, 85)*.
- Adjunctive brexpiprazole may have unique clinical benefits, including improving anxiety, irritability, sleep, and improving symptoms depression in patients with anxiety, all of which impact QoL in patients with MDD despite the use of ADT *(86-89)* (section 6.2.3 and 6.4).
- Adjunctive brexpiprazole may improve patient life engagement (i.e., outcomes reflecting life fulfilment, well-being, and participation in valued and meaningful activities) beyond the core symptoms of depression.

- Based on a pooled analysis of exit interviews from three exploratory studies of adjunctive brexpiprazole in MDD (n=105), four patient life engagement domains were identified: emotional (affect/mood), physical (energy), social (interest), and cognitive (alertness/thinking). Overall, 88.6% of patients reported improvements in at least one domain, with most experiencing improvements in two or three domains. Improvements were most common in the emotional domain (77.1%), followed by physical (75.2%), social (41.9%), and cognitive domains (36.2%) *(102)*.
- These findings were further confirmed in the real-world. A real-world analysis to explore the impact of brexpiprazole on life engagement in patients with MDD (n=624) reported that in 624 adult patients there were significant improvements in life engagement were observed as early as one month after starting brexpiprazole, with 53.9% of patients showing improvement within six months of treatment. The most notable gains were in the emotional and social aspects, indicating that brexpiprazole may enhance overall life engagement in MDD patients *(103)*.
- Improvement of patient life engagement beyond the core symptoms of depression including emotional (affect/mood), physical (energy), social (interest), and cognitive (alertness/thinking) could potentially help reduce caregiver burden.

- Overall adjunctive brexpiprazole could potentially improve patient well-being, life engagement, and social functioning in patients with MDD. This could potentially mitigate the negative impact on work and social activities, caregiver burden, medical complications, and increased healthcare costs.

6.4 Alternative Treatment Options and Unmet Need

MDD is highly heterogeneous, and patients require an effective treatment to avoid the increase in clinical, humanistic, and economic burden associated with delayed treatment.

- MDD is one of the most burdensome illnesses globally, with significant negative impacts on activities of daily living, QoL, cognitive function, and employment status and work productivity (section 6.2). MDD also poses a significant economic and societal burden globally (section 6.2.2). The goals of treatment in MDD include full recovery from the MDE, preserving social functioning (e.g., holding a job, retaining relationships), and prevention of relapse *(32, 104, 105)*.
- The treatment pathways for MDD are highly varied and complex, with patients following completely unique sequences of medications *(106-108)*. This heterogeneity makes it challenging to understand and optimise treatment recommendations in clinical practice. Despite the availability of treatment options, significant challenges still exist surrounding the treatment of MDD. These may include poor response/remission, low adherence to and persistence to therapy, and poor tolerability of treatment options (section 6.2.1). Effective treatment is important to prevent the long-term consequences of prolonged MDD. Delayed treatment leads to heightened risk of residual functional deficits, patient's loss of faith in treatment, increased depression-related morbidity, and mortality (section 6.2.1 and 6.2.3).

Despite the availability of multiple ADTs across various therapeutic classes, a significant proportion of patients with MDD do not achieve adequate response or remission.

- The current WHO EML (23rd list, 2023) includes the following ADTs
  - Amitriptyline and fluoxetine (with a boxed warning) for depressive disorders.

- Additionally, citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline are listed as therapeutic alternatives.
- Currently there are no adjunctive therapy to ADTs included for the treatment of MDD in adults.

- Although multiple ADTs are available in various therapeutic classes, most patients with MDD do not achieve adequate response or remission. Approximately 50% of patients with MDD experience inadequate responses to ADT, which are frequently associated with worse outcomes (section 6.2.1).
  - Only 36.8% of patients with MDD achieved remission following first-line treatment with a SSRI in the STAR*D trial. Even fewer patients (30.6%) with MDD who received a second ADT achieved remission in the trial *(39)*.
- Polypharmacy (i.e., being prescribed three or more medications) is relatively common in patients with MDD *(107-111)*.
  - An analysis of four US-based administrative claims databases from 2014 to 2019 (n=269,668) found that more than 10% of patients received at least four distinct treatment lines during the follow-up period *(107)*.
  - Similarly, a cross-sectional study in a LMIC reported that elderly patients (>60 years old) with MDD (n=30) received a median (range) of 3.5 (1.0 to 11.0) medications. Additionally, patients with MDD showed a significantly higher odds for polypharmacy compared with cognitively healthy participants (age-adjusted odds ratio [AOR]: 14.52, 3.59, 58.62; P<0.001) *(111)*.
- Hence, inadequate response to ADTs and polypharmacy are associated with negative outcomes, significant impairments in social functioning and often fail to regain a normal QoL (section 6.2). Work productivity loss of those employed and higher unemployment, along with higher emergency room utilisation and hospitalisation are also associated with an inadequate response to ADT (section 6.2).

Non-adherence to ADTs is a major challenge in treating MDD, driven by lack of efficacy, delayed onset of effect, and poor tolerability.

- Non-adherence to ADTs remains a common problem and has been widely recognised as one of the reasons for treatment failure in MDD; with the evidence reporting rates of non-adherence of up to 56% *(112-115)*. Low rates of adherence and persistence to therapy may result from perceived lack of efficacy and side effects of treatment *(116-119)*.
- A survey conducted in the US, Canada, UK, Germany, France, and Spain (n=2,096; conducted between March 15 and June 16, 2016) reported that inadequate response to ADTs in patients with MDD is associated with high levels of frustration which lead to poor adherence *(68)*.
  - The most frequent emotion reported by patients regarding their medication was frustration (29.8%), followed by hopelessness (27.4%), and anxiety (27.4%). The main reasons for frustration were poor symptom control (59.3%) and tolerability issues (19.7%).
  - Longer episode duration and greater disruption to daily living increased feelings of frustration. This frustration led to adherence issues, with 33.3% wanting to quit their medication and 27.3% wanting to quit due to frustration with their HCP.

- Around one in six patients frustrated with their medication or HCP did not take their medication regularly *(68)*.

- Further, non-adherence rate is higher in LMICs due to barriers such as comorbidities, stigma around the disease, poor access to healthcare facilities, and AEs due to ADTs *(117, 120-124)*.
    - An interview study including 30 patients with MDD receiving treatment ADT in Malaysia reported medication-specific barriers by 63% of patients, and consists of four main themes namely side effects, pill burden, treatment duration, and cost of treatment. The majority of patients reported that they had experienced significant side effects with ADTs, which caused them to stop taking their medication. Further, multiple prescriptions reduced patients' confidence in the treating physician, subsequently influencing their medication-taking behaviour. Other factors included problems communicating with healthcare providers, long waiting time at the clinic, frequent medication refills, frequent clinic visits, and no supply of medications *(121)*.
    - A prospective cross-sectional study (September 2016 to January 2017; n=217) in Ethiopia reported that over 85% of the participants with MDD experienced adverse drug reactions due to ADT, with the most common being weight gain. The study also reported that older generation ADTs are associated with wide range of side-effects, and they were commonly prescribed in Ethiopia due to reduced cost *(120)*.

- A SLR (conducted in May 2024) of discrete choice experiments on patient preferences for MDD demonstrated treatment efficacy, relapse prevention, and symptom relief were among the most important attributes for patients, while they were willing to accept larger risks to achieve symptom improvement *(125)*. This highlights that patients with MDD need of effective early strategies which maintain QoL and aid recovery.

- High relapse rates in patients with MDD needing multiple treatments (section 6.2.1) highlight the need for effective early strategies to maintain QoL and aid recovery. The first strategy to manage inadequate response to ADT is to ensure patients take an adequate dose for an appropriate duration, with measures to improve adherence. If unsuccessful, other strategies include increasing the dose, switching to a different, augmenting with psychotherapy or non-ADT medications (e.g., lithium or antipsychotics), or combining with another ADT *(126)*.

Early augmentation with antipsychotics offers improved treatment response in MDD, however a tailored approach considering individual tolerability and side effect profile is crucial in treatment decisions.

- Adjunctive treatment of MDD with AAPs, as recommended by national and international guidelines, can potentially assist patients in achieving remission *(127-129)* (section 9).

- The currently available and Food and Drug Administration (FDA) approved adjunct treatments include brexpiprazole, aripiprazole, quetiapine, and cariprazine for the treatment of MDD *(93, 130-132)*. A combination product of olanzapine and fluoxetine is indicated for TRD (MDD in adults who do not respond to two separate trials of different ADTs of adequate dose and duration in the current episode) *(133)*.

- Ziprasidone is used off-label as adjunct treatment for TRD *(134)* and risperidone as augment ADT in the treatment of non-psychotic unipolar depression in the US *(135)*.

- Additionally, lithium, thyroid hormone, lamotrigine, bupropion, buspirone, and psychostimulants are sometimes combined with ADTs to augment response, although these agents are not FDA-approved *(136, 137)*. Lithium is effective for treating affective disorders with evidence of reduction

of suicidal risk and mortality but is not used in MDD due to uncertainty around the clinical benefits *(138)*. Other concerns that limit the use of lithium include a narrow therapeutic index, with risks of intoxication at circulating concentrations only 2-3 times above therapeutic levels, as well as of adverse long-term effects on thyroid and renal function *(139)*.

- AAPs, due to their broad receptor-binding profiles, are a rational adjunctive therapy to ADTs, with substantial evidence supporting their use *(33, 140)*.
- Adjunctive AAP for treating MDD are effective and can consequently improve treatment response and benefit patient QoL. However, it is important to consider tolerability. Side effects, including activation symptoms and sedation, and bothersome side effects (e.g., weight gain, sexual dysfunction, and hyperprolactinemia) are considerations when selecting the use of an adjunctive AAP (section 8.2.2).
    - For instance, pharmacokinetic factors play a role, as seen with quetiapine co-administered with venlafaxine, which may increase the serum levels of venlafaxine's active metabolites. This can potentiate treatment effects but also raise the risk of AEs (section 6.3.2).
- In a qualitative study of focused groups comprised of 42 patients, of whom 25 presented with MDD and treated with second-generation antipsychotics (quetiapine, aripiprazole, risperidone, lurasidone, and clozapine), the most bothersome AEs in patients with MDD included cognitive issues, weight gain, excessive sleepiness, and low energy. The authors concluded that the wide range of TEAEs that are both frequent and bothersome highlight the need for a tailored TEAE-awareness approach when choosing an antipsychotic *(141)*. Hence, a tailored approach that considers individual tolerability and the specific side effect profile is crucial when selecting an antipsychotic for adjunctive treatment in MDD.

Patients with MDD need an effective, tolerable treatment to enhance response to ADTs.

- Despite the availability of treatment options, significant challenges still exist surrounding the treatment of MDD. These include poor adherence and persistence to therapy, residual disease symptoms, and AEs of some of the available treatment options. Delayed treatment leads to increased risk of residual functional deficits, patient’s loss of faith in treatment, increased depression-related morbidity, and mortality (section 6.2.1 and 6.2.3).
- Thus, an unmet need exists for an agent that effectively augments the effects of ADTs; is well-tolerated, particularly in the face of multiple comorbid conditions; works toward helping patients achieve complete remission, including improving QoL; and addresses residual symptoms. Initiating adjunctive therapy early in treatment could potentially increases the likelihood of remission. Further, timely treatment adjunct antipsychotics also could potentially reduce the healthcare resource utilisation, and lead to improved employment and productivity.

7. Treatment Details

FDA label: *REXULTI (brexpiprazole) is an atypical antipsychotic indicated as an adjunctive therapy to antidepressants for the treatment of MDD in adults (Approval: October 2015) (93).*

Brexpiprazole is also indicated for the following indications (FDA label):

- *REXULTI (brexpiprazole) is indicated for the treatment of schizophrenia in adults and paediatric patients ages 13 years and older and for treatment of agitation associated with dementia due to Alzheimer's disease (93)*.

Brexpiprazole is currently approved by the European Medicines Agency (EMA) for the treatment of schizophrenia in adults and not for the treatment of MDD *(142)*.

7.1 Dosage Regimen and Duration of Treatment

The recommended starting brexpiprazole dosage for the adjunctive treatment of MDD in adults is 0.5 mg or 1 mg orally once daily. The dose can be titrated to 1 mg once daily, then titrated to the target dosage of 2 mg once daily (based on the patient's clinical response and tolerability, with the dosage increased at weekly intervals). The maximum recommended daily dosage is 3 mg. The dose can be periodically reassessed to determine the continued need and appropriate dosage for treatment *(93)*. After single-dose administration of brexpiprazole tablets, the peak plasma brexpiprazole concentrations occur within 4 hours after administration, and the absolute oral bioavailability is 95%. Brexpiprazole steady-state concentrations were attained within 10 to 12 days of dosing *(93)*.

7.2 Requirements to Ensure Appropriate Use of the Medicine

Brexpiprazole is available as a tablet and is administered orally, once daily with or without food. It is available as: 0.25 mg/0.5 mg/1 mg/2 mg/3 mg/4 mg tablets.

For use as adjunctive treatment of MDD in adults the recommended starting dosage is 0.5 mg or 1 mg. The dose can be titrated to 1 mg once daily, then titrated to the target dosage of 2 mg once daily (based on the patient's clinical response and tolerability, with the dosage increased at weekly intervals) *(93)*.

The maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) is 2 mg orally once daily in patients with MDD. The maximum recommended dosage in patients with creatinine clearance <60 mL/minute is 2 mg orally once daily in patients with MDD *(93)*. In the clinical studies examining the use of brexpiprazole for the adjunctive treatment of MDD, dosage was not adjusted for strong cytochrome P450 2D6 (CYP2D6) inhibitors (e.g., paroxetine, fluoxetine). Thus, CYP considerations are already factored into general dosing recommendations, and brexpiprazole may be administered without dosage adjustment in patients with MDD *(93)*. The recommended dosage for brexpiprazole is the same in males and females, in different racial groups, and in smokers and nonsmokers *(93)*.

Brexpiprazole is contraindicated in patients with a known hypersensitivity to brexpiprazole or any of its components. Reactions have included rash, facial swelling, urticaria, and anaphylaxis *(93)*.

There are no requirements for diagnostic tests, specialised treatment facilities, or skill level of health care providers for the use of brexpiprazole. There are no requirements for post-dose monitoring with brexpiprazole.

8. Review of Evidence for Benefits and Harms

8.1 Summary of Available Evidence for Comparative Effectiveness

In the clinical development programme for brexpiprazole, four 6-week studies (Pyxis *(76)*, Polaris *(77)*, Sirius *(143)* and Delphinus *(144)*) were conducted to evaluate the efficacy of brexpiprazole in the adjunctive treatment of MDD. The approval of adjunctive oral brexpiprazole in patients with MDD is based largely on two pivotal trials (Pyxis and Polaris; fixed-dose studies), conducted between 2011 and 2013. The details of all the trials have been presented in Appendix A.4.

Brexpiprazole is available in the US for the treatment of schizophrenia and adjunctive treatment of MDD. In the EU, brexpiprazole is available for the treatment of schizophrenia only, and not for the adjunctive treatment of MDD (section 7).

Brexpiprazole is available worldwide and is currently authorised for use in over 60 countries and territories globally (all indications of brexpiprazole; section 11.1). The estimated cumulative worldwide post-approval exposure to brexpiprazole from launch (first distribution in July 2015 to July 2024; data extracted August 12, 2024) is 2,229,637 patient-years (all indications of brexpiprazole).

8.1.1 Clinical Studies Demonstrating Comparative Efficacy and Safety with Brexpiprazole

The Pyxis *(76)*, Polaris *(77)*, Sirius *(143)* trials were placebo controlled trials in patients with inadequate response to ADTs while the Delphinus *(144)* was a randomised, active-referenced (adjunctive quetiapine extended release [XR]), placebo-controlled study in patients with MDD.

An overview of the key completed study (Delphinus) demonstrating the comparative effectiveness and safety of brexpiprazole vs. other antipsychotics as an adjunctive treatment to ADT has been presented in Table 3. Additionally, the pivotal studies demonstrating the efficacy and safety of brexpiprazole are presented in Appendix A.4.

Table 3: Overview of key studies demonstrating the comparative effectiveness of adjunct brexpiprazole of vs. other adjunct antipsychotics in MDD

Study type and design	Study objectives	Study treatments	Results
Delphinus (NCT01727726) Multi-centre, randomised, active-referenced, placebo-controlled study to determine efficacy and safety of flexibly dosed brexpiprazole for the adjunctive treatment of MDD *(144)*	To assess the efficacy, safety, and tolerability of brexpiprazole as adjunctive treatment in adults with MDD and an inadequate response to prior ADT	• Adjunctive brexpiprazole 2 to 3 mg day (n=197) • Adjunctive placebo (n=206) • Adjunctive quetiapine XR 150 to 300 mg/day (target dose 150 mg/day; n=100)	• A total of 2,174 patients entered the prospective treatment phase, of whom 277 (12.7%) discontinued before the end of the phase, 1,394 (64.1%) responded to ADT + placebo at some point in the prospective treatment phase and were, therefore, excluded from randomised treatment, and 503 (23.1%) had an inadequate response to ADT + placebo and were, therefore, randomised • Inadequate responders continued on the same ADT and were randomised to adjunctive brexpiprazole adjunctive placebo, or adjunctive quetiapine XR 150 to 300 mg/day • Randomised treatment phase was completed by 171 (86.8%) patients receiving ADT + brexpiprazole, 186 (90.3%) patients receiving ADT + placebo, and 86 (86.0%) patients receiving ADT + quetiapine XR • The primary efficacy endpoint of change from baseline to Week 6 in MADRS total score the ADT + brexpiprazole group changed by a LSM (SE) of -6.0 (0.4) points, and the ADT + placebo group changed by -4.6 (0.4) points. The difference between groups at week 6 was statistically significant in favour of ADT + brexpiprazole (LSMD: 1.48; 95% CI: -2.56, -0.39; P=0.0078). The ADT + quetiapine XR group did not separate from ADT + placebo at week 6, changing by -4.9 (0.6) points (LSMD: -0.30; 95% CI: -1.63, -1.04; P=0.66). ADT+ quetiapine XR did, however, show a benefit over ADT + placebo at Week 2 (P=0.010) • On the key secondary efficacy endpoint of change from baseline to Week 6 in SDS mean score, ADT + brexpiprazole showed improvement from baseline with a numerical benefit over ADT + placebo; however, this benefit was not statistically significant (LSMD: -0.23; 95% CI:-0.52, -0.07; P=0.13). In contrast, the ADT + quetiapine XR group showed less improvement from baseline than ADT + placebo (LSMD: -0.42; 95% CI: -0.06, -0.78; P=0.024) • ADT + brexpiprazole showed a benefit over ADT + placebo on the family life item (LSMD: 0.35; 95% CI: 0.69, 0.01]; P=0.042) and the social life item LSMD: 0.34; 95% CI: 0.66, 0.01; P=0.044), but not on the work/studies item LSMD: 0.16; 95% CI: 0.25, 0.56; P=0.45). In contrast, ADT + quetiapine XR showed no benefit over ADT + placebo on each of the three item scores: family life social life, and work/studies • From baseline of the randomised treatment phase, the most frequent TEAEs (≥5%) in patients receiving ADT + brexpiprazole were akathisia (6.1%), somnolence (5.6%), and headache (5.6%) (all mild to moderate in severity). Aside from akathisia, other activating side effects were reported by only a few patients receiving ADT +

Study type and design	Study objectives	Study treatments	Results
			brexpiprazole (restlessness: 2.5%; insomnia: 2.5%; agitation: 0.5%; anxiety: 0.5%). Sedating side effects other than somnolence were also uncommon with ADT + brexpiprazole (fatigue: 1.5%; sedation 0.0%). The most frequent TEAEs (≥5%) in patients receiving ADT + quetiapine XR were somnolence (18.0%), dry mouth (6.0%), and increased appetite (5.0%). Sedation was reported by 3% patients • The most frequently reported EPS-related TEAE was akathisia (6.1% in the ADT + brexpiprazole group; 1.9% in the ADT + placebo group; 3.0% in the ADT + quetiapine XR group) • Body weight increase (≥7%) at any post-baseline visit was reported by 5.7% patients in the ADT + brexpiprazole group, 2.4% patients in the ADT + placebo group, and 5.1% patients in the ADT + quetiapine XR group • The assessment of electrocardiograms, vital signs, and laboratory measurements (including glucose, cholesterol, and triglycerides) did not show any consistent differences between the three treatment groups • Changes in serum prolactin concentration in the ADT + brexpiprazole and ADT + quetiapine XR groups were comparable with those in the ADT + placebo group

Abbreviations: ADT: antidepressant therapy; CI: confidence interval; EPS: extrapyramidal symptoms; LSM: least squares mean; LSMD: least squares mean difference; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; SDS: Sheehan Disability Scale; SE: standard error; TEAE: treatment-emergent adverse event; XR: extended release

8.1.2 Real-World Studies on Comparative Efficacy and Safety

8.1.3 Non-Randomised Studies

The safety of brexpiprazole is regularly assessed in accordance with pharmacovigilance standards for evaluating safety data from global sources. The labels in markets where brexpiprazole is authorised reflect the current understanding of its safety profile. The warnings and precautions for brexpiprazole are consistent with the warnings for other antipsychotics. Likewise, the black-box warning in the US prescribing information (PI) for brexpiprazole for increased mortality in elderly patients with dementia-related psychosis is a class-labelling requirement for all antipsychotics. Further the black box warning in the US prescribing information for brexpiprazole for suicidal thoughts and behaviours is due to the use of ADTs (ADTs increased the risk of suicidal thoughts and behaviours in paediatric patients and young adult patients). Safety and effectiveness of brexpiprazole have not been established in paediatric patients with MDD *(93)*.

No dosage adjustment for brexpiprazole is required on the basis of a patient's sex, race, or smoking status. Dosing modifications and information for use of brexpiprazole has been outlined in section 7.2 and Appendix A.3.

8.1.3.1 Description of Adverse Events

The safety of brexpiprazole has been demonstrated in two long-term, open-label studies to evaluate the safety and tolerability as an adjunctive therapy in adults with MDD.

- Overall, the long-term studies demonstrated no new safety or tolerability concerns (compared to the four 6-week RCTs) with adjunctive brexpiprazole (Table 4).
- The open-label, long-term safety and tolerability study of flexible-dose brexpiprazole adjunct to ADT in elderly patients with MDD demonstrated brexpiprazole to be generally well-tolerated. Around 66.7% of patients completed the treatment and 33.3% withdrew, with 18.2% discontinuing due AEs. Most (77.3%) of the patients experienced at least one TEAE which were mild to moderate in severity (Table 4).

Table 4: Long-term, open-label studies to evaluate the safety and tolerability of brexpiprazole as an adjunctive therapy in adults with MDD

Study	Methodology	Results
Orion Study (NCT01360866) Open-label, multicentre, long-term safety and tolerability of adjunctive treatment with brexpiprazole was evaluated in patients with MDD and inadequate response to ADTs *(84)*	Patients rolled over into this 52-week study (amended to 26 weeks) from three randomised, double-blind, placebo-controlled studies (the Pyxis, Polaris, and Delphinus). Flexible dose brexpiprazole 0.5 mg to 3 mg/day was administered as adjunct to current ADT. The primary outcome was frequency and severity of TEAEs	• A total of 2,944 patients were enrolled (1,547 for 52 weeks and 1,397 for 26 weeks) and, of these, 64.4% (n=1,895) completed the study. The mean brexpiprazole dose at the last visit was 1.5 mg/day • Overall, 2,132 patients had ≥6 months of exposure (72.6%). The proportion of patients who experienced ≥1 TEAE during treatment with brexpiprazole was 72.3% (n=2,123) • The TEAEs with an incidence of ≥5% were weight increase (17.7%), somnolence (8.0%), headache (7.2%), akathisia (6.7%), increased appetite (6.3%), insomnia (6.3%), fatigue (6.1%), viral upper respiratory tract infection (5.4%), and anxiety (5.2%). Most TEAEs were mild or moderate in severity; 215 patients (7.3%) experienced a severe TEAE • Discontinuation due to TEAEs occurred in 8.7% of patients; the only TEAE associated with discontinuation in ≥1.0% of patients was weight increase (60 patients; 2.0%). The mean weight gain from baseline was 2.7 kg at Week 26 (n=2,068) and 3.2 kg at Week 52 (n=771) • The percentage of patients who had a weight increase or weight decrease of ≥7% in body weight was 25.8% and 2.8%, respectively • There were no clinically meaningful changes in other metabolic parameters, including lipid profiles and glycaemic parameters • Treatment-emergent suicidal ideation occurred in 0.4% of patients. Suicide accounted for 2 of the 4 deaths during the study. One death (suicide) of the 3 was considered by the investigator to be possibly related to adjunctive brexpiprazole treatment

Study	Methodology	Results
Aquila study (NCT02400346) Open-label, multicentre, long-term safety and tolerability study of flexible-dose brexpiprazole adjunct to ADT in elderly patients with MDD *(145)*	Elderly patients (≥65 years) with MDD and an inadequate response to ≥1 ADT during the current episode participated in a 26-week, interventional, open-label study conducted at outpatient centres. All patients received brexpiprazole 1 to 3 mg/day in addition to their current ADT. Safety outcomes assessed included AEs, movement disorder scales, and standard safety evaluations (vital signs, laboratory safety parameters, physical examination, electrocardiograms)	• A total of 132 patients were enrolled and treated, of whom 88 (66.7%) completed 26 weeks of treatment and 44 (33.3%) withdrew from the study, including 24 who withdrew because of AEs (18.2%) • The mean (SD) of each patient's mean and modal doses of brexpiprazole across the entire study was 1.8 (0.6) mg and 1.9 (0.7) mg, respectively • Overall, 102 patients (77.3%) experienced at least one TEAE. Of these patients, 25 (18.9%) had only mild TEAEs, 66 (50.0%) had at least one moderate TEAE (but no severe TEAEs), and 11 (8.3%) had at least one severe TEAE • Fatigue and restlessness were the 2 most frequently reported TEAEs, and the only TEAEs with incidence ≥10% • Overall, 25 patients (18.9%) discontinued the study because of TEAEs, the most frequent of which were fatigue (n=4; 3.0%), akathisia, tremor (both n=3; 2.3%), anxiety, and depression (both n=2; 1.5%) • No patients died during the 26-week open-label treatment period • EPS-related TEAEs were reported by 21 patients (15.9%), most commonly akathisia (n=11; 8.3%) and tremor (n=9; 6.8%). All other EPS-related TEAEs (muscle spasms, masked facies, parkinsonism, and dyskinesia) occurred in ≤2 patients • Weight increase was reported as a TEAE in 11 patients (8.3%). Mean (SD) change in body weight from baseline was 0.9 (3.6) kg at week 26 (n=89). A total of 16 patients (12.3%) had a ≥7% weight increase from baseline, whereas 4 patients (3.1%) had a ≥7% weight decrease from baseline • Aside from mild increases in mean prolactin level, there were no consistent clinically relevant findings observed with regard to laboratory measurements (including glucose, cholesterol, and triglycerides), or vital signs • The mean change from baseline in QT_c interval on ECG readings was small, and not considered to be clinically relevant • One patient without suicidal ideation at baseline experienced treatment-emergent suicidal ideation (C-SSRS score of 1). There were no instances of suicidal ideation with intent or a plan (score of 4 or 5), no instances of suicidal behaviour (score of 6-10), and no reports of suicide-related TEAEs

Abbreviations: ADT: antidepressant therapy; AE: adverse events; C-SSRS: Columbia Suicide Severity Rating Scale; ECG: electrocardiogram; EPS: extrapyramidal symptoms; MDD: major depressive disorder; QT_c: heart rate-corrected QT interval; SD: standard deviation; TEAE: treatment emergent adverse events

8.1.3.2 Safety Topics of Clinical Interest

The safety topics of interest presented below are as per the US PI *(93)* and a long-term open-label safety study (52-week Orion study [amended to 26 weeks] from the three placebo controlled trials: Pyxis, Polaris, and Delphinus trials) *(84)*. Brexpiprazole demonstrated a generally similar safety profile in real-world use compared to the findings from clinical trials.

- **Neuroleptic malignant syndrome (NMS):** NMS, a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs, including brexpiprazole. No cases of NMS have been observed in the RCTs or open-label studies (Appendix A.4).
- **Tardive dyskinesia/EPS:** Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is impossible to predict which patients will develop the syndrome *(146)*. Whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is unknown. Around 12.1% (355/2938) of patients had an EPS-related TEAE during the long-term open-label. The most frequently reported EPS-related TEAE was akathisia (6.7%) *(84)*.
- **Hyperglycaemia/diabetes mellitus/dyslipidaemia:** AAP drugs, including brexpiprazole, have caused metabolic changes including hyperglycaemia, diabetes mellitus, dyslipidaemia. Although all the drugs in the class to date have been shown to produce some metabolic changes, each drug has its own specific risk profile *(146)*. During the long-term open-label study, the mean prolactin level changes from baseline to week 26 were 2.4 ng/mL in females (n=1381) and 1.1 ng/mL in males (n=656), and those from baseline to week 52 were 0.5 ng/mL in females (n=511) and 0.4ng/mL in males (n=237). The mean change in fasting glucose from baseline to week 26 was 3.1 mg/dL (n=1766), and that from baseline to week 52 was 4.6 mg/dL (n=678). The proportion of patients meeting the criteria for treatment-emergent metabolic syndrome (i.e., ≥3 of central obesity, dyslipidaemia, increased blood pressure, and increased fasting serum glucose levels) at any visit was 2.9% (65/2276 patients who did not meet the criteria at baseline and who had a postbaseline measurement) *(84)*.
- **Weight gain:** Weight gain has been observed in patients treated with AAPs including brexpiprazole and therefore, weight should be monitored at baseline and frequently thereafter *(146)*. During the long-term open-label study, the mean increase in body weight from baseline to week 26 was 2.7 kg (n=2,068) and from baseline to week 52 was 3.2 kg (n=771). The incidence of an increase in body weight of 7% or greater at any post-baseline visit was 25.8%, and the incidence of a decrease in body weight of 7% or greater at any postbaseline visit was 2.8% *(84)*.
- **Pathological gambling and other compulsive behaviours**: Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking brexpiprazole. Other compulsive urges, reported less frequently, include sexual urges, shopping, eating, or binge eating, and other impulsive or compulsive behaviours *(93)*.
- **Leukopenia, neutropenia, and agranulocytosis:** Leukopenia and neutropenia have been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in this class *(93)*. No cases have been reported in patients receiving brexpiprazole in RCTs or open label studies (Appendix A.4).
- **Orthostatic hypotension and syncope:** AAP cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose. In the short-term, placebo-controlled clinical studies of brexpiprazole plus ADT in adult patients with MDD, the incidence of orthostatic hypotension-related adverse reactions in brexpiprazole plus ADT-treated patients compared to placebo plus ADT-treated patients included: dizziness (2% vs. 2%) and orthostatic hypotension (0.1% vs. 0%) *(93)*.
- Other safety topics of interest include falls, seizures, body temperature dysregulation, dysphagia, and potential for cognitive and motor impairment *(93)*.

8.1.3.3 Potential of Inappropriate Use

- The recommended starting brexpiprazole dosage for the adjunctive treatment of MDD in adults is 0.5 mg or 1 mg orally once daily. Dose can be titrated to 1 mg once daily, then titrated to the target dosage of 2 mg once daily (based on the patient's clinical response and tolerability, with the dosage increased at weekly intervals. Periodic reassessments are required to determine the continued need and appropriate dosage for treatment *(93)*.
- Brexpiprazole is not a controlled substance, and the potential for inappropriate use/administration is considered low. No cases of overdose associated with adverse reactions were reported in clinical studies with brexpiprazole *(93)*.
    - **Abuse:** Animals given access to brexpiprazole did not self-administer the drug, suggesting that brexpiprazole does not have rewarding properties.
    - **Dependence:** Humans and animals that received chronic brexpiprazole administration did not demonstrate any withdrawal signs upon drug discontinuation. This suggests that brexpiprazole does not produce physical dependence *(93)*.

8.2 Systematic Reviews and Meta-analyses

8.2.1 Search Strategy and Selection Criteria

A literature search was performed in PubMed on July 2, 2024, to identify publications from clinical studies on the comparative effectiveness and safety of brexpiprazole vs. other adjunct antipsychotics to ADT for the treatment of MDD. The databases searched and the search strategy are presented in Appendix A.5. The literature search output was reviewed for SLRs or meta-analyses in peer-reviewed publications that compared the efficacy or safety outcomes of brexpiprazole vs. other adjunct AAPs to ADT and been presented in section 8.2.2.

8.2.2 Comparison of Adjunct Treatments

From the 11 studies meeting the inclusion criteria, the most recent and comprehensive systematic reviews and meta-analyses, including network meta-analysis focussing on both efficacy and safety of antipsychotics in adjunctive treatment of MDD, were prioritised to present in this section (n=4). Appendix A.6 presents the remaining (n=8) studies.

Studies demonstrate a high to low quality of evidence and risk of bias. The summary of the SLRs and network meta-analyses (NMAs) have been presented below. Overall, the SLRs and NMAs demonstrated that all the adjunctive agents (more specifically AAPs) including brexpiprazole demonstrate a higher or comparable efficacy to ADT + adjunctive placebo. There was variation observed across the four studies relating to tolerability, therefore side effect profile should be considered when selecting an augmentation agent. Overall, adjunct brexpiprazole demonstrated superior efficacy compared to adjunct placebo in achieving a response and remission. Further, across studies brexpiprazole demonstrated a favourable tolerability and acceptability profile (Table 5).

Table 5: Studies demonstrating the comparative effectiveness and safety of brexpiprazole vs. adjunct agents for MDD

Author	Study type	Results
Wang 2023 *(147)*	SLR and comparative meta-analysis of the efficacy and safety of four AAPs (aripiprazole, quetiapine XR, brexpiprazole, and quetiapine) as an adjunctive treatment with ADT, compared to placebo + ADT of MDD	• Overall, 56 studies (comprising 11,448 patients) met the inclusion criteria for the SLR and network analysis. The studies examined the outcomes of four AAPs (olanzapine, aripiprazole, quetiapine, and brexpiprazole) approved by the US FDA for adjunctive treatment of MDD • In terms of primary efficacy outcome, a total of 23 studies (comprising four AAPs) were included in the primary efficacy analysis (depressive symptom score [MADRS]). Quetiapine (standardised mean difference [SMD]: −0.40; 95% CI: −0.68, −0.12), olanzapine (SMD: −0.35; 95% CI: −0.59, −0.11), aripiprazole (SMD: −0.28; 95% CI: −0.47, −0.09), and brexpiprazole (SMD: −0.25; 95% CI: −0.42, −0.07) were significantly more effective compared with the placebo (PBO). However, there was no significant difference in efficacy among the AAPs • In terms of response rate, compared with the PBO, a significant increase was found in all AAPs. Among AAPs, aripiprazole (surface under the cumulative ranking curve [SUCRA] %: 96.6) was associated with the highest response rate followed by brexpiprazole (SUCRA %: 73.6) • In terms of acceptability, 20 studies (comprising 7,524 patients) were included in the acceptability analysis; no significant difference was observed between the four AAPs and PBO • In terms of tolerability, a total of 20 studies (comprising 6,524 patients) were included in the tolerability analysis. Compared with the PBO, quetiapine (risk ratio [RR]: 0.24; 95% CI: 0.11, 0.53), olanzapine (RR: 0.30; 95% CI: 0.10, 0.55): aripiprazole (RR: 0.39; 95% CI: 0.22, 0.69), and brexpiprazole (RR: 0.37; 95% CI: 0.18, 0.75) were significantly less well-tolerated. However, no significant difference in safety was found among the four AAPs • The NMA represented that brexpiprazole had better acceptability compared to the other AAPs and placebo, but this difference was not significant. Brexpiprazole has demonstrated a lower risk for akathisia than aripiprazole and a lower risk for somnolence than quetiapine XR in other studies • The summary for GRADE of response rate and AE rate and the comparison and ranking of all 4 AAPs on the basis of efficacy and safety has been presented in Appendix A.7. Overall, the quality of evidence was very low to moderate • Overall, the authors concluded that all AAPs were superior to PBO in reducing depression scores and improving response rates, which is consistent with previous studies. This study further validates the effectiveness of adjunctive AAPs in the treatment of MDD. Meanwhile, these results are consistent with guidelines for adjunctive AAPs for MDD as a first-line treatment after inadequate response to ADTs

Author	Study type	Results
Kishimoto 2023 *(148)*	A SLR and a meta-analysis were conducted on RCTs that reported on the efficacy and safety/tolerability of antipsychotics as adjunctive treatment for adults with MDD. Data of both monotherapy and adjunctive antipsychotic use were extracted but analysed separately using a random-effects model	• Of the 45 included studies (n=12,724), 13 studies (n=4,375) were conducted as antipsychotic monotherapy. All of them were double-blind studies. Thirty-two RCTs (n=8349) were conducted with antipsychotic treatment adjunctive to ADTs, 30 studies were double-blind, one each single-blind and open-label. There were 11 antipsychotic–placebo pairs in trials with adjunctive therapy (aripiprazole, brexpiprazole, cariprazine, iloperidone, olanzapine, oxypertine, pipamperone, quetiapine, risperidone, thioridazine, ziprasidone) • Overall, in the pooled analysis adjunctive antipsychotics were significantly superior to PBO + ADT regarding treatment response (N=28, n=7,366, RR: 1.35; 95% CI: 1.26, 1.45; P<0.001; number needed to treat [NNT]: 12; 95% CI: 9, 16). Individually, brexpiprazole demonstrated an RR of 1.41 (95% CI: 1.21, 1.66; P<0.001; NNT: 14, 95% CI: 9, 27) with superior treatment response compared to PBO. Individually, ziprasidone, risperidone, aripiprazole, brexpiprazole, cariprazine, and quetiapine demonstrated a significantly superior response compared to PBO + ADT. Conversely, iloperidone, olanzapine, perphenazine, and thioridazine did not significantly improve treatment response compared to PBO + ADT • Overall, adjunctive antipsychotic therapy was associated with significantly higher intolerability-related discontinuation than PBO (N=26, n=7,553, RR: 2.39; 95% CI: 1.69, 3.38; P<0.001; number needed to harm [NNH]: 37; 95% CI: 27, 73). Individually, ziprasidone (RR: 18.2), quetiapine (RR: 4.19), cariprazine (RR: 3.30), brexpiprazole (RR: 3.24), and aripiprazole (RR: 2.08) were associated with significantly higher intolerability-related discontinuation. Conversely, iloperidone, pipamperone, risperidone, and thioridazine were not significantly different from placebo in intolerability-related discontinuation • Overall, risk/benefit balance of antipsychotic varied by specific antipsychotic and their dose and should be factored into decision making for patients with MDD. Additional results regarding the risk/benefit ratio among antipsychotics for MDD are presented in Appendix A.7

Author	Study type	Results
Mishra 2022 *(149)*	A meta-analysis evaluating the effect of augmentation with serotonin-dopamine activity modulators (SDAM) drugs (aripiprazole and brexpiprazole) in patients with MDD. Primary analysis was presented with pooled results across SDAMs with subgroup analysis by each type of treatment	• 15 studies were included in the meta-analysis, of which 2 trials have not been published in article format and the results were available from ClinicalTrials.gov. Of the 15 studies, 8 trials used augmentation with aripiprazole, while 7 trials were with brexpiprazole. Both drugs were used in fixed-or flexible-dose regimens for the duration of the trial • In terms of remission rate, all 15 RCTs demonstrated that remission rates were better in the experimental group (aripiprazole and brexpiprazole) than in the PBO + ADT group, represented by a pooled OR of 1.55 (95% CI: 1.32, 1.84; P<0.0001), thereby suggesting a better efficacy of SDAM drugs in relieving symptoms of depression. In subgroup analysis, the pooled OR for remission in aripiprazole over PBO + ADT was 1.82 (95% CI: 1.52, 2.19; P=0.65), while for brexpiprazole vs. PBO + ADT, it was 1.37 (95% CI: 1.09, 1.1.73; P=0.10) • Overall, 14 studies reported a RR and demonstrated the OR of the treatments over PBO + ADT was 1.62 (95% CI: 1.42, 1.84; P<0.0001). The pooled OR for brexpiprazole vs. PBO + ADT was 1.46 (95% CI: 1.24, 1.71; P=0.50), while for aripiprazole vs. PBO + ADT, it was 1.8 (95% CI: 1.54, 2.19; P=0.72) • The change in MADRS score from baseline was greater in SDAM group when compared with PBO + ADT with a mean difference of 2.01 (95% CI: 1.50, 2.52; P<0.0001). The mean difference for remission with aripiprazole over PBO + ADT was 2.61 (95% CI: 1.93, 3.28; P=0.29) while for brexpiprazole vs. PBO + ADT, it was 1.56 (95% CI: 0.92, 2.19; P<0.01) • Overall, 14 trials included in this meta-analysis reported a change in CGI-S scores The overall mean difference between the treatment and PBO + ADT groups was 0.23 (95% CI: 0.11, 0.35; P=0.001). The mean difference for change in CGI-S score for brexpiprazole vs. PBO + ADT was 0.16 (95% CI: 0.09, 0.23; P=0.02) and that for aripiprazole vs. PBO + ADT was 0.33 (95% CI: 0.04, 0.62; P=not reported) • The pooled OR for AEs in treatment group when compared with PBO + ADT was 1.58 (95% CI: 1.37, 1.83; P=0.0001). On subgroup analysis, the pooled odds of AEs in brexpiprazole group were 1.37 (95% CI: 1.21, 1.56; P=0.65) and in aripiprazole group, it was 1.95 (95% CI: 1.52, 2.51; P=0.04) • The pooled OR for SAEs in experimental group was not statistically different from that in PBO + ADT group (OR: 0.72; 95% CI: 0.48, 1.08; P=0.113). The pooled OR of SAE in aripiprazole vs. PBO + ADT was 0.94 (95% CI: 0.43, 0.03; P=0.85) and that of brexpiprazole vs. PBO + ADT was 0.65 (95% CI: 0.40, 1.05; P=0.88) • There were no serious concerns in the domains of study design, inconsistency, imprecision, indirectness, and publication bias; and thus, the quality of evidence of all outcomes is graded as of high level of certainty • Adjunctive SDAM drugs have a beneficial effect on efficacy outcomes in patients with MDD. There was no significant difference in SAEs compared to ADT alone. In subgroup analysis, both the drugs had comparable efficacy, but the odds of AEs including SAEs were lower in brexpiprazole subgroup. The certainty of evidence has been presented in Appendix A.7

Author	Study type	Results
Vázquez 2021 *(150)*	SLR and NMA to compare efficacy and tolerability of combination treatments for MDD: ADTs + second-generation antipsychotics (SGAs) vs. ADTs + esketamine vs. ADT + lithium. The assessments and comparisons are based on meta-analysis to estimate and compare OR as well as NNT to indicate efficacy, and NNH arising from commonly clinically encountered adverse effects	• Among the 49 included trials (from 43 reports), four trials involving SGAs had more than one drug arm. This resulted in a total of 28 trials for SGAs, 14 for lithium carbonate, and 7 for intranasal esketamine, making up 49 drug-placebo comparisons overall. A total of 8,104 subjects were included in the 28 add-on SGA trials: 4,030 randomised to combination with an SGA, and 4,074 (3,008 unique participants owing to repeated use of some controls) with added placebo • Random-effects meta-analysis of trials of adding SGAs vs. placebo to ADTs yielded highly significant superiority of SGAs overall (OR: 1.59; 95% CI: 1.44, 1.75; P<0.0001). The efficacy of intranasal esketamine was intermediate between SGAs and lithium (OR: 1.94; 95% CI:1.52, 2.46; P<0.0001), and the efficacy of lithium was highest (OR: 2.22; 95% CI: 1.44, 3.43; P=0.0003) • NNT values for response among individual drugs or types did not differ significantly (overlapping CIs) but tended to be lower (more favourable) with lithium (NNT: 5; 95% CI: 4, 10) than with esketamine (NNT: 7; 95% CI: 5, 10) or SGAs overall (NNT: 11; 95% CI: 9, 15). NNT among SGAs ranked: risperidone (NNT: 6; 95% CI: 3, 13) = olanzapine/fluoxetine (which includes an ADT; NNT: 6; 95% CI: 4, 19) ≤ ziprasidone (NNT: 7; 95% CI: 3, ∞) ≤ aripiprazole (NNT: 9; 95% CI: 5, 24) ≤ cariprazine (NNT: 16; 95% CI: 8, 52) = brexpiprazole (NNT: 16; 95% CI: 10,34) • NNH for lithium was highest (lowest risk) at 9 (95% CI: 5, 106), and greater than with intranasal esketamine (NNH: 5; 95% CI: 4, 6) or all SGAs pooled (NNH: 5; 95% CI: 4, 6). For individual SGAs, NNH ranged from 19 with brexpiprazole to 3 with quetiapine indicating that brexpiprazole has the lowest risk of AE compared to other SGAs • Overall, SGAs were more effective than placebo (OR: 1.59; 95% CI: 1.44, 1.75; NNT: 11; 95% CI: 9, 15). Individually, aripiprazole, olanzapine + fluoxetine, risperidone, and ziprasidone all were more effective than quetiapine, brexpiprazole, or cariprazine (with overlapping CIs) • Apparent risk of adverse effects, as NNH (higher value with lower risk) for most frequently reported effects among SGAs vs. placebo, was highest with quetiapine (NNH = 3) and lowest with brexpiprazole (NNH: 19). Forest plot for the study has been presented in Appendix A.7 • However, the authors concluded that the trials included are heterogeneous, and computed values of NNT for individual SGAs had overlapping CIs, limiting their potential value in guiding recommendations regarding which drug should be used as a first choice. Additionally, most trials of adding lithium involved older, mainly tricyclic, ADTs, and the dosing of adjunctive treatments were not optimised

Abbreviations: AAP: atypical antipsychotics; ADT: antidepressant therapy; AE: adverse event; CGI-S: Clinical Global Impressions-Severity; CI: confidence interval; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: major depressive disorder; NNH: number needed to harm; NNT: number needed to treat; OR: odds ratio; PBO: placebo; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; SDAM: serotonin–dopamine activity modulator; SGA: second-generation antipsychotic; SMD: standardised mean difference; SUCRA: surface under the cumulative ranking curve; XR: extended release

8.2.3 Assessment of Applicability of the Available Evidence Across Diverse Populations and Settings

- Brexpiprazole demonstrated no difference in efficacy or safety across all RCTs with relation to gender, race, or age. Of the total number of brexpiprazole-treated patients in the clinical studies for the adjunctive therapy to ADTs for MDD and for schizophrenia, 248 (3%) were 65 years of age and older (which included 45 [18%] patients who were 75 years of age and older) *(93)*. Results of studies conducted in in elderly patients (≥65 years) and Asian adults with MDD and has been presented in Table 6.
- Overall brexpiprazole adjunct to ADT is effective and well-tolerated in patients who are 65 years of age and older with MDD. However, in general, dosage selection for the treatment of MDD in a geriatric patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function, concomitant diseases, and other drug therapy *(93)*.
- The safety and effectiveness of brexpiprazole for treatment of MDD has not been established in paediatric patients. ADTs increased the risk of suicidal thoughts and behaviours in paediatric patients *(93)*. Adequate and well-controlled studies have not been conducted with adjunct brexpiprazole in pregnant women to inform drug-associated risks. Hence it is not recommended in pregnancy *(93)*.

Table 6: Applicability of evidence across diverse populations and settings

Study	Results
Aquila study (NCT02400346) Open-label, long-term safety and tolerability study of flexible-dose brexpiprazole adjunct to ADT in elderly patients (≥65 years) with MDD *(145)*	Overall, the study demonstrated that adjunctive brexpiprazole was generally well-tolerated in elderly patients with inadequate response to prior ADT • Of the 132 treated patients, 88 (66.7%) completed the study, while 44 (33.3%) withdrew, including 24 (18.2%) due to AEs • Overall, 102 patients (77.3%) experienced at least one TEAE, mostly mild or moderate. The most common TEAEs were fatigue (15.2%) and restlessness (12.9%), with fatigue being the leading cause of withdrawal (3.0%) • Weight increase was reported as a TEAE in 11 patients (8.3%). Aside from mild increases in mean prolactin level, there were no consistent clinically relevant findings observed relating to laboratory measurements (including glucose, cholesterol, and triglycerides), or vital signs • No consistent clinically relevant findings were noted on movement disorder scales or safety assessments. Mean MADRS total score changes from baseline to week 26 were: MADRS total: -14.5 (0.9); CGI-S: -1.8 (0.1); and SASS: 3.2 (0.5) • Further, improvements were also observed in depressive symptoms and social functioning

Study	Results
Prospective, observational 3-month study to investigate the effectiveness and safety of brexpiprazole as an adjunctive treatment to ADT in Asian adults with MDD and inadequate response in a real-life clinical setting in Singapore *(151)*	• The study demonstrated that adjunctive brexpiprazole is effective and well-tolerated in the Asian population with MDD and findings were consistent with findings from clinical trials • 20 patients were enrolled in the study, with 16 completing it. At Week 12, there were notable improvements from baseline in the PHQ-9, CGI-S, SDS, and GAD-7 scores, with mean differences of −4.8, −1.3, −8.5, and −6.2, respectively. The CGI-I score also improved, with a mean score of 2.3 at Week 12. One-third of the participants achieved a response and 25% reached remission based on PHQ-9 scores at Week 12. Similar response and remission rates were observed using CGI-S scores (38% each) • AEs were reported in 55% (11/20) of the cases, with 50% (10/20) experiencing treatment-related AEs. No deaths or severe AEs occurred, though two patients discontinued brexpiprazole during the study *(151)*

Abbreviations: ADT: antidepressant treatment; AE: adverse events; CGI-I: Clinical Global Impression - Improvement; CGI-S: Clinical Global Impression - Severity; GAD-7: Generalised Anxiety Disorder 7-item scale; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: major depressive disorder; PHQ-9: Patient Health Questionnaire-9; TEAE: treatment emergent adverse events

9. Summary of Recommendations in Current Clinical Guidelines

9.1 Recommendations in Existing WHO Guidelines

- The WHO EML - 23rd list, 2023 currently recommends the ADTs, amitriptyline tablet (25 mg or 75 mg [hydrochloride]) and fluoxetine (20 mg) with a square box warning with citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline (20 mg each) as therapeutic alternatives for the treatment of major depression. Currently there are no adjunctive therapy to ADTs included in the WHO EML for the treatment of MDD in adults *(152)*.
- The WHO Mental Health Gap Action Programme (mhGAP) guidelines (3rd edition, 2023) *(153)* currently recommend:
    - Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline (SSRIs) or amitriptyline (tricyclic antidepressant [TCA]) should be considered for the treatment of adults with moderate-to-severe depression (strength of recommendation: conditional; certainty of evidence: very low).
    - The guidelines also recommend to regularly review the effectiveness of the medicine and side-effects during the first three months of treatment and every three months afterwards. For adults who experience side-effects after starting a medicine, consider closer monitoring of their symptoms, reducing the dose of the medicine or stopping the medicine gradually and offering alternative interventions.
    - Additionally, in adults with moderate-to-severe depression, psychological interventions or combined treatment should be considered based on individual preferences and careful consideration of the balance of benefits and harms. Antidepressant medicine alone for adults with moderate-to-severe depression should only be considered when psychological interventions are not available. Providers should keep in mind the possible adverse effects associated with ADTs, and individual preferences *(153)*.
- Although adjunct treatments are not currently listed on the EML or included in the mhGAP guidelines, they are recommended in other national and society clinical guidelines (see section 9.2).
    - The goals of treatment in MDD include full recovery from the major depressive episode, preserving social functioning (e.g., holding a job, retaining relationships), and prevention of relapse.
    - MDD is a prevalent, chronic, recurrent and highly disabling condition. The treatment pathways for MDD are highly varied and complex, with patients following completely unique sequences of medications. This heterogeneity makes it challenging to understand and optimise treatment recommendations in clinical practice (section 6.2.1).
    - Approximately 50% of patients with MDD experience inadequate responses to ADTs, which are frequently associated with worse outcomes (section 6.2.1).
    - Despite the availability of treatment options, significant challenges still exist surrounding the treatment of MDD. These may include poor response/remission, low adherence to and persistence to therapy, and tolerability of treatment options (section 6.2.1).

- Given the complex treatment patterns and the high clinical and economic burden of MDD, it is crucial to offer additional treatment options for patients who do not respond to ADTs in order to enhance their functioning and health-related quality of life (HRQoL; section 6.2).
    - Despite advancements in treatment, a significant number of individuals with MDD, particularly in LMICs, still do not respond adequately to ADTs. Many continue to face ongoing psychological, psychosocial, and functional challenges even after an acute episode has been managed (section 6.2).
    - MDD remains a major health issue in LMICs, necessitating a prioritisation of interventions and healthcare resources to alleviate the disorder's impact on these vulnerable populations (section 6.2).
    - The persistence of unresolved symptoms, along with their effects on patient functioning and disease progression, underscores the need for effective treatment options from the outset. Therefore, it is essential to promptly identify patients with inadequate responses and ensure they receive appropriate and effective treatment (section 6.2).

9.2 National and Society Guidelines

Guidelines from several major organisations, including the American Psychiatric Association (APA) the British Association for Psychopharmacology (BAP), Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines, NICE, World Federation of Societies of Biological Psychiatry guidelines (WFSBP), American College of Physicians (ACP), the Royal Australian and New Zealand College of Psychiatrists (RANZCP), and the Malaysian clinical practice guidelines recommend adjunct antipsychotics for patients with depression that do not no respond to or a limited response to ADTs *(127-129, 154-158)*. For additional details refer to Appendix A.8.

- All guidelines recommend the use of second-generation AAPs, which includes brexpiprazole, as an adjunctive treatment for adults with MDD.
- Brexpiprazole is recommended as one of the adjunct antipsychotic medications for use for the treatment of MDD by the CANMAT guidelines (Evidence level: 1) and the RANZCP guidelines (Grade: consensus-based recommendation) (Appendix A.8).

10. Summary of Available Data on Comparative Cost and Cost-Effectiveness

10.1 Data on Comparative Cost-Effectiveness

MDD poses a significant economic and societal burden. The use of adjunct AAPs for the treatment of patients with TRD leads to overall cost savings.

- MDD imposes a significant economic and societal burden, which worsens with inadequate treatment. Most indirect costs arise from work-related issues such as presenteeism, absenteeism, unemployment, mortality, and disability, as well as the impact on household members.
- The burden is particularly high among patients who relapse, leading to increased healthcare resource utilisation (HCRU). TRD further exacerbates the economic burden, with inadequate response to ADT being linked to lower employment rates and reduced work productivity (section 6.2.2).

Early initiation of adjunctive AAP treatment in patients with MDD significantly reduces hospitalisations, healthcare utilisation, and medical costs.

- The use of adjunctive AAPs in patients with MDD is associated with significant reductions in all-cause and MDD-related hospitalisations and ED visits compared to ADTs alone. Furthermore, early treatment (within the first year of initial ADT or within six months of evidence of inadequate therapy) is associated with significantly lower all-cause costs and a greater reduction in hospitalisation and overall medical costs compared to delayed treatment (section 6.3.2).
    - A US-based study compared healthcare utilisation and costs in patients with MDD (n=1,380; identified in IQVIA's PharMetrics Plus Adjudicated Claims database) before and after starting adjunctive AAP treatment (brexpiprazole, aripiprazole, quetiapine, or lurasidone) between October 1, 2014 and September 30, 2015. The analysis found that initiating adjunctive AAP treatment reduced all-cause and MDD-related hospitalisations by 12.2% and 10.4%, respectively compared to ADT monotherapy. Initiation of AAP treatment led to significant decreases in mean hospital costs ($6,217 and $1,166 per patient, both P<0.001) compared to ADT monotherapy. Additionally, mean all-cause medical costs significantly dropped by $4,513 per patient (P=0.025). Pharmacy costs increased by $4,236 per patient (P<0.001), mainly due to higher psychotropic drug use *(159)*.
    - Overall, initiation of adjunctive AAP treatment in MDD resulted in lower HCRU and medical costs compared to ADT monotherapy, primarily through reduced hospitalisations, which can potentially offset the higher pharmacy costs *(159)*.
- To explore the economic impact of delayed use of adjunctive AAPs, a real-world study in the US examined adjunctive treatment patterns in MDD patients and compared HCRU and costs between those who received AAPs as their first adjunctive therapy and those who received AAPs after other treatments (ADT monotherapy, non-ADT monotherapy for second line of therapy [LOT] and onward only, and adjunctive therapy [i.e., ADT combination, other adjunctive therapy, and AAP adjunctive therapy]). The Merative MarketScan Commercial Database (January 1, 2014, to June 30, 2019) was used to identify patients with administrative claims.

- The study included 508,830 patients, of whom 4% received an AAP and 24% received any other adjunctive treatment. Patients who initiated an AAP as their first adjunctive therapy compared with patients who initiated an AAP as their subsequent adjunctive therapy had fewer LOTs on average (0.9 vs. 3.9) and shorter time between index diagnosis date and initiation of an AAP (5 months vs. 12 months) *(80)*.
- Subsequent AAP initiators had higher HCRU and incurred greater healthcare costs compared with patients who received AAP as their first adjunctive treatment regimen, with annual differences of $2,441 for all-cause and $1,762 for mental health-related costs (both P<0.05) *(80)*.
- Hence, delay in starting an adjunctive AAPs was associated with negative impacts on HCRU and health care costs. The findings suggest that initiating adjunctive AAPs as early as possible in the disease course leads to improved adherence, lower HCRU, and lower health care costs *(80)*.

Brexpiprazole outperforms other AAPs by improving treatment adherence and reducing the overall medical costs through reduced HCRU.

- In the real-world setting, the use of brexpiprazole leads to medical care cost savings although total costs are higher than other adjunctive treatments and ADTs. In a cost-effectiveness study (US payer perspective) was conducted to compare the impact of brexpiprazole vs. other adjunctive treatments and ADT alone on total costs, focusing on treatment response and remission *(160)*.
  - In a hypothetical cohort of 1,000 patients with MDD with inadequate ADT response, brexpiprazole showed higher clinical response and remission rates after 6 weeks compared with quetiapine 150 mg/day, quetiapine 300 mg/day, olanzapine/fluoxetine, and ADT alone. At 48 weeks, brexpiprazole had 484 responders and 224 remitters, vs. 325 responders and 104 remitters for ADT alone *(160)*.
  - The total costs per patient were the highest for brexpiprazole ($11,511) and the lowest for ADT alone ($7,255). Brexpiprazole resulted in the lowest care-related medical costs despite higher pharmacy costs *(160)*.
  - Costs per additional responder and remitter were the highest for olanzapine/fluoxetine and the lowest for quetiapine XR 300 mg/day. Sensitivity analyses confirmed that brexpiprazole led to more responders and remitters but at a higher cost. Scenario analyses over a 6-week horizon showed consistent trends, reinforcing brexpiprazole's higher costs which is mitigated by lower HCRU related costs and improved clinical outcomes *(160)*.
  - Although total costs were higher, medical care cost savings are observed with the use of brexpiprazole in the real-world setting *(160)*.
- A real-world retrospective study (utilising patient-level data from IQVIA Real-World Data – US Adjudicated Claims between July 2014 and September 2016) compared the HCRU and costs in patients with MDD treated with brexpiprazole or quetiapine XR as adjunctive treatment to ADT *(161)*. Brexpiprazole was associated with significantly lower medical costs, particularly those related to hospitalisations. While total healthcare costs per patient were similar between the two treatments, the breakdown showed lower medical costs but higher pharmacy costs for brexpiprazole compared to quetiapine XR.
  - Patients in the brexpiprazole cohort were initiated on either 1 mg (45.5%), 2 mg (39.1%), or 0.50 mg (11.8%) per day. Over one-third of patients (34.6%) in the quetiapine XR cohort

were initiated on low-dose 50 mg quetiapine XR per day; 30.4% were initiated on 150 mg quetiapine XR per day. During follow-up, patients filled 3.9 (SD 2.4) prescriptions for brexpiprazole and 3.7 (SD 2.6) prescriptions for quetiapine XR *(161)*.

- HCRU and medical costs associated with brexpiprazole and quetiapine XR for adjunctive treatment of MDD are presented in Table 7.
- Medical cost of a brexpiprazole-treated patient was 16.1% lower than that of a quetiapine XR-treated patient (exponentiated coefficient: 0.839; 95% CI: 0.725, 0.971; P=0.0186) *(161)*.
- Hospitalisation costs were $1,299 (95% CI: 135, 2,464) lower with brexpiprazole. Costs for ED visits and other outpatient services were $182 (95% CI: 52, 311) and $907 (95% CI: 71, 1,744) lower, respectively, with brexpiprazole. However, physician office visit costs were $336 (95% CI: 101, 507) higher with brexpiprazole *(161)*.
- Overall, brexpiprazole offers potential economic benefits through reduced hospitalisations and emergency visits, despite higher pharmacy and office visit costs.

Table 7: HCRU and medical costs associated with brexpiprazole and quetiapine XR for adjunctive treatment of MDD in the US

	Brexpiprazole	Quetiapine XR	P-value
Proportion of patients with all-cause hospital stay (6-month post-index period)	6.6%	12.5%	<0.0001
Proportion of patients with ED visit for any reason	16.9%	27.5%	<0.0001
Mean number of all-cause hospitalisations per patient	0.10	0.21	0.0002
Mean number of ED visits per patient	0.30	0.55	<0.0001
Mean number of all-cause physician office visits per patient	14.89	12.57	0.0008
Mean total healthcare costs per patient (SD)	$13,821 (15,543)	$13,235 (22,293)	0.545
Mean medical costs per patient (SD)	$6,421 (13,055)	$8,545 (19,939)	0.012
Mean pharmacy costs per patient (SD)	$7,401 (7,564)	$4,691 (8,314)	<0.0001

Source: *(161)*
Abbreviations: ED: emergency department; HCRU: healthcare resource utilisation; MDD: major depressive disorder; SD: standard deviation; US: United States; XR: extended-release
Note: All costs presented were adjusted to the 2016 USD

- Another real-world retrospective cohort study in the US was conducted to compare the medication adherence, HCRU, and costs among patients receiving adjunctive brexpiprazole, quetiapine, or lurasidone for MDD (using the Truven Health Analytics MarketScan Commercial, Medicaid, and Medicare Supplemental Databases from July 1, 2015 to June 30, 2016 for Medicaid data and July 1, 2015 to March 31, 2016 for Commercial and Medicare) *(101)*. The study reported that brexpiprazole use was associated with statistically significantly lower risks of

discontinuation, risk of hospital care (hospitalisation and ED visits), and all-cause medical costs compared with adjunctive quetiapine and lurasidone; however, differences between brexpiprazole and lurasidone were not statistically significant *(101)*.

- The study included patients who initiated therapy with brexpiprazole (n=778), lurasidone (n=626), and quetiapine (n=3,458). After adjusting for baseline differences, the risk of discontinuing the index AAP was significantly higher for quetiapine compared to brexpiprazole (HR: 1.13; 95% CI: 1.02, 1.25; P=0.023) and similar between lurasidone and brexpiprazole (HR: 1.14; 95% CI: 1.00, 1.29; P=0.054) *(101)*.
- The adjusted rate of all-cause hospitalisation or ED visits was lowest for brexpiprazole at 27.4% (95% CI: 24.0, 31.0), compared with 31.1% (95% CI: 27.3, 35.2) for lurasidone and 35.3% (95% CI: 33.5, 37.1) for quetiapine (P<0.001 for all comparisons) *(101)*.
- Quetiapine users had significantly higher all-cause costs compared with brexpiprazole users ($2,309; 95% CI: 31, 4,587; P=0.047), while there was no significant difference in all-cause medical costs between lurasidone and brexpiprazole ($913; 95% CI: -2,033, 3,859; P=0.543) *(101)*.
- Adjusted psychiatric hospital care, psychiatric costs, and proportion of dates covered (defined as days with index therapy available divided by 180), did not differ significantly among the groups *(101)*.

Adjunctive AAPs, including brexpiprazole, could potentially be a cost-effective treatment option in LMICs, particularly by improving treatment response and reducing HCRU.

- A budget impact analysis (BIA) from the perspective of the Mexican National Health System (MNHS) was conducted to determine the financial impact of the inclusion of brexpiprazole as adjunctive treatment in patients with MDD in Mexico. Brexpiprazole, when used as adjunctive treatment with ADT, resulted in statistically significant differences vs. ADT monotherapy in remission rate (RR: 1.28; 95% CI: 1.01, 1.62; P=0.04). The BIA showed inclusion of brexpiprazole as adjunctive treatment in adults with MDD has an annual mean budget impact in a 5-year horizon of Mexican Peso (MXN) 21,543,663 (USD $1,077,183; 2021 exchange rate), representing 0.0124% of their pharmacotherapy budget for all conditions *(162)*.
- A SLR including 22 studies published between January 1, 2000 and December 3, 2022 was conducted to determine the cost-effectiveness of treatments for depression in LMICs, overall reporting mixed evidence regarding the cost-effectiveness of depression treatments in LMICs *(52)*. Studies that examined the cost-effectiveness of AAPs (e.g., aripiprazole, olanzapine and quetiapine) for managing treatment-resistant MDD were included in the SLR. Of the studies included in the SLR, two studies reported data on adjunct AAP use and have been presented below.
    - An economic model (patient-level simulation from the payer perspective) comparing aripiprazole with other AAPs found that aripiprazole was the dominant adjunctive treatment compared to adjunctive quetiapine and olanzapine in TRD in the Turkish setting. Despite the higher drug acquisition cost, on average, the total cost for a patient starting with adjunctive aripiprazole was less than those for a patient starting with adjunctive quetiapine and olanzapine, respectively. The increased remission rate of adjunctive AAP (aripiprazole) led to the health gains and cost savings *(69)*. The study concluded that savings were mainly explained by less hospitalisation costs and fewer psychiatrist visits. Adjunct AAPs which improve remission and reduce economic burden could potentially lead to cost savings in other LMICs.

- By contrast, a cost-utility analysis (CUA) (cost year 2009; over a 6-week time horizon) that compared aripiprazole with placebo for Thai patients with MDD who showed an inadequate response to at least one prospective ADT, concluded that aripiprazole was not cost-effective due to its high incremental cost-effectiveness ratio (ICER) value (Baht 2,561 or USD $267/remission; 3,201 Baht or USD $333/quality adjusted life year [QALY]) *(52, 163)*. Remission rates and unit cost were the key parameters involving the cost-effectiveness of aripiprazole *(163)*. However, the estimated willingness to pay (WTP) threshold in Thailand ranges between Baht 59,000 (USD $5,600) and Baht 285,000 (USD $27,052), or 0.4–2 times the gross domestic product (GDP) per capita. Therefore, the ICER value associated with aripiprazole is less than the estimated WTP or below the WHO's cost-effectiveness recommendation of 1 to 3 GDP or alternative suggestions such as GDP-based criteria of 0.5 to 1.5 GDP and opportunity cost thresholds of 0.5 GDP *(52)*. As a result, adjunctive AAPs may be a cost-effective option for patients with MDD and inadequate response to ADTs in Thailand.
- Overall, by improving response and adherence, while reducing the HCRU and healthcare costs, adjunct AAPs could further drive down costs in LMICs *(52)*. Initiation of adjunct treatment with AAPs earlier in the duration in treatment can lead to further cost savings (section 6.3.2).

- Adjunctive AAPs are effective in reducing healthcare costs for patients with MDD by significantly decreasing hospitalisations and ED visits. Brexpiprazole, in particular, demonstrates superior economic benefits compared to other adjunctive AAPs. In the real-world setting, while brexpiprazole has higher pharmacy costs, it is associated with improved treatment response and adherence (section 6.3.1 and 8.1). This translates into reduced HCRU and lower all-cause medical costs. Thus, brexpiprazole not only offers better clinical outcomes but also more efficient use of healthcare resources compared to alternatives, making it a cost-effective option for managing MDD in LMICs.

10.2 Data on the Price of the Medicine

- Brexpiprazole tablets are available in 6 dose strengths (0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg) and the cost per patient will vary. Prices vary based on country specific value assessments, population coverage, local pricing & reimbursement negotiations, and local regulations.
- The lowest list price in high-income countries ranges from USD $6.17 to USD $0.82, and for LMICs ranges from USD $5.09 to USD $0.89 according to the dose strength (Table 8).

Table 8: Brexpiprazole price list according to dose strength

Tablet dose strength	Lowest list price (USD/Unit)	
	High-income countries	Low- and middle-income countries
0.25 mg	2.59 (Canada) to 0.82 (Saudi)	NA
0.5 mg	2.59 (Canada) to 1.35 (Saudi)	4.23 (Nicaragua) to 0.89 (Brazil)
1 mg	4.80 (Lebanon) to 1.20 (Spain)	2.98 (Slovenia) to 1.12 (Hungary)

Tablet dose strength	Lowest list price (USD/Unit)	
	High-income countries	Low- and middle-income countries
2 mg	5.32 (Nicaragua) to 1.20 (Spain)	5.09 (Indonesia) to 1.88 (Chile)
3 mg	5.02 (Liechtenstein) to 1.20 (Spain)	5.09 (Indonesia) to 2.15 (Turkey)
4 mg	6.17 (Liechtenstein) to 1.20 (Spain)	5.09 (Indonesia) to 2.15 (Turkey)

Abbreviations: NA: not applicable; USD: United States Dollar.

10.2.1 Otsuka's Public Health Commitment

- Otsuka is passionate and committed about helping others. Otsuka's approach to social impact is grounded in the idea of creating better health worldwide. We envision a world where everyone can access the healthcare they need. Our promise is to invest in products, programs, policies, and advocacy efforts that help remove stigma and discrimination, increase access to care, and address social determinants of health.
- Otsuka is deeply committed to advancing public health and promoting equality worldwide. We believe that every individual deserves access to high-quality healthcare, regardless of their socioeconomic status or geographic location. With the aim of contributing to improved access to pharmaceuticals, the Otsuka group researches, develops and extends therapeutic drugs and IV solutions that address unmet medical needs. We also work to provide pharmaceuticals at fair prices to support improved healthcare infrastructure. As a way of example, Otsuka is actively engaging with the WHO in the fight against tuberculosis. Otsuka is part of the global effort to combat pulmonary tuberculosis, a leading infectious disease killer worldwide, through development of a treatment supported by a grant from the Bill and Melinda Gates Foundation *(164, 165)*.
- Otsuka strive to make our medications affordable and accessible, particularly in LMICs. By supporting the inclusion of essential medicines like brexpiprazole on the WHO EML, we aim to provide vital treatment options for chronic conditions such as MDD.

11. Regulatory Status, Market Availability and Pharmacopoeial Standards

11.1 Regulatory Status of the Proposed Medicine

Brexpiprazole has been approved under the trade name REXULTI by the US FDA and is indicated as an adjunctive therapy to antidepressants for the treatment of MDD in adults *(93)*. Brexpiprazole has not been approved by the EU EMA for the adjunctive treatment of MDD but is used for the treatment of schizophrenia *(142)*.

Across all approved indications, brexpiprazole is approved in over 60 countries globally. Brexpiprazole has been approved in the following countries:

- **Asia Pacific:**
  - Australia, China, Hong Kong, Indonesia, Japan, Kazakhstan, Malaysia, Myanmar, Philippines, Singapore, Taiwan, Thailand
- **Europe, Middle East, Africa, and the Caribbean:**
  - Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Israel, Italy, Kuwait, Latvia, Lebanon, Liechtenstein, Lithuania, Luxembourg, Malta, Morocco, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Saudi Arabia, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, United Arab Emirates, United Kingdom (Great Britain), United Kingdom (Northern Ireland)
- **North/Central America:**
  - Canada, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, United States
- **South America:**
  - Argentina, Brazil, Chile, Ecuador, Peru

Brexpiprazole is approved in the following countries for the adjunctive treatment of MDD:

- **Asia Pacific:**
  - Hong Kong, Indonesia, Japan, Malaysia, Myanmar, Philippines, Singapore, Thailand
- **Europe, Middle East, Africa, and the Caribbean:**
  - Dominican Republic, Israel, Kuwait, Lebanon, Saudi Arabia, Turkey, United Arab Emirates
- **North/Central America:**
  - Canada, Costa Rica, El Salvador, Guatemala , Honduras, Mexico, Nicaragua, Panama, United States
- **South America:**
  - Argentina, Brazil, Chile, Ecuador, Peru

11.2 Market Availability of the Proposed Medicine

Market availability: Brexpiprazole is available in the following countries:

- **Asia Pacific:**
  - Australia, Hong Kong, Indonesia, Japan, Kazakhstan, Malaysia, Philippines, Singapore, Taiwan, Thailand
- **Europe, Middle East, and Africa:**
  - Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kuwait, Latvia, Lebanon, Liechtenstein, Lithuania, Luxembourg, Malta, Morocco, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Saudi Arabia, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, United Arab Emirates, United Kingdom
- **North America:**
  - Canada, Costa Rica, Guatemala, Mexico, Nicaragua, United States
- **South America:**
  - Argentina, Brazil, Chile

Access: There are no anticipated distribution restrictions, supply limitations, shortages, or prescribing restrictions of brexpiprazole

Patent Information: The US patent information listed in the FDA Orange Book for REXULTI shows a last patent expiration of April 12, 2033 (US10307419).

No generic formulations are currently available for brexpiprazole. However, Otsuka is committed to a responsible pricing strategy that prioritises patient access and treatment affordability for brexpiprazole.

11.3 Pharmacopoeial Standards

There are currently no inclusions of brexpiprazole for MDD in any pharmacopoeia.

12. Reference List

1. WHO. Depressive disorder (depression) Fact Sheets [website]. 2023 (https://www.who.int/news-room/fact-sheets/detail/depression).
2. Chand SP AH. Depression [website]. StatPearls Publishing; 2023 (https://www.ncbi.nlm.nih.gov/books/NBK430847/).
3. Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M et al. Major depressive disorder. Nature Reviews Disease Primers. 2016;2(1):16065 (https://doi.org/10.1038/nrdp.2016.65).
4. Bains N AS. Major Depressive Disorder [website]. StatPearls Publishing; 2024 (https://www.ncbi.nlm.nih.gov/books/NBK559078/).
5. Liu J, Liu Y, Ma W, Tong Y, Zheng J. Temporal and spatial trend analysis of all-cause depression burden based on Global Burden of Disease (GBD) 2019 study. Scientific Reports. 2024;14(1):12346 (https://doi.org/10.1038/s41598-024-62381-9).
6. GBD. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Psychiatry. 2022;9(2):137-50 (https://doi.org/10.1016/S2215-0366(21)00395-3).
7. Thornicroft G, Chatterji S, Evans-Lacko S, Gruber M, Sampson N, Aguilar-Gaxiola S et al. Undertreatment of people with major depressive disorder in 21 countries. Br J Psychiatry. 2017;210(2):119-24 (https://doi.org/10.1192/bjp.bp.116.188078).
8. SSHB. Low- or Middle-Income Country (LMIC) [website]. 2024 (https://www.sshb.org/lmic/).
9. Xiong J, Lipsitz O, Nasri F, Lui LMW, Gill H, Phan L et al. Impact of COVID-19 pandemic on mental health in the general population: A systematic review. J Affect Disord. 2020;277:55-64 (https://doi.org/10.1016/j.jad.2020.08.001).
10. Santomauro DF, Mantilla Herrera AM, Shadid J, Zheng P, Ashbaugh C, Pigott DM et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet. 2021;398(10312):1700-12 (https://doi.org/10.1016/s0140-6736(21)02143-7).
11. Zhang Z, Jackson SL, Gillespie C, Merritt R, Yang Q. Depressive Symptoms and Mortality Among US Adults. JAMA Network Open. 2023;6(10):e2337011-e (https://doi.org/10.1001/jamanetworkopen.2023.37011).
12. Madsen KB, Plana-Ripoll O, Musliner KL, Debost J-CP, Petersen LV, Munk-Olsen T. Cause-specific life years lost in individuals with treatment-resistant depression: A Danish nationwide register-based cohort study. Journal of Affective Disorders. 2021;280:250-7 (https://doi.org/https://doi.org/10.1016/j.jad.2020.11.042).
13. 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).
14. Kern DM, Canuso CM, Daly E, Johnson JC, Fu DJ, Doherty T et al. Suicide-specific mortality among patients with treatment-resistant major depressive disorder, major depressive disorder with prior suicidal ideation or suicide attempts, or major depressive disorder alone. Brain and Behavior. 2023;13(8):e3171 (https://doi.org/https://doi.org/10.1002/brb3.3171).
15. Corral R, Alessandria H, Agudelo Baena LM, Ferro E, Duque X, Quarantini L et al. Suicidality and Quality of Life in Treatment-Resistant Depression Patients in Latin America: Secondary Interim Analysis of the TRAL Study. Front Psychiatry. 2022;13:812938 (https://doi.org/10.3389/fpsyt.2022.812938).
16. Lundberg J, Cars T, Lööv S, Söderling J, Tiihonen J, Leval A et al. Clinical and societal burden of incident major depressive disorder: A population-wide cohort study in Stockholm. Acta Psychiatr Scand. 2022;146(1):51-63 (https://doi.org/10.1111/acps.13414).

17. Lundberg J, Cars T, Lampa E, Ekholm Selling K, Leval A, Gannedahl A et al. Determinants and Outcomes of Suicidal Behavior Among Patients With Major Depressive Disorder. JAMA Psychiatry. 2023;80(12):1218-25 (https://doi.org/10.1001/jamapsychiatry.2023.2833).
18. Cui L, Li S, Wang S, Wu X, Liu Y, Yu W et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduction and Targeted Therapy. 2024;9(1):30 (https://doi.org/10.1038/s41392-024-01738-y).
19. Yu Q, Xue F, Gao M, Wik SL, Chan SC, Chow SH et al. AB013. Major depressive disorder and its risk factors in low- and middle-income countries. Journal of Public Health and Emergency. 2024;8 (https://jphe.amegroups.org/article/view/9865).
20. Moitra M, Santomauro D, Collins PY, Vos T, Whiteford H, Saxena S et al. The global gap in treatment coverage for major depressive disorder in 84 countries from 2000–2019: A systematic review and Bayesian meta-regression analysis. PLOS Medicine. 2022;19(2):e1003901 (https://doi.org/10.1371/journal.pmed.1003901).
21. Li S, Xu Y, Zheng L, Pang H, Zhang Q, Lou L et al. Sex Difference in Global Burden of Major Depressive Disorder: Findings From the Global Burden of Disease Study 2019. Front Psychiatry. 2022;13:789305 (https://doi.org/10.3389/fpsyt.2022.789305).
22. Proudman D, Greenberg P, Nellesen D. The Growing Burden of Major Depressive Disorders (MDD): Implications for Researchers and Policy Makers. Pharmacoeconomics. 2021;39(6):619-25 (https://doi.org/10.1007/s40273-021-01040-7).
23. Arnaud AM, Brister TS, Duckworth K, Foxworth P, Fulwider T, Suthoff ED et al. Impact of Major Depressive Disorder on Comorbidities: A Systematic Literature Review. J Clin Psychiatry. 2022;83(6) (https://doi.org/10.4088/JCP.21r14328).
24. Berk M, Köhler-Forsberg O, Turner M, Penninx B, Wrobel A, Firth J et al. Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management. World Psychiatry. 2023;22(3):366-87 (https://doi.org/10.1002/wps.21110).
25. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). Jama. 2003;289(23):3095-105 (https://doi.org/10.1001/jama.289.23.3095).
26. Fava M, Hwang I, Rush AJ, Sampson N, Walters EE, Kessler RC. The importance of irritability as a symptom of major depressive disorder: results from the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15(8):856-67 (https://doi.org/10.1038/mp.2009.20).
27. Fava M, Alpert JE, Carmin CN, Wisniewski SR, Trivedi MH, Biggs MM et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychological Medicine. 2004;34(7):1299-308 (https://doi.org/10.1017/S0033291704002612).
28. Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry. 2008;165(3):342-51 (https://doi.org/10.1176/appi.ajp.2007.06111868).
29. McIntyre RS, Weiller E. Real-world determinants of adjunctive antipsychotic prescribing for patients with major depressive disorder and inadequate response to antidepressants: a case review study. Adv Ther. 2015;32(5):429-44 (https://doi.org/10.1007/s12325-015-0207-3).
30. Brasso C, Cisotto M, Del Favero E, Giordano B, Villari V, Rocca P. Impact of COVID-19 pandemic on major depressive disorder in acute psychiatric inpatients. Front Psychol. 2023;14:1181832 (https://doi.org/10.3389/fpsyg.2023.1181832).
31. Dunlop BW. Evidence-Based Applications of Combination Psychotherapy and Pharmacotherapy for Depression. Focus (Am Psychiatr Publ). 2016;14(2):156-73 (https://doi.org/10.1176/appi.focus.20150042).
32. Saltiel PF, Silvershein DI. Major depressive disorder: mechanism-based prescribing for personalized medicine. Neuropsychiatr Dis Treat. 2015;11:875-88 (https://doi.org/10.2147/ndt.S73261).

33. Papakostas GI. Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. J Clin Psychiatry. 2009;70 Suppl 6:16-25 (https://doi.org/10.4088/JCP.8133su1c.03).
34. Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. J Clin Psychiatry. 2001;62 Suppl 16:5-9 (https://pubmed.ncbi.nlm.nih.gov/11480882/).
35. Dold M, Kasper S. Evidence-based pharmacotherapy of treatment-resistant unipolar depression. International Journal of Psychiatry in Clinical Practice. 2017;21(1):13-23 (https://doi.org/10.1080/13651501.2016.1248852).
36. Zanardi R, Carminati M, Attanasio F, Fazio V, Maccario M, Colombo C. How different definition criteria may predict clinical outcome in treatment resistant depression: Results from a prospective real-world study. Psychiatry Research. 2024;334:115818 (https://doi.org/https://doi.org/10.1016/j.psychres.2024.115818).
37. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatr Dis Treat. 2020;16:221-34 (https://doi.org/10.2147/ndt.S198774).
38. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P et al. The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. J Clin Psychiatry. 2021;82(2) (https://doi.org/10.4088/JCP.20m13699).
39. Rush J, Trivedi M, Wisniewski S, Nierenberg AA, Stewart JW, Warden D et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. American Journal of Psychiatry. 2006;163(11):1905-17 (https://doi.org/10.1176/ajp.2006.163.11.1905).
40. Thomas L, Kessler D, Campbell J, Morrison J, Peters TJ, Williams C et al. Prevalence of treatment-resistant depression in primary care: cross-sectional data. Br J Gen Pract. 2013;63(617):e852-8 (https://doi.org/10.3399/bjgp13X675430).
41. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry. 2023;22(3):394-412 (https://doi.org/10.1002/wps.21120).
42. Haddad PM, Talbot PS, Anderson IM, McAllister-Williams RH. Managing inadequate antidepressant response in depressive illness. British Medical Bulletin. 2015;115(1):183-201 (https://doi.org/10.1093/bmb/ldv034).
43. Zajecka J, Kornstein SG, Blier P. Residual Symptoms in Major Depressive Disorder: Prevalence, Effects, and Management. The Journal of Clinical Psychiatry. 2013;74(04):407-14 (https://doi.org/10.4088/jcp.12059ah1).
44. Wiethoff K, Bauer M, Baghai T, Möller H-J, Fisher R, Hollinde D et al. Prevalence and Treatment Outcome in Anxious Versus Nonanxious Depression: Results From the German Algorithm Project. The Journal of clinical psychiatry. 2010;71:1047-54 (https://doi.org/10.4088/JCP.09m05650blu).
45. Fekadu A, Demissie M, Birhane R, Medhin G, Bitew T, Hailemariam M et al. Under detection of depression in primary care settings in low and middle-income countries: a systematic review and meta-analysis. Systematic Reviews. 2022;11(1):21 (https://doi.org/10.1186/s13643-022-01893-9).
46. Rezaiye M, Radfar M, MaslakPak MH. Quality of life among Iranian major depressive disorder patients: a qualitative study. Middle East Current Psychiatry. 2023;30(1):22 (https://doi.org/10.1186/s43045-023-00299-0).
47. Rathod S, Pinninti N, Irfan M, Gorczynski P, Rathod P, Gega L et al. Mental Health Service Provision in Low- and Middle-Income Countries. Health Serv Insights. 2017;10:1178632917694350 (https://doi.org/10.1177/1178632917694350).
48. Habert J, Katzman MA, Oluboka OJ, McIntyre RS, McIntosh D, MacQueen GM et al. Functional Recovery in Major Depressive Disorder: Focus on Early Optimized Treatment. Prim Care Companion CNS Disord. 2016;18(5) (https://doi.org/10.4088/PCC.15r01926).

49. Greenberg PE, Fournier AA, Sisitsky T, Simes M, Berman R, Koenigsberg SH et al. The Economic Burden of Adults with Major Depressive Disorder in the United States (2010 and 2018). Pharmacoeconomics. 2021;39(6):653-65 (https://doi.org/10.1007/s40273-021-01019-4).
50. Greenberg P, Chitnis A, Louie D, Suthoff E, Chen SY, Maitland J et al. The Economic Burden of Adults with Major Depressive Disorder in the United States (2019). Adv Ther. 2023;40(10):4460-79 (https://doi.org/10.1007/s12325-023-02622-x).
51. Chisholm D, Sweeny K, Sheehan P, Rasmussen B, Smit F, Cuijpers P et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. The Lancet Psychiatry. 2016;3(5):415-24 (https://doi.org/10.1016/S2215-0366(16)30024-4).
52. Belay YB, Engel L, Lee YY, Le N, Mihalopoulos C. Cost Effectiveness of Pharmacological and Non-pharmacological Treatments for Depression in Low- and Middle-Income Countries: A Systematic Literature Review. PharmacoEconomics. 2023;41(6):651-73 (https://doi.org/10.1007/s40273-023-01257-8).
53. Sadaf T, Iqbal MA, Jamil F, Raza MH, Nazir A. Cost of Mental Illness and Depression in Developing Countries: A Case Study of Pakistan. Journal of Education and Social Studies. 2022;3(2):84-94 (https://doi.org/10.52223/jess.20223204).
54. Painchault C, Brignone M, Lamy FX, Diamand F, Saragoussi D. Economic Burden of Major Depressive Disorder (Mdd) in Five European Countries: Description of Resource use by Health State. Value in Health. 2014;17(7):A465 (https://doi.org/10.1016/j.jval.2014.08.1300).
55. Mrazek DA, Hornberger JC, Altar A, Degtiar I. A Review of the Clinical, Economic, and Societal Burden of Treatment-Resistant Depression: 1996–2013. Psychiatric Services. 2014;65(8):977-87 (https://doi.org/10.1176/appi.ps.201300059).
56. Kailey R, Safinia L, Denee T, Wood R, Tritton T, Massey O. PMH11 Quantifying the Real-World Economic Burden of Major Depressive Disorder and Treatment-Resistant Depression in England: National and Regional Estimates. Value in Health. 2020;23:S585-S6 (https://doi.org/10.1016/j.jval.2020.08.1089).
57. Knoth RL, Bolge SC, Kim E, Tran QV. Effect of inadequate response to treatment in patients with depression. Am J Manag Care. 2010;16(8):e188-96 (https://pubmed.ncbi.nlm.nih.gov/20690785/).
58. Arnaud A, Suthoff E, Tavares RM, Zhang X, Ravindranath AJ. The Increasing Economic Burden with Additional Steps of Pharmacotherapy in Major Depressive Disorder. PharmacoEconomics. 2021;39(6):691-706 (https://doi.org/10.1007/s40273-021-01021-w).
59. Amos TB, Tandon N, Lefebvre P, Pilon D, Kamstra RL, Pivneva I et al. Direct and Indirect Cost Burden and Change of Employment Status in Treatment-Resistant Depression: A Matched-Cohort Study Using a US Commercial Claims Database. J Clin Psychiatry. 2018;79(2) (https://doi.org/10.4088/JCP.17m11725).
60. Kessler RC. The costs of depression. Psychiatr Clin North Am. 2012;35(1):1-14 (https://doi.org/10.1016/j.psc.2011.11.005). Licence: NIHMS338335.
61. Iliou K, Balaris D, Dokali AM, Fotopoulos V, Kouletsos A, Katsiana A. Exploring the Effects of Major Depressive Disorder on Daily Occupations and the Impact of Psychotherapy: A Literature Review. Cureus. 2024;16(3):e55831 (https://doi.org/10.7759/cureus.55831).
62. Bonicatto SC, Dew MA, Zaratiegui R, Lorenzo L, Pecina P. Adult outpatients with depression: worse quality of life than in other chronic medical diseases in Argentina. Soc Sci Med. 2001;52(6):911-9 (https://doi.org/10.1016/s0277-9536(00)00192-1).
63. Vilhauer JS, Cortes J, Moali N, Chung S, Mirocha J, Ishak WW. Improving Quality of Life for Patients with Major Depressive Disorder by Increasing Hope and Positive Expectations with Future Directed Therapy (FDT). Innov Clin Neurosci. 2013;10(3):12-22 (https://pmc.ncbi.nlm.nih.gov/articles/PMC3638844/).
64. Zhou Y, Cao Z, Yang M, Xi X, Guo Y, Fang M et al. Comorbid generalized anxiety disorder and its association with quality of life in patients with major depressive disorder. Scientific Reports. 2017;7(1):40511 (https://doi.org/10.1038/srep40511).

65. Wersebe H, Lieb R, Meyer AH, Miche M, Mikoteit T, Imboden C et al. Well-being in major depression and social phobia with and without comorbidity. International Journal of Clinical and Health Psychology. 2018;18(3):201-8 (https://doi.org/10.1016/j.ijchp.2018.06.004).
66. Ishak WW, Mirocha J, James D, Tobia G, Vilhauer J, Fakhry H et al. Quality of life in major depressive disorder before/after multiple steps of treatment and one-year follow-up. Acta Psychiatr Scand. 2015;131(1):51-60 (https://doi.org/10.1111/acps.12301). Licence: NIHMS599002.
67. McCrone P, Rost F, Koeser L, Koutoufa I, Stephanou S, Knapp M et al. The economic cost of treatment-resistant depression in patients referred to a specialist service. Journal of Mental Health. 2018;27(6):567-73 (https://doi.org/10.1080/09638237.2017.1417562).
68. Mago R, Fagiolini A, Weiller E, Weiss C. Understanding the emotions of patients with inadequate response to antidepressant treatments: results of an international online survey in patients with major depressive disorder. BMC Psychiatry. 2018;18(1):33 (https://doi.org/10.1186/s12888-018-1625-y).
69. Saylan M, Treur MJ, Postema R, Dilbaz N, Savas H, Heeg BM et al. Cost-Effectiveness Analysis of Aripiprazole Augmentation Treatment of Patients with Major Depressive Disorder Compared to Olanzapine and Quetiapine Augmentation in Turkey: A Microsimulation Approach. Value in Health Regional Issues. 2013;2(2):171-80 (https://doi.org/10.1016/j.vhri.2013.06.004).
70. Holubova M, Prasko J, Ociskova M, Marackova M, Grambal A, Slepecky M. Self-stigma and quality of life in patients with depressive disorder: a cross-sectional study. Neuropsychiatr Dis Treat. 2016;12:2677-87 (https://doi.org/10.2147/ndt.S118593).
71. Corrigan PW, Kuwabara S, Tsang H, Shi K, Larson J, Lam CS et al. Disability and work-related attitudes in employers from Beijing, Chicago, and Hong Kong. Int J Rehabil Res. 2008;31(4):347-50 (https://doi.org/10.1097/MRR.0b013e3282fb7d61).
72. Vaishnav M, Javed A, Gupta S, Kumar V, Vaishnav P, Kumar A et al. Stigma towards mental illness in Asian nations and low-and-middle-income countries, and comparison with high-income countries: A literature review and practice implications. Indian Journal of Psychiatry. 2023;65(10) (https://journals.lww.com/indianjpsychiatry/fulltext/2023/65100/stigma_towards_mental_illness_in_asian_nations_and.2.aspx).
73. Zendjidjian X, Richieri R, Adida M, Limousin S, Gaubert N, Parola N et al. Quality of life among caregivers of individuals with affective disorders. J Affect Disord. 2012;136(3):660-5 (https://doi.org/10.1016/j.jad.2011.10.011).
74. Rane LJ, Fekadu A, Papadopoulos AS, Wooderson SC, Poon L, Markopoulou K et al. Psychological and physiological effects of caring for patients with treatment-resistant depression. Psychological Medicine. 2012;42(9):1825-33 (https://doi.org/10.1017/S0033291711003035).
75. Connolly KR, Thase ME. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. Drugs. 2011;71(1):43-64 (https://doi.org/10.2165/11587620-000000000-00000).
76. 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).
77. 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).
78. Nelson JC, Thase ME, Bellocchio EE, Rollin LM, Eudicone JM, McQuade RD et al. Efficacy of adjunctive aripiprazole in patients with major depressive disorder who showed minimal response to initial antidepressant therapy. Int Clin Psychopharmacol. 2012;27(3):125-33 (https://doi.org/10.1097/YIC.0b013e3283502791).
79. Han C, Wang SM, Kato M, Lee SJ, Patkar AA, Masand PS et al. Second-generation antipsychotics in the treatment of major depressive disorder: current evidence. Expert Rev Neurother. 2013;13(7):851-70 (https://doi.org/10.1586/14737175.2013.811901).

80. 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).

81. Hamon M, Blier P. Monoamine neurocircuitry in depression and strategies for new treatments. Prog Neuropsychopharmacol Biol Psychiatry. 2013;45:54-63 (https://doi.org/10.1016/j.pnpbp.2013.04.009).

82. Al Shirawi MI, Edgar NE, Kennedy SH. Brexpiprazole in the Treatment of Major Depressive Disorder. Clinical Medicine Insights: Therapeutics. 2017;9:1179559X17731801 (https://doi.org/10.1177/1179559x17731801).

83. Maeda K, Lerdrup L, Sugino H, Akazawa H, Amada N, McQuade RD et al. Brexpiprazole II: antipsychotic-like and procognitive effects of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014;350(3):605-14 (https://doi.org/10.1124/jpet.114.213819).

84. 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).

85. Fava M, Okame T, Matsushima Y, Perry P, Weiller E, Baker RA. Switching from Inadequate Adjunctive or Combination Treatment Options to Brexpiprazole Adjunctive to Antidepressant: An Open-Label Study on the Effects on Depressive Symptoms and Cognitive and Physical Functioning. Int J Neuropsychopharmacol. 2017;20(1):22-30 (https://doi.org/10.1093/ijnp/pyw087).

86. McIntyre RS, Bubolic S, Zhang Z, MacKenzie EM, Therrien F, Miguelez M et al. Effects of Adjunctive Brexpiprazole on Individual Depressive Symptoms and Functioning in Patients With Major Depressive Disorder and Anxious Distress: Post Hoc Analysis of Three Placebo-Controlled Studies. J Clin Psychopharmacol. 2024;44(2):133-40 (https://doi.org/10.1097/jcp.0000000000001825).

87. Davis LL, Ota A, Perry P, Tsuneyoshi K, Weiller E, Baker RA. Adjunctive brexpiprazole in patients with major depressive disorder and anxiety symptoms: an exploratory study. Brain Behav. 2016;6(10):e00520 (https://doi.org/10.1002/brb3.520).

88. Krystal AD, Mittoux A, Meisels P, Baker RA. Effects of Adjunctive Brexpiprazole on Sleep Disturbances in Patients With Major Depressive Disorder: An Open-Label, Flexible-Dose, Exploratory Study. Prim Care Companion CNS Disord. 2016;18(5) (https://doi.org/10.4088/PCC.15m01914).

89. Fava M, Ménard F, Davidsen CK, Baker RA. Adjunctive Brexpiprazole in Patients With Major Depressive Disorder and Irritability: An Exploratory Study. J Clin Psychiatry. 2016;77(12):1695-701 (https://doi.org/10.4088/JCP.15m10470).

90. Weisler RH, Ota A, Tsuneyoshi K, Perry P, Weiller E, Baker RA et al. Brexpiprazole as an adjunctive treatment in young adults with major depressive disorder who are in a school or work environment. J Affect Disord. 2016;204:40-7 (https://doi.org/10.1016/j.jad.2016.06.001).

91. Stahl SM. Mechanism of action of brexpiprazole: comparison with aripiprazole. CNS Spectrums. 2016;21(1):1-6 (https://doi.org/10.1017/S1092852915000954).

92. Nelson JC, Zhang P, Skuban A, Hobart M, Weiss C, Weiller E et al. Overview of short-term and long-term safety of brexpiprazole in patients with major depressive disorder and inadequate response to antidepressant treatment. Current Psychiatry Reviews. 2016;12(3):278-90 (https://doi.org/10.2174/1573400512666160816095900).

93. FDA. Highlights of Prescirbing Information: REXULTI® (brexpiprazole) tablets, for oral use [website]. 2024 (www.otsuka-us.com/sites/g/files/qhldwo8931/files/media/static/Rexulti-PI.pdf).

94. Seetasith A, Greene M, Hartry A, Burudpakdee C. Changes in healthcare resource use and costs associated with early versus delayed initiation of atypical antipsychotic adjunctive treatment in major depressive disorder. J Med Econ. 2018;21(9):888-901 (https://doi.org/10.1080/13696998.2018.1484373).

95. Yermilov I, Greene M, Chang E, Hartry A, Yan T, Broder MS. Earlier Versus Later Augmentation with an Antipsychotic Medication in Patients with Major Depressive Disorder Demonstrating Inadequate Efficacy in Response to Antidepressants: A Retrospective Analysis of US Claims Data. Adv Ther. 2018;35(12):2138-51 (https://doi.org/10.1007/s12325-018-0838-2).
96. Shivanshu A, Dusica H, Sandipan B, Shivani K. Early adjunctive brexpiprazole initiation for major depressive disorder: Impact on healthcare resource utilization and cost — a US real-world analysis. In: AMCP 2024 Annual Meeting. New Orleans, Louisiana, USA: Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA.; 2024.
97. Nelson JC, Papakostas GI. Atypical Antipsychotic Augmentation in Major Depressive Disorder: A Meta-Analysis of Placebo-Controlled Randomized Trials. American Journal of Psychiatry. 2009;166(9):980-91 (https://doi.org/10.1176/appi.ajp.2009.09030312).
98. Chokhawala K SL. Antipsychotic Medications [website]. StatPearls [Internet]. Treasure Island (FL); 2024 (https://www.ncbi.nlm.nih.gov/books/NBK519503/).
99. Thase ME, Zhang P, Weiss C, Meehan SR, Hobart M. Efficacy and safety of brexpiprazole as adjunctive treatment in major depressive disorder: overview of four short-term studies. Expert Opinion on Pharmacotherapy. 2019;20(15):1907-16 (https://doi.org/10.1080/14656566.2019.1638913).
100. Paulzen M, Schoretsanitis G, Hiemke C, Gründer G, Haen E, Augustin M. Reduced clearance of venlafaxine in a combined treatment with quetiapine. Prog Neuropsychopharmacol Biol Psychiatry. 2018;85:116-21 (https://doi.org/10.1016/j.pnpbp.2018.04.014).
101. Broder MS, Greene M, Yan T, Chang E, Hartry A, Yermilov I. Medication Adherence, Health Care Utilization, and Costs in Patients With Major Depressive Disorder Initiating Adjunctive Atypical Antipsychotic Treatment. Clinical Therapeutics. 2019;41(2):221-32 (https://doi.org/10.1016/j.clinthera.2018.12.005).
102. Weiss C, Meehan SR, Brown TM, Gupta C, Mørup MF, Thase ME et al. Effects of adjunctive brexpiprazole on calmness and life engagement in major depressive disorder: post hoc analysis of patient-reported outcomes from clinical trial exit interviews. J Patient Rep Outcomes. 2021;5(1):128 (https://doi.org/10.1186/s41687-021-00380-4).
103. Wee SN, Liman C, Waters HC, Houle CR, Renteria M, Mukherjee SS et al. Life Engagement Improvement Following Initiation of Brexpiprazole Treatment in Patients with MDD: A Naturalistic, Retrospective Real-World Study. Clinicoecon Outcomes Res. 2023;15:195-208 (https://doi.org/10.2147/ceor.S395255).
104. Gautam S, Jain A, Gautam M, Vahia VN, Grover S. Clinical Practice Guidelines for the management of Depression. Indian J Psychiatry. 2017;59(Suppl 1):S34-s50 (https://doi.org/10.4103/0019-5545.196973).
105. McNaughton EC, Curran C, Granskie J, Opler M, Sarkey S, Mucha L et al. Patient attitudes toward and goals for MDD treatment: a survey study. Patient Prefer Adherence. 2019;13:959-67 (https://doi.org/10.2147/ppa.S204198).
106. Hripcsak G, Ryan PB, Duke JD, Shah NH, Park RW, Huser V et al. Characterizing treatment pathways at scale using the OHDSI network. Proc Natl Acad Sci U S A. 2016;113(27):7329-36 (https://doi.org/10.1073/pnas.1510502113).
107. Kern DM, Cepeda MS, Defalco F, Etropolski M. Treatment patterns and sequences of pharmacotherapy for patients diagnosed with depression in the United States: 2014 through 2019. BMC Psychiatry. 2020;20(1):4 (https://doi.org/10.1186/s12888-019-2418-7).
108. Wu T, Dong S, Yang L, Qiu H, Qiu H, Mellor D et al. Investigation of the pharmacological treatment patterns of Chinese patients with major depressive disorder under real-world settings using multi-channel sequence analysis. Frontiers in Psychiatry. 2023;14 (https://doi.org/10.3389/fpsyt.2023.1089504).
109. Benz MB, Epstein-Lubow G, Weinstock LM, Gaudiano BA. Polypharmacy Among Patients With Major Depressive Disorder and Co-occurring Substance Use Disorders in a Psychiatric Hospital Setting: Prevalence and Risk Factors. J Clin Psychopharmacol. 2023;43(3):273-7 (https://doi.org/10.1097/jcp.0000000000001681). Licence: NIHMS1874772.

110. Wiersema C, Oude Voshaar RC, van den Brink RHS, Wouters H, Verhaak P, Comijs HC et al. Determinants and consequences of polypharmacy in patients with a depressive disorder in later life. Acta Psychiatrica Scandinavica. 2022;146(1):85-97 (https://doi.org/https://doi.org/10.1111/acps.13435).

111. de Lima JD, Teixeira IA, Silva FdO, Deslandes AC. The comorbidity conditions and polypharmacy in elderly patients with mental illness in a middle income country: a cross-sectional study⋆. IBRO Reports. 2020;9:96-101 (https://doi.org/https://doi.org/10.1016/j.ibror.2020.07.008).

112. Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC. Methods for Evaluating Patient Adherence to Antidepressant Therapy: A Real-World Comparison of Adherence and Economic Outcomes. Medical Care. 2006;44(4) (https://journals.lww.com/lww-medicalcare/fulltext/2006/04000/methods_for_evaluating_patient_adherence_to.2.aspx).

113. Garrido MM, Boockvar KS. Perceived symptom targets of antidepressants, anxiolytics, and sedatives: the search for modifiable factors that improve adherence. J Behav Health Serv Res. 2014;41(4):529-38 (https://doi.org/10.1007/s11414-013-9342-2). Licence: NIHMS523675.

114. Lee MS, Lee HY, Kang SG, Yang J, Ahn H, Rhee M et al. Variables influencing antidepressant medication adherence for treating outpatients with depressive disorders. J Affect Disord. 2010;123(1-3):216-21 (https://doi.org/10.1016/j.jad.2009.10.002).

115. Sawada N, Uchida H, Suzuki T, Watanabe K, Kikuchi T, Handa T et al. Persistence and compliance to antidepressant treatment in patients with depression: A chart review. BMC Psychiatry. 2009;9(1):38 (https://doi.org/10.1186/1471-244X-9-38).

116. Baryakova TH, Pogostin BH, Langer R, McHugh KJ. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. Nat Rev Drug Discov. 2023;22(5):387-409 (https://doi.org/10.1038/s41573-023-00670-0).

117. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. The New England journal of medicine. 2005;353:487-97 (https://doi.org/10.1056/NEJMra050100).

118. Ho SC, Chong HY, Chaiyakunapruk N, Tangiisuran B, Jacob SA. Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. J Affect Disord. 2016;193:1-10 (https://doi.org/10.1016/j.jad.2015.12.029).

119. Akerblad AC, Bengtsson F, von Knorring L, Ekselius L. Response, remission and relapse in relation to adherence in primary care treatment of depression: a 2-year outcome study. Int Clin Psychopharmacol. 2006;21(2):117-24 (https://doi.org/10.1097/01.yic.0000199452.16682.b8).

120. Abegaz TM, Sori LM, Toleha HN. Self-Reported Adverse Drug Reactions, Medication Adherence, and Clinical Outcomes among Major Depressive Disorder Patients in Ethiopia: A Prospective Hospital Based Study. Psychiatry J. 2017;2017:5812817 (https://doi.org/10.1155/2017/5812817).

121. Ho SC, Jacob SA, Tangiisuran B. Barriers and facilitators of adherence to antidepressants among outpatients with major depressive disorder: A qualitative study. PLoS One. 2017;12(6):e0179290 (https://doi.org/10.1371/journal.pone.0179290).

122. Shrestha Manandhar J, Shrestha R, Basnet N, Silwal P, Shrestha H, Risal A et al. Study of Adherence Pattern of Antidepressants in Patients with Depression. Kathmandu Univ Med J (KUMJ). 2017;15(57):3-9.

123. Al Jumah K, Hassali MA, Al Qhatani D, El Tahir K. Factors associated with adherence to medication among depressed patients from Saudi Arabia: a cross-sectional study. Neuropsychiatr Dis Treat. 2014;10:2031-7 (https://doi.org/10.2147/ndt.S71697).

124. Taj F, Tanwir M, Aly Z, Khowajah AA, Tariq A, Syed FK et al. Factors associated with non-adherence among psychiatric patients at a tertiary care hospital, Karachi, Pakistan: a questionnaire based cross-sectional study. J Pak Med Assoc. 2008;58(8):432-6.

125. dosReis S, Espinal Pena D, Fincannon A, Gorman EF, Amill-Rosario A. Discrete Choice Experiments to Elicit Patient Preferences for the Treatment of Major Depressive Disorder: A Systematic Review. The Patient - Patient-Centered Outcomes Research. 2024 (https://doi.org/10.1007/s40271-024-00706-6).

126. Palaniyappan L, Insole L, Ferrier N. Combining antidepressants: a review of evidence. Advances in Psychiatric Treatment. 2009;15(2):90-9 (https://doi.org/10.1192/apt.bp.107.004820).

127. Gelenberg A. The American Psychiatric Association Treatment Guideline for Major Depressive. Ann Gen Psychiatry. 2010;9(Suppl 1):S1-S46 (https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf).
128. 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: Réseau canadien pour les traitements de l'humeur et de l'anxiété (CANMAT) 2023 : Mise à jour des lignes directrices cliniques pour la prise en charge du trouble dépressif majeur chez les adultes. The Canadian Journal of Psychiatry.0(0):07067437241245384 (https://doi.org/10.1177/07067437241245384).
129. NICE. Depression in adults: treatment and management (NG222) [website]. 2022 (https://www.nice.org.uk/guidance/ng222/resources/depression-in-adults-treatment-and-management-pdf-66143832307909).
130. FDA. Highlights of Prescirbing Information: ABILIFY® (aripiprazole) Tablets, for oral use [website]. 2022 (https://otsuka-us.com/sites/g/files/qhldwo9046/files/media/static/Abilify-PI.pdf).
131. FDA. Highlights of Prescribing information: SEROQUEL XR® (quetiapine) extended-release tablets [website]. 2022 (http://www.azpicentral.com/pi.html?product=seroquelxr).
132. FDA. Highlights of Prescribing Information: VRAYLAR® (cariprazine) capsules [website]. 2024 (https://www.rxabbvie.com/pdf/vraylar_pi.pdf).
133. FDA. Highlights of Prescribing Information: ZYPREXA (olanzapine) Table [website]. 2021 (https://pi.lilly.com/us/zyprexa-pi.pdf).
134. Bouchette D FK, Patel P, et al. Ziprasidone. StatPearls [Internet] Treasure Island (FL): StatPearls Publishing; 2024. 2024 (https://www.ncbi.nlm.nih.gov/books/NBK448157/).
135. McNeil SE GJ, Cogburn M. Risperidone. StatPearls [Internet] Treasure Island (FL): StatPearls Publishing; 2024. 2023 (https://www.ncbi.nlm.nih.gov/books/NBK459313/).
136. Barowsky J, Schwartz TL. An Evidence-Based Approach to Augmentation and Combination Strategies for: Treatment-Resistant Depression. Psychiatry (Edgmont). 2006;3(7):42-61 (
137. Ruberto VL, Jha MK, Murrough JW. Pharmacological Treatments for Patients with Treatment-Resistant Depression. Pharmaceuticals. 2020;13(6):116 (https://www.mdpi.com/1424-8247/13/6/116).
138. Undurraga J, Sim K, Tondo L, Gorodischer A, Azua E, Tay KH et al. Lithium treatment for unipolar major depressive disorder: Systematic review. Journal of Psychopharmacology. 2019;33(2):167-76 (https://doi.org/10.1177/0269881118822161).
139. Chokhawala K LS, Saadabadi A. . Lithium [website]. Treasure Island (FL): StatPearls Publishing; 2024 (https://www.ncbi.nlm.nih.gov/books/NBK519062/).
140. Grinchii D, Dremencov E. Mechanism of Action of Atypical Antipsychotic Drugs in Mood Disorders. Int J Mol Sci. 2020;21(24) (https://doi.org/10.3390/ijms21249532).
141. Llorca P-M, Lançon C, Hartry A, Brown TM, DiBenedetti DB, Kamat SA et al. Assessing the burden of treatment-emergent adverse events associated with atypical antipsychotic medications. BMC Psychiatry. 2017;17(1):67 (https://doi.org/10.1186/s12888-017-1213-6).
142. EMA. REXULTI: Summary of Product Characteristics [website]. 2023 (https://www.ema.europa.eu/en/documents/product-information/rxulti-epar-product-information_en.pdf).
143. 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) (https://doi.org/10.4088/JCP.17m12058).
144. 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. Current Medical Research and Opinion. 2018;34(4):633-42 (https://doi.org/10.1080/03007995.2018.1430220).

145. 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).

146. FDA. Highlights of Prescirbing Information: REXULTI® (brexpiprazole) tablets, for oral use [website]. 2024 (www.otsuka-us.com/sites/g/files/qhldwo8931/files/media/static/Rexulti-PI.pdf).

147. 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).

148. 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).

149. 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. The Journal of Clinical Pharmacology. 2022;62(6):721-32 (https://doi.org/https://doi.org/10.1002/jcph.2022).

150. 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).

151. Mok YM, Tan PLL, Bose R, Herr KJ, Ung KEK. A Real-life Study of Brexpiprazole as an Adjunctive Treatment for Major Depressive Disorder in Asian Patients in Singapore (BADA). Clin Psychopharmacol Neurosci. 2024;22(3):531-6 (https://doi.org/10.9758/cpn.23.1143).

152. WHO. WHO Model List of Essential Medicines - 23rd list, 2023 [website]. 2023 (https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02).

153. WHO. Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders [website]. 2023 (https://www.who.int/publications/i/item/9789240084278).

154. 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 guidelines. J Psychopharmacol. 2015;29(5):459-525 (https://doi.org/10.1177/0269881115581093).

155. 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. The World Journal of Biological Psychiatry. 2013;14(5):334-85 (https://doi.org/10.3109/15622975.2013.804195).

156. ACP. Nonpharmacologic and Pharmacologic Treatments of Adults in the Acute Phase of Major Depressive Disorder: A Living Clinical Guideline From the American College of Physicians. Annals of Internal Medicine. 2023;176(2):239-52 (https://doi.org/10.7326/m22-2056 %m 36689752).

157. 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. Australian & New Zealand Journal of Psychiatry. 2021;55(1):7-117 (https://doi.org/10.1177/0004867420979353).

158. MaHTAS. Management of major depressive diorder: Clinical practive guidelines [website]. 2019 (https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Psychiatry%20&%20Mental%20health/CPG_Management_of_MDD_(Second_Edition)_04092020.pdf).

159. 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 in Health. 2018;21:S186 (https://doi.org/10.1016/j.jval.2018.04.1265).

160. 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).

161. Seetasith A, Greene M, Hartry A, Burudpakdee C. Real-World Economic Outcomes of Brexpiprazole and Extended-Release Quetiapine Adjunctive Use in Major Depressive Disorder. ClinicoEconomics and Outcomes Research. 2019;11(null):741-55 (https://doi.org/10.2147/CEOR.S220007).

162. Soto Molina H, Escobar Juárez Y, Frias Gasga A, Romero Tapia C, Diaz Alvarez O, Campos Ramírez O et al. EE443 Economic Evaluation of Brexpiprazole As Adjunctive Treatment of Major Depressive Disorder in the Mexican National Health System. Value in Health. 2022;25(7):S421 (https://doi.org/10.1016/j.jval.2022.04.691).

163. Leelahanaj T. The cost-effectiveness of aripiprazole as adjunctive therapy in major depressive disorder: Thai economic model. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2010;93 Suppl 6:S43-50 (http://europepmc.org/abstract/MED/21284136).

164. Otsuka. What We Do: Research [website]. 2024 (https://www.otsuka-us.com/research).

165. WHO. Global tuberculosis report 2023 [website]. 2023 (https://www.who.int/publications/i/item/9789240083851).

166. Bauer M, Hefting N, Lindsten A, Josiassen MK, Hobart M. A randomised, placebo-controlled 24-week study evaluating adjunctive brexpiprazole in patients with major depressive disorder. Acta Neuropsychiatrica. 2019;31(1):27-35 (https://doi.org/10.1017/neu.2018.23).

167. 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).

168. 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).

169. 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. Psychological Medicine. 2022;52(12):2224-31 (https://doi.org/10.1017/S0033291722001246).

170. 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).

171. 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).

172. 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).

173. 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).

A. Appendix

A.1 Consultation with WHO Technical Department

Advice was sought on the positioning of brexpiprazole within the EML. Description of the written email correspondence/advice from the WHO technical department of their support of the submission has been presented below.

Notification to submit an application was shared with the WHO EML Secretariat (emlsecretariat@who.int) on May 28, 2024.

Response received on May 29, 2024, acknowledged the application and noted that:

- *"Bexpiprazole, (nor any other medicines for treatment of agitation associated with dementia, MDD and/or schizophrenia), has not been previously evaluated by WHO for EML inclusion. Any submission(s) for bexpiprazole should follow the instructions for applicants for the addition of a new medicine."*

The WHO Department of Mental Health and Substance Use (mhgap-info@who.int) was contacted on July 19, 2024, for advice regarding the positioning of brexpiprazole in MDD.

Response received on August 8, 2024, noted that:

- *"I confirm that any submission(s) for brexpiprazole should follow the instructions for applicants for the addition of a new medicine "Please consider being as clear as possible about the target population and therefore the proposed indication. If you are going to apply for brexpiprazole as an adjunct to antidepressants for the treatment of major depressive disorder (MDD) in adults, we assume that the target population will be patients with MDD who do not improve after standard treatment, i.e. treatment-resistant depression (TRD)".*

However, the company believes that while some patients might respond well to ADT monotherapy, the majority of individuals with MDD demonstrate inadequate response to first-line treatments.

- Inadequate response is typically defined as a failure to achieve response to an ADT at an adequate dose and duration (i.e., at least 6 to 8 weeks) *(35)*.
- There is a lack of consensus around the definition of TRD *(36, 37)*. However, failure to respond or achieve remission after 2 or more trials of medication treatment for MDD can be considered TRD *(12, 38)*. The prevalence of TRD in MDD rages from 12% to 55% *(38-41)*.
- The term TRD has limitations, as it arbitrarily defines treatment responsiveness, overlooks psychological treatments, and often fails to consider factors like partial response, treatment intolerance, and illness characteristics. The 2009 NICE depression guideline shifted away from using TRD, focusing instead on sequenced treatment options for inadequate response *(42)*. Hence TRD can be considered as a subset of patients with MDD who have an inadequate response to ADTs.
- Additionally, the key trials (including the pivotal trials) had an inclusion criteria of adults with MDD who had an inadequate response to the trial of 1 to 3 ADTs (Appendix A.4).

Based on the above, the company provided the above context relating to the target population to the WHO Department of Mental Health and Substance Use (mhgap-info@who.int) on August 27, 2024.

A.2 Expert Statements/Letters of Support

Psychiatry Research

75-59 263rd Street Glen Oaks, NY 11004 Tel: (718) 470-4812 Fax: (718) 343-1659 Email: ccorrell@northwell.edu

Christoph U. Correll, M.D.

Professor of Psychiatry and Molecular Medicine,
Donald and Barbara Zucker School of Medicine at Hofstra Northwell, New York
Medical Director, Recognition and Prevention (RAP) Program
The Zucker Hillside Hospital, Northwell Health
Investigator
Center for Psychiatric Neuroscience
The Feinstein Institute for Medical Research Northwell Health

October 24, 2024

Re: Application for the Addition Brexpiprazole Oral Tablet for the Treatment of Adults with Major Depressive Disorder to the WHO Model List of Essential Medications

To Whom It May Concern:

I am writing this expert report accompanying the application for the addition of brexpiprazole (Rexulti) oral tablet as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults to the WHO Essential Medicines List (EML).

I am both a general as well as child and adolescent psychiatrist at The Zucker Hillside Hospital, Northwell Health, and a Professor of Psychiatry and Molecular Medicine at the Zucker School of Medicine at Hofstra / Northwell, Hempstead, New York. My clinical work and research focus on the identification, characterization, and psychopharmacological management of adults and youth with severe psychiatric disorders, including an emphasis on indicated prevention of severe mood and psychotic disorders, psychopharmacology, risk-benefit evaluation of psychotropic medications, clinical trials, epidemiology, meta-analyses and physical health in mental health. I am a clinical scientist managing patients. I have published over 900 articles in peer-reviewed journals. including specifically on antipsychotics both in oral and in long-acting-injectable

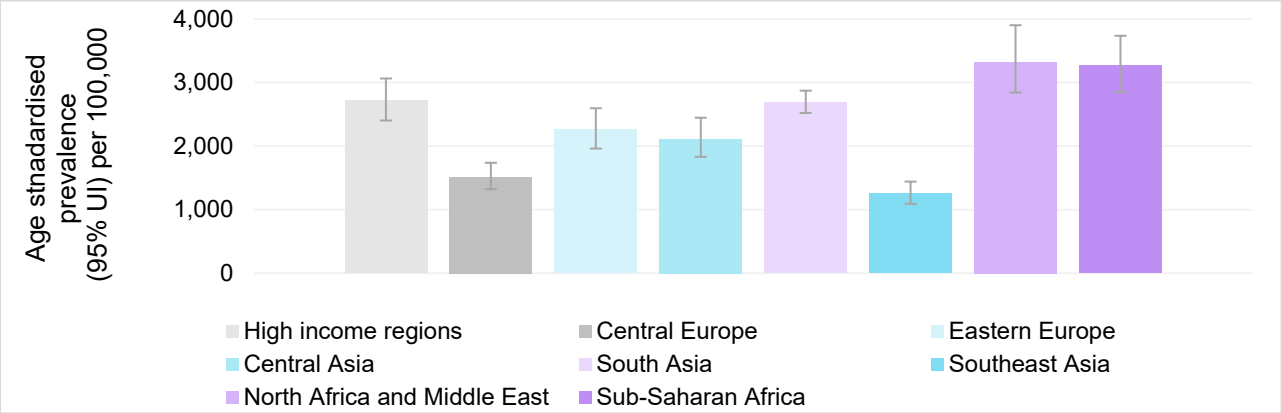
formulations. I am the Principal Investigator and Steering Committee member of several large, federally funded grants and have received over 40 national and international research awards and fellowships for my work. Since 2014, the inception of this metric, I have been listed annually by Thomson Reuters/Web of Science as one of the most influential scientific minds" and "top 1% cited scientists in the area of psychiatry". In particular, since 2017 I have been ranked as the single most highly cited researcher by Expertscape based on publications during the last 10 years, including in October 2024 in the following two of ten pertinent areas to this letter:

1. Central Nervous System Depressants, out of 259,989 ranked scientists (http://expertscape.com/ex/central+nervous+system+depressants)
2. Psychotropic Drugs, out of 138,731 scientists (http://expertscape.com/ex/psychotropic+drugs)

MDD is a global health issue, with the latest data reporting a global incidence rate of >2.7 billion cases, with females experiencing higher rates of depression.[1] This staggering statistic currently places MDD as the third leading cause of global disease burden, with projections placing it as the leading cause of global disease burden by 2030.[2,3]

MDD prevalence is also notably higher in low- and middle-income countries (LMICs) (Figure 1). Indeed, the LMIC regions of North Africa, Sub-Saharan Africa and the Middle East show the highest prevalence of MDD (Figure 1). This is a stark reminder of the high unmet need for patients with MDD in LMICs. There are a multitude of factors that lead to such high rates, ranging from availability of healthcare professionals, cost of medical treatment and access to medicines. I believe the availability of brexpiprazole would be a significant positive step forward towards offering patients in general but also patients in LMICs an effective treatment option, helping to address the healthcare gap in LMICs.

Figure 1. Age standardized prevalence per 100,000. [4]



In addition to addressing critical healthcare gaps, having the latest treatments available for MDD, such as brexpiprazole, will be critical to reducing downstream effects of MDD, such as suicide and all-cause mortality.[5,6] Indeed, individuals with MDD have a 20-fold increased risk of suicide relative to the general population.[5] Therefore, it is critically important not only to consider the improvement of health when treating individuals with MDD but also reduce associated fatal

consequences of the disease. By including brexpiprazole on the WHO EML, I believe we can help reduce preventable deaths globally that are still too often due to MDD.

In patients with MDD, up to 50% will fail first line antidepressant treatment (ADT).[7] As such, current scientific consensus dictates that those who fail to respond to first line ADTs will either undergo a dosage increase with the current ADT, switch to a different ADT or add another ADT (i.e. adjunctive treatment).[8] The use of adjunctive treatment is a popular and favorable option. The use of adjunctive treatment with atypical antipsychotic agents has been recognized by national and international guidelines (including the American Psychiatric Association, Canadian Psychiatric Association, the Canadian Network for Mood and Anxiety Treatments [CANMAT] and the International Consensus Group on Depression) and are recommended to help achieve symptom improvement in patients who have an inadequate response to their previous and/or current ADT.[9–11] Given the high rate of primary ADT failure, a recent systematic literature review and meta-analysis supported brexpiprazole as a useful adjuvant ADT for MDD patients who have experienced at least one failure of ADT.[12]

Further, in patients with inadequate response to ADTs, lower response rates are observed with subsequent ADTs.[7,13–15] The STAR*D trial reported response rates of less than 20% when switching to a third ADT after two consecutive unsuccessful ADTs.[13] Hence, early use of adjunctive treatment with antipsychotics such as brexpiprazole may be considered after previous failure of monotherapy ADT(s) to avoid chronicity of disease and reduce healthcare resource utilization costs associated with low treatment response rates. Indeed, it has been shown that introducing adjunctive therapy earlier in the treatment of MDD increases remission rates and reduces healthcare utilization costs,[16] translating to not only a patient benefit, but also into a societal benefit for health systems and societies.

I am aware that the WHO Department of Mental health and Substance Use has considered the target population for brexpiprazole as patients with treatment-resistant depression (TRD). This is certainly an important and underserved MDD patient subpopulation that will benefit from access to the latest generation of treatments such as brexpiprazole. However, I would strongly caution against reserving use of adjunctive brexpiprazole for this population alone. Given the demonstrated clinical evidence and personal experience in prescribing brexpiprazole, I believe it is best placed as an adjunctive treatment for MDD in the context of insufficient response to the past and/or current ADT. This is also how the target population was defined in the pivotal randomized controlled trials leading to regulatory approval. Moreover, TRD is poorly defined and thus there is a lack of consensus on the definition of TRD.[17,18] TRD is referred to as “the failure to obtain an acceptable outcome”.[19] Yet what is considered an “acceptable” outcome is not a universally agreed-upon definition.[19] This inconsistency of definition results in heterogeneity between published studies, posing methodological challenges for between-study comparisons,[20] thus limiting the power of comparative evidence based on this definition. Therefore, I believe that inclusion of brexpiprazole on the WHO EML should focus its target patient population on adult patients who had an inadequate response to prior ADT (1-3 courses) in the current episode and who had also demonstrated an inadequate response throughout the

8 weeks of prospective ADT treatments. This definition of the target population aligns closely with the pivotal clinical studies for brexpiprazole.[21,22] Within this definition, the proposed target population by extension also includes patients who have TRD, thereby ensuring that patients across the MDD disease spectrum can benefit from adjunctive brexpiprazole.

Overall, including brexpiprazole to the WHO EML as an adjunctive treatment to ADTs for adult patients with MDD and insufficient response to ADTs in the current episode can address several healthcare gaps globally. First, it can help prevent low treatment response rates following failure with initial ADTs, while also increasing symptomatic remission and paving the way for functional restoration and quality of life, reducing associated humanistic burden and healthcare costs. Secondly, it can help target unmet needs in LMICs, by offering a treatment option which can help address the high burden of MDD in LMICs, which have some of the highest rates in the world. Importantly, brexpiprazole demonstrates efficacy and early treatment effect and has a very favorable tolerability and safety profile, with a low risk of activating or sedating side effects, cardiometabolic burden, and sexual side effects.

In summary, I highly recommend the inclusion of brexpiprazole oral tablet in the WHO EML. Should there be any questions with regard to this report, I would be happy to be contacted and respond to them.

Sincerely,

Christoph U Correll, MD

References

1. Liu, J., Liu, Y., Ma, W., Tong, Y. & Zheng, J. Temporal and spatial trend analysis of all-cause depression burden based on Global Burden of Disease (GBD) 2019 study. *Scientific Reports 2024 14:1* 14, 1–17 (2024).
2. Yu, Q. *et al.* AB013. Major depressive disorder and its risk factors in low- and middle-income countries. *J Public Health Emerg* 8, AB013–AB013 (2024).
3. Cui, L. *et al.* Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal Transduction and Targeted Therapy 2024 9:1* 9, 1–32 (2024).
4. Ferrari, A. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* 9, 137–150 (2022).
5. Kern, D. M. *et al.* Suicide-specific mortality among patients with treatment-resistant major depressive disorder, major depressive disorder with prior suicidal ideation or suicide attempts, or major depressive disorder alone. *Brain Behav* 13, e3171 (2023).

6. Lundberg, J. *et al.* Determinants and Outcomes of Suicidal Behavior Among Patients With Major Depressive Disorder. *JAMA Psychiatry* 80, 1218–1225 (2023).
7. Papakostas, G. I. Managing Partial Response or Nonresponse: Switching, Augmentation, and Combination Strategies for Major Depressive Disorder. *J Clin Psychiatry* 70, 11183 (2009).
8. McIntyre, R. S. & Weiller, E. Real-world determinants of adjunctive antipsychotic prescribing for patients with major depressive disorder and inadequate response to antidepressants: a case review study. *Adv Ther* 32, 429–444 (2015).
9. Lam, R. W. *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. *J Affect Disord* 117 Suppl 1, (2009).
10. Nutt, D. J. *et al.* International consensus statement on major depressive disorder. *J Clin Psychiatry* 71 Suppl E1, (2010).
11. Gelenberg, A. J. *et al.* Practice Guideline for the Treatment of Patients With Major Depressive Disorder Third Edition WORK GROUP ON MAJOR DEPRESSIVE DISORDER. (2010).
12. Kishi, T. *et al.* 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. *International Journal of Neuropsychopharmacology* 22, 698 (2019).
13. Fava, M. *et al.* A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. *Am J Psychiatry* 163, 1161–1172 (2006).
14. Han, C. *et al.* Second-generation antipsychotics in the treatment of major depressive disorder: current evidence. *Expert Rev Neurother* 13, 851–870 (2013).
15. Rush, A. J. *et al.* Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 163, 1905–1917 (2006).
16. Jain, R. *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* 29, 896–906 (2023).
17. Zanardi, R. *et al.* How different definition criteria may predict clinical outcome in treatment resistant depression: Results from a prospective real-world study. *Psychiatry Res* 334, 115818 (2024).
18. Dold, M. & Kasper, S. Evidence-based pharmacotherapy of treatment-resistant unipolar depression. *Int J Psychiatry Clin Pract* 21, 13–23 (2017).
19. Demyttenaere, K. & Van Duppen, Z. The Impact of (the Concept of) Treatment-Resistant Depression: An Opinion Review. *Int J Neuropsychopharmacol* 22, 85–92 (2019).
20. Johnston, K. M., Powell, L. C., Anderson, I. M., Szabo, S. & Cline, S. The burden of treatment-resistant depression: A systematic review of the economic and quality of life literature. *J Affect Disord* 242, 195–210 (2019).
21. Thase, M. E. *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* 76, 1232–1240 (2015).
22. Thase, M. E. *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* 76, 1224–1231 (2015).

27th October 2024

Correspondence:

Dr Muzaffer Kaser MD PhD MPhil MRCPsych

Expert Witness Cambridge Limited

Future Business Centre, Kings Hedges Road

Cambridge, United Kingdom, CB4 2HY

To Whom it May Concern,

I am Dr Muzaffer Kaser, consultant psychiatrist in general adult and liaison psychiatry currently working in a substantive NHS role, predominantly treating depression, anxiety, and stress-related conditions. I am also an affiliated assistant professor at Department of Psychiatry at University of Cambridge. My research work involved studied understanding the pathophysiology of depression and investigating treatments for unmet needs in depressive disorders.

(Kaser et al. 2017; https://doi.org/10.1016/j.bpsc.2016.11.009, Kaser et al. 2022; https://doi.org/10.1016/j.bbih.2021.100409)

The case for better treatment regimes for depression is clear. According to the World Health Organisation, depression is the leading cause of disability worldwide. Among other mental health conditions, depressive disorders accounted for 37.3% of mental disorder Disability Adjusted Life Years (DALYs) in 2019 (GBD 2019 Mental Disorders Collaborators, 2022; https://doi.org/10.1016/S2215-0366(21)00395-3). Depression affects all countries, but it should be noted that the incidence is higher in Low and Middle Income Countries (LMICs). Added impact on a relatively younger population considering the recurrent nature of depression, the overall economic and societal impact is likely to be more prominent in LMICs. Despite the significant impact, the treatment gap in depression is huge. Firstly, the access to timely treatments is a major challenge. Secondly, the response rates to first and indeed second line treatments are problematic. Between 20% and 50% of patients do not respond to both first- and second-line treatments, a condition known as treatment-resistant depression (TRD). TRD is linked to a poorer prognosis, higher mortality rates, and a greater prevalence of physical comorbidities compared to non-TRD. Additionally, TRD is associated with increased healthcare utilization, with patients experiencing more frequent inpatient stays and emergency visits (Zhdanava et al. 2021; https://doi.org/10.4088/JCP.20m13699). A systematic review also found that both direct and indirect economic costs are significantly higher for TRD than for non-TRD (Johnston et al. 2019 https://doi.org/10.1016/j.jad.2018.06.045).

The challenges that clinicians face in inadequate response to depression treatments are all too familiar to me. Many of the patients I see in the clinic have tried different antidepressants (at least 2, occasionally more) and talking therapies. However, they have not benefitted that led to significant loss of social and occupational functioning. The suffering linked to longer periods of depressive mood and persistent residual symptoms in the context of suboptimal treatments mean that the burden gets bigger. National Institute for Clinical Excellence (NICE) recommend augmentation with second generation antipsychotics alongside other options such as lithium or lamotrigine. The evidence base for add-on antipsychotics in depression is

robust. Relevant to this call, adjunctive brexpiprazole for depression showed efficacy in at least six randomised controlled trials (Kishimoto et al. 2023, https://doi:10.1017/S0033291722000745). There is evidence to suggest a similar safety profile of brexpiprazole compared to other antipsychotics with relatively better acceptability (Wang et al. 2023, https://doi:10.1097/MD.0000000000034670).

At present, no adjunctive therapies to antidepressants are included in the WHO Essential Medicines List (EML) for adult treatment of major depressive disorder (MDD). Although absent from the EML and global guidelines, adjunct treatments are recommended in several national guidelines due to the substantial impact of MDD. As mentioned above, the economic impact of unmet treatment needs in depression is huge. In this part of the letter, I would like to provide a critical appraisal of the published evidence on the health economics of adjunctive antipsychotic use. In a study investigating the direct and indirect costs of adjunctive antipsychotics in depression, a significant reduction in MDD-related hospitalisations and all-cause hospitalisations. Additionally, mean all-cause medical costs significantly decreased by $4,513 per patient (Seetasith et al. 2018, https://doi:10.1080/13696998.2018.1484373). In another study comparing the costs associated with brexpiprazole and quetiapine augmentation, brexpiprazole was associated with significantly lower medical costs, particularly hospitalization-associated costs, but higher pharmacy costs compared to patients treated with quetiapine (Seetasith et al. 2019, https://doi:10.2147/CEOR.S231824). Such approaches are important to document real-life implications for healthcare systems. However, more refined health economics approaches are critical to understand the resource use and the overall impact on quality of life.

Since most effectiveness studies with adjunctive antipsychotics cover a time horizon of 6-8 weeks, economic evaluations focussed on similar periods. However, longer periods can be modelled to help understand the overall impact on healthcare costs. In such a study from Turkey, patients treated with adjunctive aripiprazole spent shorter depressive periods compared to patients on adjunctive quetiapine or olanzapine. They also reported higher quality of life, all translating to 0.054 and 0.039 QALY gains, respectively (Saylan et al. 2013, https://doi.org/10.1016/j.vhri.2013.06.004). Another study modelled the impact of adjunctive treatments on healthcare costs in a 48 months period. Brexpiprazole augmentation was associated with higher response and remission rates compared to other treatments (Sussman et al. 2017, https://doi.org/10.1016/j.jad.2016.09.006). Although the initial costs of treatment with brexpiprazole was higher, better clinical efficacy meant that the total healthcare costs incurred were lower. Sensitivity analyses showed that incremental cost effectiveness ratios were in the upper right quadrant meaning higher costs but higher clinical efficacy. They did not report the willingness to pay threshold that may vary across the health insurance systems. For instance, a study from Thailand concluded that aripiprazole was not cost effective due to high ICERs. However, this was partly due to the willingness to pay thresholds in Thailand. In another study examining records of more than 500 thousand patients, the patients who were offered adjunctive atypical antipsychotics as first option incurred significantly lower healthcare costs compared to the patients who were offered adjunctive antipsychotics further down the line of their treatment (Jain et al. 2023, https://doi.org.10.18553/jmcp.2023.29.8.896). This study highlights the economic impact of providing effective treatments early in the course of depressive illness. The evidence mentioned above suggested an important decision-making process that is investing early to save later. More often than not, the stakeholders do have a focus on immediate gains which is not applicable to treatment resistant depression which is highly complex with long-term implications for healthcare systems. The end result usually is that people suffer for longer with added effects on poorer occupational and social function.

In summary, adjunctive brexpiprazole is an effective treatment option for depression that has been evidenced by randomised controlled trials and recognised by treatment guidelines. There is a need for further head-to-head health economics evaluation studies of brexpiprazole that consider wider impact on different healthcare systems, particularly in LMICs. Available evidence on atypical antipsychotics'

favourable impact on healthcare utilisation costs is key to consider investing early to save in long term. According to my appraisal of the literature, I can support the application of brexpiprazole to be added to WHO EML list.

Dr Muzaffer Kaser MD PhD MPhil MRCPsych

A.3 Treatment Details

The details presented are based on the US FDA label *(93)*.

- Recommended dosage in patients with hepatic impairment:
  - The maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) is 2 mg orally once daily in patients with MDD.
- Recommended dosage in patients with renal impairment:
  - The maximum recommended dosage in patients with creatinine clearance (CrCl) <60 mL/minute is 2 mg orally once daily in patients with MDD.
- In the clinical studies examining the use of brexpiprazole for the adjunctive treatment of MDD, dosage was not adjusted for strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine). Thus, CYP considerations are already factored into general dosing recommendations, and REXULTI may be administered without dosage adjustment in patients with MDD.

Use in special populations:

- **Pregnancy**: Adequate and well-controlled studies have not been conducted with brexpiprazole in pregnant women to inform drug-associated risks. However, neonates whose mothers are exposed to antipsychotic drugs, like brexpiprazole, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms.
- **Lactation:** Lactation studies have not been conducted to assess the presence of brexpiprazole in human milk, the effects of brexpiprazole on the breastfed infant, or the effects of brexpiprazole on milk production.
- **Paediatric use:** The safety and effectiveness of brexpiprazole for treatment of major depressive disorder have not been established in paediatric patients. ADTs increased the risk of suicidal thoughts and behaviours in paediatric patients.

A.4 Summary of Key Trials Demonstrating the Effectiveness and Safety

Pyxis Trial

The Pyxis (NCT01360645) trial was an 8-week, single-blind, prospective phase followed by 6-week, randomised, double-blind, placebo-controlled phase fixed dose adjunctive brexpiprazole (2 mg) trial *(76)*.

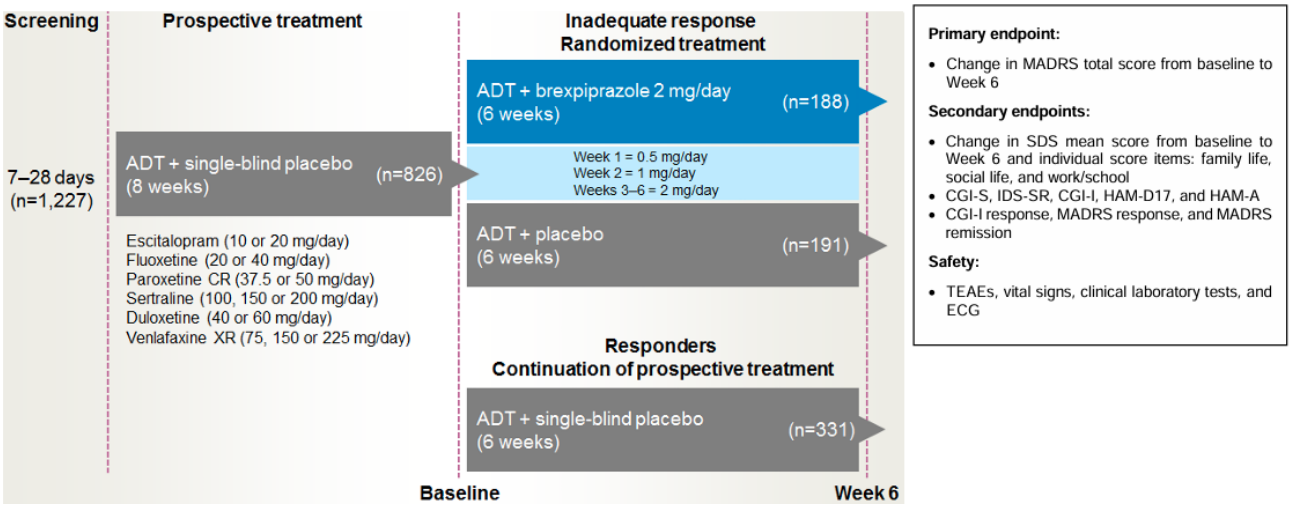
Study Population

Outpatients aged 18 to 65 years with a diagnosis of single or recurrent non-psychotic episode of MDD of at least 8 weeks duration were included in the study. During the current episode, patients must have had inadequate response, defined as <50% reduction in Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ) score to an adequate trial of 1 to 3 ADTs. Eligible patients had a 17-item Hamilton Depression Rating Scale (HDRS)-17 total score ≥18 both at screening and on the first day of prospective treatment *(76)*.

Study design

The study design has been presented in Figure 2.

Figure 2: Study design and endpoints of the Pyxis trial



Source: *(76)*
Note: In order to exclude patients with seemingly variable response to ADT, this study's protocol was amended to specify that patients had to meet a more refined inadequate response criteria throughout prospective treatment (HAM-D17 score ≥14; <50% reduction from baseline in HAM-D17, as well as <50% reduction in MADRS total score between start of prospective treatment and each scheduled visit, and CGI-I score ≥3 at each scheduled visit) to be eligible for randomisation and also to blind the investigator to the revised criteria.
Abbreviations: ADT: antidepressant treatment; CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity of Illness; CR: controlled release; ECG: electrocardiogram; HAM-A: Hamilton Anxiety Rating Scale; HAM-D17: 17-item Hamilton Depression Rating Scale; IDS-SR: Inventory of Depressive Symptomatology – Self-Report; MADRS: Montgomery-Åsberg Depression Rating Scale; SDS: Sheehan Disability Scale; TEAE: treatment-emergent adverse event; XR: extended release

Efficacy results

A total of 379 patients were randomised to brexpiprazole (n=188) or placebo (n=191) *(76)*.

- Mean reduction from baseline to week 6 in MADRS total score was greater for brexpiprazole compared with placebo (LSM: −8.36 vs. −5.15; least squares mean difference [LSMD]: −3.21; 95% CI: −4.87, −1.54; P=0.0002; efficacy population per final protocol) with difference between treatment groups apparent from the first week onward.
- Similar results were seen for brexpiprazole vs. placebo in the efficacy population (LSM: −8.27 vs. −5.15; LSMD: −3.12; 95% CI: −4.70, −1.54; P=0.0001).
- Brexpiprazole produced a greater reduction from baseline to week 6 than placebo in mean SDS score. Brexpiprazole produced numerical improvements on work/school, social life, and family life subscales.
- Greater improvements from baseline to week 6 in the brexpiprazole group compared with placebo were also seen in physician-rated HDRS-17 and CGI-S (P<0.001).
- Greater improvement in the brexpiprazole group compared with placebo was seen in CGI-I score at week 6 (P=0.0003) and change from baseline to week 6 in HARS total score (P=0.0376).
- There was a higher proportion of responders at week 6, whether defined by MADRS score (P=0.0429) or CGI-I (P=0.0002), in the brexpiprazole group compared with placebo *(76)*.
- Mean reduction from baseline to week 6 in HAM-A total score was greater for brexpiprazole compared with placebo (LSM: −2.77 vs. −3.94; LSMD: −1.17; 95% CI: −2.17, −0.17; P=0.0219)

Safety Results

- The most frequent TEAEs (≥5%) in patients receiving brexpiprazole were weight gain (8.0%) and akathisia (7.4%), which were generally considered by investigators to be mild to moderate.
- Activating side effects such as restlessness, insomnia, and anxiety were reported by only a few patients (restlessness: 6/188 [3.2%] vs. 0%; insomnia: 4/188 [2.1%] vs. 4/191 [2.1%]; anxiety: 7/188 [3.7%] vs. 3/191 [1.6%], for brexpiprazole vs. placebo, respectively).
- Somnolence, fatigue, and sedation were also uncommon (somnolence: 8/188 [4.3%] brexpiprazole vs. 1/191 [0.5%] placebo; fatigue: 3/188 [1.6%] brexpiprazole vs. 3/191 [1.6%] placebo; and sedation: brexpiprazole 2/188 [1.1%] vs. 0% placebo).
- Mean body weight change at week 6 (observed cases) was 1.64 kg for brexpiprazole vs. 0.36 kg for placebo (LSMD: 1.28 kg; P<0.0001).
- Mean prolactin concentrations in the brexpiprazole group increased from baseline to last visit by 8.3 ng/mL in female patients and 2.2 ng/mL in male patients (baseline: 10.0 and 7.5 ng/mL, respectively); smaller mean changes were seen in the placebo group (female: +0.3 ng/mL; male: +0.3 ng/mL; baseline: 9.9 and 7.1 ng/mL, respectively).
- Metabolic-related TEAEs were reported by 2 brexpiprazole patients (dyslipidaemia; hypercholesterolemia) and 1 placebo patient (increased triglycerides).
- Two of the three EPS rating scales used showed small increases in mean scores for the brexpiprazole group over the randomised treatment phase. LSM changes from baseline to last visit for brexpiprazole vs. placebo were 0.18 vs. −0.02 for Simpson-Angus Scale (SAS) total score (LSMD: 0.20; P=0.0038), 0.03 vs. 0.04 for AIMS total score (LSMD: −0.01; P=0.8663), and 0.14 vs. −0.04 for Barnes Akathisia Rating Scale (BARS) global score (LSMD: 0.18; P=0.0005). One patient from the brexpiprazole group discontinued treatment due to akathisia.

- There were no other consistent differences between treatment groups in clinical laboratory results, vital signs, and electrocardiograms (ECGs). No suicide, attempted suicide, or deaths were reported during the study *(76)*.

Polaris Trial

The Polaris trial (NCT01360632) was an 8-week, single-blind, prospective phase followed by 6-week, randomised, double-blind, placebo-controlled phase, fixed dose adjunctive brexpiprazole (1 mg, 3 mg) trial *(77)*.

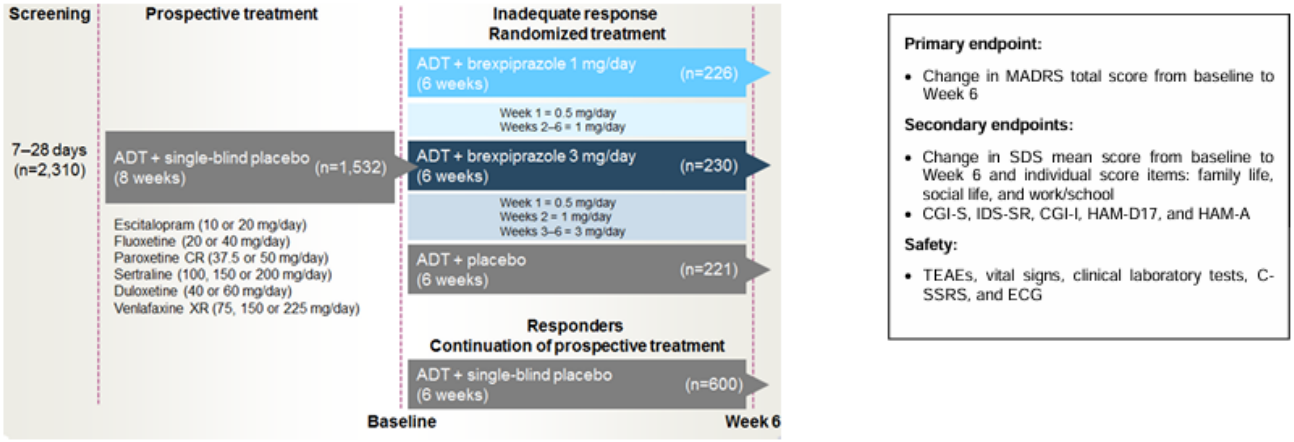
Study population

Outpatients aged 18 to 65 years with a diagnosis of single or recurrent non-psychotic episode of MDD of at least 8 weeks duration were included in the study. During the current episode, patients must have had inadequate response, defined as s <50% reduction in ATRQ score to an adequate trial of 1 to 3 ADTs. Eligible patients had a HDRS-17 total score ≥18 both at screening and on the first day of prospective treatment phase *(77)*.

Study design

The study design has been presented in Figure 3.

Figure 3: Study design and endpoints of the Polaris trial



Source: *(77)*
Note: Based on results from earlier completed studies, the protocol was amended during the study, prior to database lock, to specify that patients had to meet additional inadequate response criteria (i.e., <50% reduction in MADRS total score at all visits during the prospective phase, in addition to the previously described criteria) to be eligible for randomisation and also to blind the investigators to the revised criteria.
Abbreviations: ADT: antidepressant treatment; C-SSRS: Columbia – Suicide Severity Rating Scale; CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity of Illness; CR: controlled release; ECG: electrocardiogram; HAM-A: Hamilton Anxiety Rating Scale; HAM-D17: 17-item Hamilton Depression Rating Scale; IDS-SR: Inventory of Depressive Symptomatology – Self-Report; MADRS: Montgomery-Åsberg Depression Rating Scale; SDS: Sheehan Disability Scale; TEAE: treatment-emergent adverse event; XR: extended release

Efficacy results

A total of 677 patients were randomised to: 1) ADT + placebo (n=221); 2) ADT + brexpiprazole 1 mg/day (n=226); or 3) ADT + brexpiprazole 3 mg/day (n=230) *(77)*.

After amendment of the protocol (in order to exclude patients with seemingly variable response to ADT, the protocol was amended to a more refined inadequate response criteria [HDRS-17 score ≥14,

<50% reduction from baseline in HDRS-17 as well as <50% reduction in MADRS total score between start of prospective treatment and each scheduled visit, and CGI-I score ≥3 at each scheduled visit) to be eligible for randomisation), a total of 627 patients were randomised to: 1) ADT + placebo (n=203); 2) ADT + brexpiprazole 1 mg/day (n=211); or 3) ADT + brexpiprazole 3 mg/day (n=213).

- For the primary endpoint (efficacy population per final protocol), the mean reduction from baseline to Week 6 in MADRS total score for brexpiprazole 3 mg was greater compared with placebo (−8.29 vs. −6.33; LSMD: −1.95; 95% CI: −3.39, −0.51; P=0.0079). Mean change in MADRS total score for brexpiprazole 1 mg was −7.64 vs. −6.33 for placebo (LSMD: −1.30;95% CI: −2.73, 0.13; P=0.0737).
- In the key secondary endpoints (efficacy population per final protocol), brexpiprazole 1 mg and brexpiprazole 3 mg showed greater improvement than placebo for the SDS mean score. Mean reductions from baseline to Week 6 were greater for family life and social life for both doses of brexpiprazole vs. placebo.
- Brexpiprazole 1 mg showed greater efficacy than placebo (P<0.05) on MADRS-defined response rate and CGI-I scale at Week 6.
- Brexpiprazole 3 mg showed greater efficacy than placebo (P<0.05) on MADRS-defined response rate, CGI-I-defined response rate, and CGI-I at Week 6, and in mean change from baseline at Week 6 in the CGI-S scale, HAM-D17, HAM-A, and IDS-SR *(77)*.

Safety results

- The most frequently (>5%) reported TEAEs were headache, nasopharyngitis, and weight gain in the brexpiprazole 1 mg group and akathisia, headache, somnolence, weight gain, and tremor in the brexpiprazole 3 mg group. Most TEAEs were considered mild-to-moderate severity.
- Activating TEAEs were infrequently reported (restlessness: 1.8% vs. 4.4% vs. 0%; anxiety: 2.2% vs. 3.5% vs. 0.5%; and insomnia: 2.2% vs. 2.6% vs. 3.2% in the brexpiprazole 1 mg, 3 mg, and placebo groups, respectively).
- Sedating TEAEs such as somnolence (4.0% vs. 5.7% vs. 0.5%), fatigue (3.1% vs. 4.8% vs. 1.8%), and sedation (0% vs. 0% vs. 0%) were also infrequent in the brexpiprazole 1 mg, 3 mg, and placebo groups, respectively.
- Mean (SD) body weight increased from 83.1 (20.8) kg at baseline to 84.6 (21.0) kg in the brexpiprazole 1 mg group at Week 6 (observed cases), and from 85.3 (21.6) kg to 85.8 (22.0) kg in the placebo group (LSM gain: 1.40 kg vs. 0.24 kg; LSMD: 1.17 kg; P<0.0001). It increased from 84.6 kg to 87.0 kg in the brexpiprazole 3 mg group (LS mean gain: 1.57 kg vs. 0.24 kg for placebo; LSMD: 1.33 kg; P<0.0001). Increased body weight ≥7% was seen at any visit in 11/225 (4.9%) brexpiprazole 1 mg, 4/228 (1.8%) brexpiprazole 3 mg, and 2/217 (0.9%) patients who received placebo.
- With respect to laboratory tests, mean low-density lipoprotein (LDL) cholesterol values decreased from baseline in all 3 groups, and there were no clinically relevant changes in high-density lipoprotein (HDL) cholesterol and triglycerides between treatment groups.
- There were small mean increases in prolactin with brexpiprazole compared with placebo; no patients on brexpiprazole 1 mg, 0.4% on brexpiprazole 3 mg, and 1.4% on placebo had prolactin levels >3 times the upper limit of normal.

- No clinically meaningful effects were observed for liver parameters (alanine transaminase and aspartate transaminase). No meaningful differences between brexpiprazole groups and placebo were seen in ECGs and vital signs.
- Fourteen patients discontinued due to TEAEs; 5 patients in the 3 mg brexpiprazole group discontinued due to akathisia. There were no deaths and no reports of suicide or attempted suicide during the study *(77)*.

Sirius Trial

The Sirius (NCT02196506) trial was an 8-week, single-blind, prospective phase followed by 6-week, randomised, double-blind, placebo-controlled phase fixed dose adjunctive brexpiprazole (2 mg) trial *(143)*.

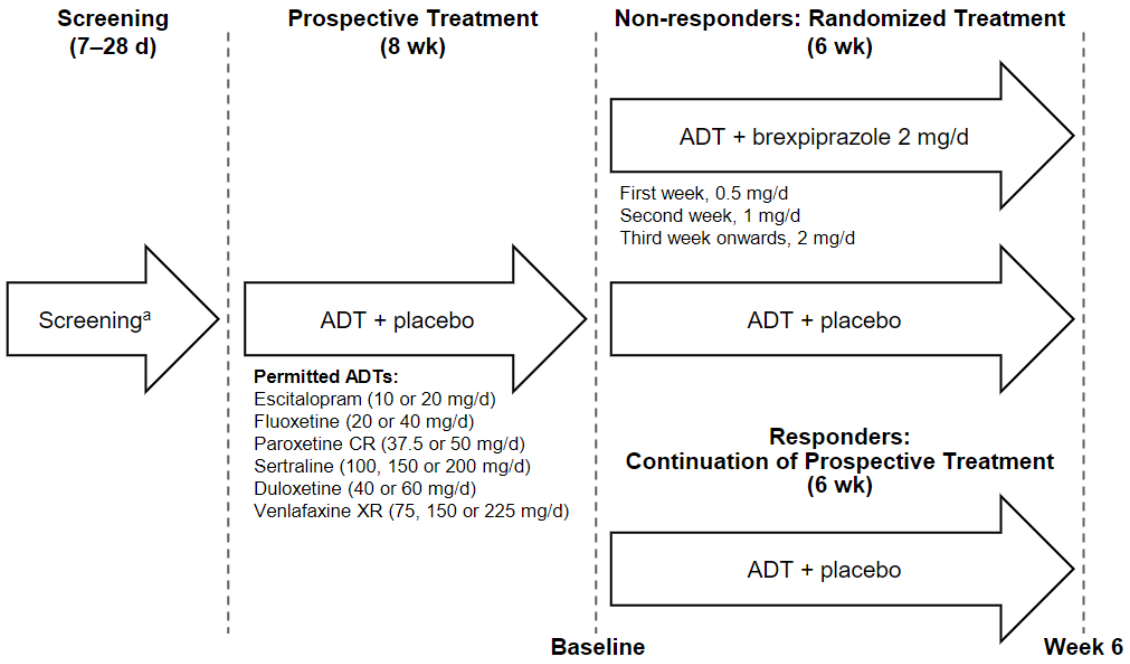
Study population

Outpatients aged 18 to 65 years with a diagnosis of single or recurrent non-psychotic episode of MDD of at least 8 weeks duration were included in the study. During the current episode, patients must have had inadequate response, defined as s <50% reduction in ATRQ score to an adequate trial of 1 to 3 ADTs. Patients were also required to have HDRS17 total score of ≥18 at screening and on the first day of prospective treatment *(143)*.

Study design

The study design is presented in Figure 4.

Figure 4: Study design and endpoints of the Sirius trial



Source: *(143)*
Note: [a] And washout of prohibited concomitant pharmacotherapy; Patients received the same ADT for the duration of the study. ADT dose changes were permitted for the first 4 weeks of prospective treatment only. During the prospective treatment phase patients visited the study centre at weekly intervals for the first 4 weeks and then every 2 weeks; visits were at weekly intervals during the randomised treatment phase
Abbreviations: ADT: antidepressant treatment; CR: controlled -release; XR: extended-release

Efficacy results

A total of 394 patients were randomised to adjunctive brexpiprazole 2 mg/d (n=191) or adjunctive placebo (n=202).

- The primary efficacy end point of change in MADRS total score from baseline to week 6 improvement was statistically significantly greater in the ADT + brexpiprazole group than in the ADT + placebo group (LSMD: −2.30; 95% CI: −3.97, −0.62; P=0.0074).
- The first key secondary efficacy end point of change in SDS mean score from baseline to week 6, the ADT + brexpiprazole group had a greater numerical improvement from baseline to week 6 than the ADT + placebo group (LSMD: −0.22; 95% CI: −0.66, 0.23); however, this difference was not statistically significant (P=0.33).
- ADT + brexpiprazole showed numerical benefits over ADT + placebo on the SDS items of social life and family life, but not work/studies.
- On the second and third key secondary efficacy end points, the ADT + brexpiprazole group showed greater improvement in MADRS total score from baseline to week 6 than the ADT + placebo group in the subgroup of patients with <25% improvement during prospective ADT and the subgroup of patients with DSM-5 anxious distress at screening, with nominal P=0.026 and P=0.0099, respectively *(143)*.

Safety results

- From baseline (the start of the randomised treatment phase), more patients experienced TEAEs in the ADT + brexpiprazole group than in the ADT+ placebo group (59.9% vs. 49.5%).
- The most frequent TEAEs in patients receiving ADT + brexpiprazole were akathisia (8.3%), restlessness (8.3%), upper respiratory tract infection (5.2%), and increased weight (5.2%). Nausea and vomiting were infrequent (≤1%) with brexpiprazole, and all sedating TEAEs had an incidence <5%. Most TEAEs were mild or moderate in severity.
- The incidence of EPS-related TEAEs was higher among patients receiving brexpiprazole (11.5%) than those receiving placebo (6.9%). The most frequently reported EPS-related TEAE was akathisia.
- The mean (SD) change in body weight from baseline to week 6 was 1.5 (2.1) kg for ADT + brexpiprazole (n=177) and 0.5 (1.9) kg for ADT + placebo (n=196; <0.0001). Increase in body weight ≥7% at any postbaseline visit was reported by 8/192 (4.2%) patients receiving ADT + brexpiprazole and 2/202 (1.0%) patients receiving ADT + placebo.
- The assessment of electrocardiograms, vital signs, and laboratory measurements (including glucose, total cholesterol, and triglycerides) did not show any consistent differences between the ADT+ brexpiprazole and ADT + placebo groups.
- No suicidal behaviour was reported on the Columbia – Suicide Severity Rating Scale (C-SSRS) during the randomised treatment phase, and the incidence of treatment-emergent suicidal ideation was lower in the ADT + brexpiprazole group (3.6%) than in the ADT + placebo group (7.4%). No patients died during the trial *(143)*.

Delphinus Trial

The Delphinus (NCT01727726) trial was an 8- or 10-week, double-blind, prospective phase followed by 6-week, randomised, double-blind, placebo-controlled, active referenced (quetiapine XR) phase, flexible dose adjunctive brexpiprazole (2-3 mg) trial *(144)*.

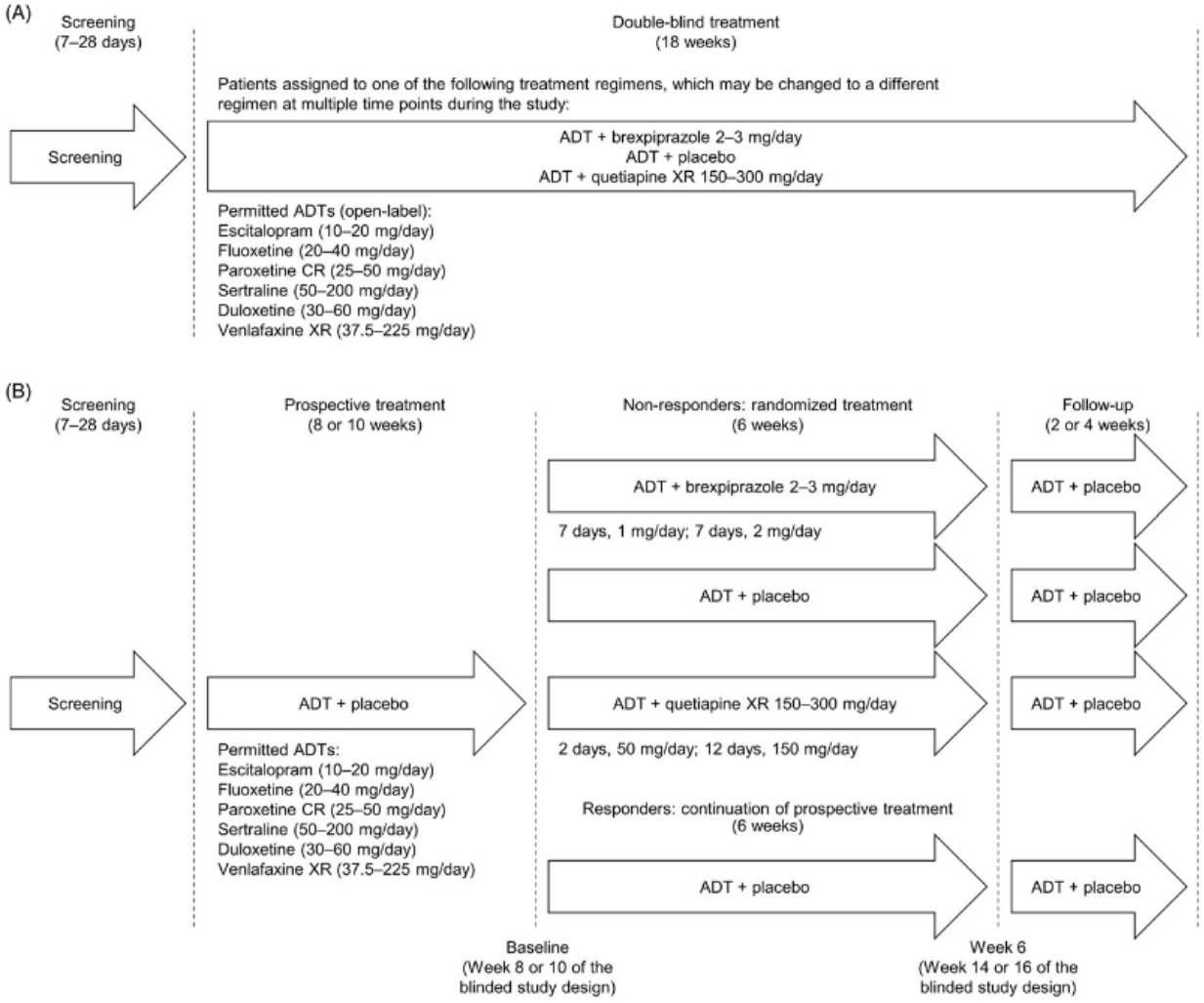
Study population

Outpatients aged 18 to 65 years with a diagnosis of single or recurrent non-psychotic episode of MDD of at least 8 weeks duration were included in the study. During the current episode, patients must have had inadequate response, defined as a <50% reduction in ATRQ score to an adequate trial of 1 to 3 ADTs *(144)*.

Study design

The study design is presented in Figure 5.

Figure 5: Study design of the Delphinus trial



Source: *(144)*
Abbreviations: ADT: antidepressant treatment; CR: controlled-release; IVRS/IWRS: interactive voice/web response system; XR: extended-release
Note: (A) Blinded study design (as provided in the protocol for the investigators). (B) Unblinded study design (as per IVRS/IWRS design). From the start of prospective treatment, patients visited the study centre at weekly intervals for the first 4 weeks and then every 2 weeks for the remainder of the 18-week treatment period

Efficacy results

- A total of 2,174 patients entered the prospective treatment phase, of whom 277 (12.7%) discontinued before the end of the phase, 1,394 (64.1%) responded to ADT + placebo at some point in the prospective treatment phase and were, therefore, excluded from randomised treatment, and 503 (23.1%) had an inadequate response to ADT + placebo and were, therefore, randomised.
- Inadequate responders continued the same ADT and were randomised to adjunctive brexpiprazole adjunctive placebo, or adjunctive quetiapine XR 150 to 300 mg/day.
- Randomised treatment phase was completed by 171 (86.8%) patients receiving ADT + brexpiprazole, 186 (90.3%) patients receiving ADT + placebo, and 86 (86.0%) patients receiving ADT + quetiapine XR.
- The primary efficacy endpoint of change from baseline to Week 6 in MADRS total score the ADT + brexpiprazole group changed by a LSM (SE) of -6.0 (0.4) points, and the ADT + placebo group changed by -4.6 (0.4) points. The difference between groups at week 6 was statistically significant in favour of ADT + brexpiprazole (LSMD: -1.48; 95% CI: -2.56, -0.39; P=0.0078). The ADT + quetiapine XR group did not separate from ADT + placebo at week 6, changing by -4.9 (0.6) points (LSMD: -0.30; 95% CI: -1.63, -1.04; P=0.66). ADT+ quetiapine XR did, however, show a benefit over ADT + placebo at Week 2 (P=0.010).
- On the key secondary efficacy endpoint of change from baseline to Week 6 in SDS mean score, ADT + brexpiprazole showed improvement from baseline with a numerical benefit over ADT + placebo; however, this benefit was not statistically significant (LSMD: -0.23; 95% CI: -0.52, -0.07; P=0.13). In contrast, the ADT + quetiapine XR group showed less improvement from baseline than ADT + placebo (LSMD: -0.42; 95% CI: -0.06, -0.78; P=0.024).
- ADT + brexpiprazole showed a benefit over ADT + placebo on the family life item and the social life item, but not on the work/studies item. In contrast, ADT + quetiapine XR showed no benefit over ADT + placebo on each of the three item scores: family life, social life, and work/studies *(144)*.

Safety results

- From baseline of the randomised treatment phase, the most frequent TEAEs (≥5%) in patients receiving ADT + brexpiprazole were akathisia (6.1%), somnolence (5.6%), and headache (5.6%) (all mild to moderate in severity). Aside from akathisia, other activating side effects were reported by only a few patients receiving ADT + brexpiprazole (restlessness: 2.5%; insomnia: 2.5%; agitation: 0.5%; anxiety: 0.5%). Sedating side effects other than somnolence were also uncommon with ADT + brexpiprazole (fatigue: 1.5%; sedation: 0%).
- The most frequent TEAEs (≥5%) in patients receiving ADT + quetiapine XR were somnolence (18.0%), dry mouth (6.0%), and increased appetite (5.0%). Sedation was reported by 3% patients.
- The most frequently reported EPS-related TEAE was akathisia (6.1% in the ADT + brexpiprazole group; 1.9% in the ADT + placebo group; 3.0% in the ADT + quetiapine XR group).
- Body weight increase (≥7%) at any post-baseline visit was reported by 5.7% patients in the ADT + brexpiprazole group, 2.4% patients in the ADT + placebo group, and 5.1% patients in the ADT + quetiapine XR group.

- The assessment of ECGs, vital signs, and laboratory measurements (including glucose, cholesterol, and triglycerides) did not show any consistent differences between the three treatment groups.
- Changes in serum prolactin concentration in the ADT + brexpiprazole and ADT + quetiapine XR groups were comparable with those in the ADT + placebo group *(144)*.

Argo Trial

The Argo (NCT01838681) trial was a Phase 3, multicentre, randomised, double-blind, parallel group, placebo-controlled, flexible-dose adjunctive brexpiprazole, long-term trial *(166)*.

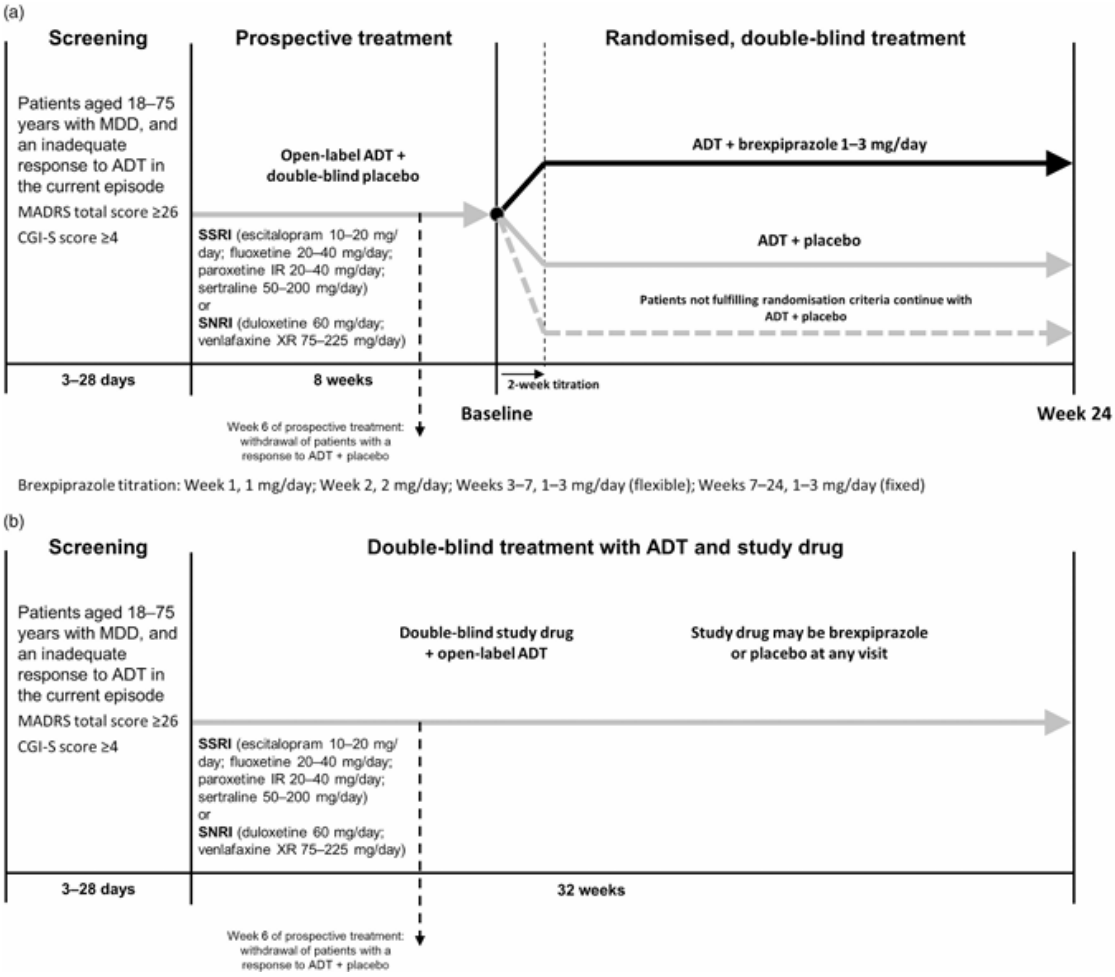
Study population

Outpatients, ≥18 and ≤75 years of age, with a primary diagnosis of MDD (current MDE confirmed using the Mini-International Neuropsychiatric Interview [MINI]) who had a MADRS total score ≥26 at the screening visit and at the start of the prospective treatment period; had a CGI-S score ≥4 at the screening visit and at the start of the prospective treatment period; had the current MDE for ≥8 weeks. Further, patients must have had inadequate response, defined as <50% reduction in ATRQ score to an adequate trial of 1 to 3 ADTs *(166)*.

Study design

The study design has been presented in Figure 6.

Figure 6: Study design of the Argo trial



Source: *(166)*
Note: (a) Unblinded study design. (b) Blinded study design
Abbreviations: ADT: antidepressant therapy; CGI-S: Clinical Global Impression-Severity; IR: immediate release; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: major depressive disorder; SNRI: serotonin–noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; XR: extended release

Efficacy results

A total of 2,517 patients were screened, and 1,986 entered the prospective treatment period. A total of 1,661 (83.8%) patients completed the prospective treatment period; 886 (44.7%) patients demonstrated inadequate response to ADT + placebo and were therefore eligible for randomisation. Inadequate responders continued the same ADT and were randomised to adjunctive brexpiprazole 1 to 3mg/day (n=444) or adjunctive placebo (n=442).

- The proportion of patients who achieved full remission was 21.4% in the ADT + brexpiprazole group and 24.9% in the ADT + placebo group (OR: 0.83; P=0.2641).
- The secondary analysis of change from baseline in MADRS total score after randomised treatment showed no difference between ADT + brexpiprazole and ADT + placebo in mean change from baseline in MADRS total score at Week 6 (−0.4; 95% CI: −1.2, 0.4; P=0.3259) *(166)*.

Safety results

- The most frequent TEAEs (≥5%) in the randomised treatment period inpatients receiving ADT+ brexpiprazole were weight increase (9.5% vs. 5.0% in ADT + placebo), headache (7.7% vs. 7.0% in ADT + placebo), nasopharyngitis (6.3% vs. 7.7% in ADT + placebo), and accidental overdose (6.1% vs. 5.7% in ADT +placebo; reported as TEAE if >1 tablet of study medication [including ADTs] had been taken).
- The majority of TEAEs were mild or moderate in severity. The overall incidence of severe TEAEs was 6% in the ADT + brexpiprazole group and 5% in the ADT + placebo group.
- In the randomised treatment period, serious adverse events (SAEs) were reported for nine patients (2.0%) in the ADT + brexpiprazole group and 13 patients (2.9%) in the ADT + placebo group.
- Activating side effects were infrequently reported (akathisia: 4.7% vs. 0.9%; restlessness: 4.1% vs. 0.5%; insomnia: 1.8% vs. 0.9%; anxiety: 1.6% vs. 0.9%; agitation: 0.7% vs. 0% for ADT + brexpiprazole and ADT + placebo, respectively). Sedating side effects were also relatively uncommon (fatigue: 3.8% vs.1.4%; somnolence: 2.9% vs.1.4%; sedation: 0% vs.0%).
- The proportion of patients with EPS-related TEAEs was 9.2% in the ADT + brexpiprazole group and 3.6% in the ADT + placebo group.
- Post-baseline elevated prolactin values (>3-times upper limit of normal) were noted for 1/132 men (0.8%) and 8/305 women (2.6%) in the ADT + brexpiprazole group and 0 men (0%) and 2/298 women (0.7%) in the ADT + placebo group.
- Mean changes in fasting glucose and lipid parameters were small. No meaningful differences between the ADT + brexpiprazole group and the ADT + placebo group were seen in ECG parameters and vital signs.
- Mean (SD) weight gain from baseline to Week 24 was 2.1 (4.2) kg in the ADT + brexpiprazole group and 0.8 (3.3) kg in the ADT + placebo group. A larger proportion of patients in the ADT + brexpiprazole group (84/441, 19%) than in the ADT + placebo group (36/436, 8%) had a ≥7% weight increase from baseline.
- The incidence of TEAEs leading to withdrawal during the randomised treatment period was 6.3% in the ADT + brexpiprazole group and 3.4% in the ADT + placebo group.
- Two patients died during the study: 1: A woman suffered from a haemorrhagic stroke that occurred during the prospective treatment period after 43 days on ADT (fluoxetine) + placebo. 2: A man committed suicide by an intentional overdose of ‘unknown drug and alcohol’ after 136 days (non-randomised patient) on ADT (duloxetine) + placebo. The SAE was considered not related to treatment by the investigator. Neither patient received brexpiprazole at any time during the study *(166)*.

A.5 Literature Search Criteria

Methodology

Evidence from recent SLRs and NMAs comparing the effectiveness and safety of adjunctive antipsychotics in the treatment of adults with MDD was summarised.

PICO

- Population (P): Adults with MDD (≥18 years)
- Intervention (I): Adjunctive brexpiprazole
- Comparator (C): Head-to-head comparison with adjunctive antipsychotics
- Outcomes (O): Efficacy (relapse prevention and acceptability, QoL) and safety outcomes (tolerability, dropouts)

Search strategy

A literature search to identify publications from studies on the comparative effectiveness and safety of brexpiprazole was performed on July 2, 2024 using PubMed database and the following search strategy:

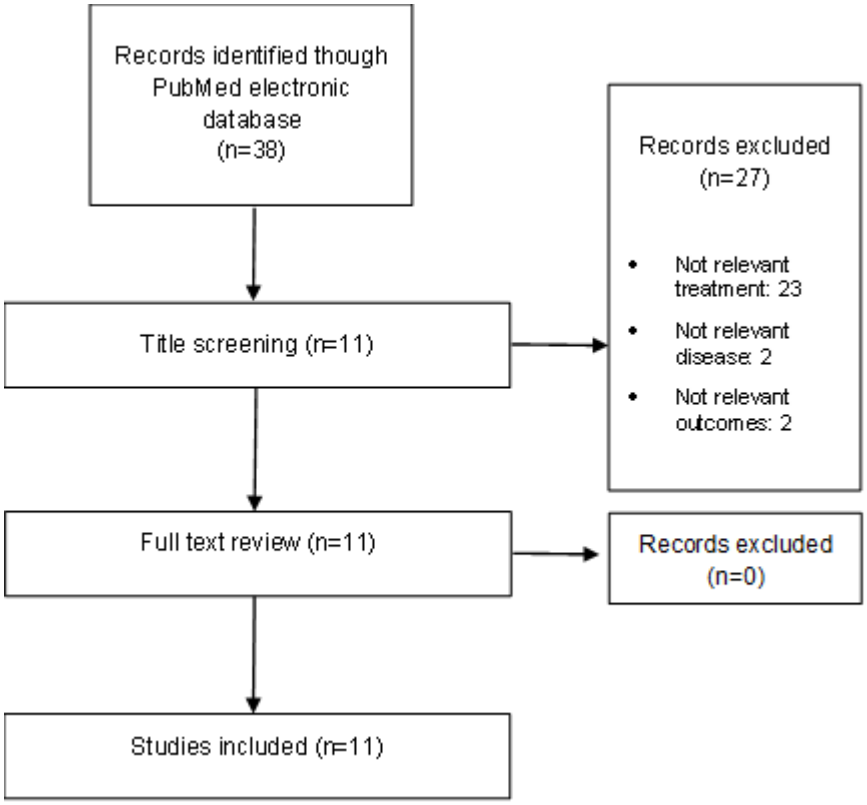
- (major depressive disorder*[Title/Abstract] OR MDD[Title/Abstract] OR major depressive episode*[Title/Abstract]) AND
- (adjunctive antidepressant treatment*[Title/Abstract] OR adjunct antidepressant treatment*[Title/Abstract] OR adjunctive antidepressant*[Title/Abstract] OR adjunct antidepressant*[Title/Abstract] OR adjunctive atypical antipsychotic*[Title/Abstract] OR adjunct atypical antipsychotic*[Title/Abstract] OR adjunct ADT[Title/Abstract] OR adjunctive ADT[Title/Abstract] OR ADT augmentation[Title/Abstract] OR adjunctive antipsychotic treatment[Title/Abstract] OR adjunct antipsychotic treatment[Title/Abstract] OR Brexpiprazole Adjunctive[Title/Abstract] OR Brexpiprazole adjunctive[Title/Abstract] OR Brexpiprazole[Title/Abstract] OR brexpiprazole[Title/Abstract] OR adjunct brexpiprazole[Title/Abstract] OR adjunct Brexpiprazole[Title/Abstract])
- (systematic review[Title/Abstract] OR systematic literature review[Title/Abstract] OR metaanalysis[Title/Abstract] OR meta-analysis[Title/Abstract] OR network meta-analysis[Title/Abstract] OR NMA[Title/Abstract])
- Date filters: from 2019 - 2024

Results were restricted to systematic reviews and meta-analyses, including network meta-analysis as the highest level of evidence. The period of the searches covered from January 1, 2019 until July 2, 2024 to identify the most recent studies. The literature search identified 38 articles.

After screening of titles and abstracts 27 studies were excluded.

From the 11 studies meeting the inclusion criteria, the most recent and comprehensive systematic reviews and meta-analyses, including NMA focussing on both efficacy and safety of antipsychotics in adjunctive treatment of MDD, were prioritised to present in section 8.2 (n=4). Appendix A.6 presents the remaining (n=8) studies along with the reason for non-inclusion in the main text.

Figure 7: Flow diagram for the inclusion and exclusion of studies on comparative effectiveness and safety adjunct antipsychotics



A.6 Literature Publications on Comparative Effectiveness and Safety of Brexpiprazole vs. Other Antipsychotics

From the 11 studies meeting the inclusion criteria, the 4 most recent and comprehensive systematic reviews and meta-analyses, including NMA focussing on both efficacy and safety of antipsychotics in adjunctive treatment of MDD were prioritised to present in section 8.2 (n=4). This section presents the remaining (n=8) studies along with the reason for non-inclusion in the main text (bolded). The comparative analysis of antipsychotics highlights varied outcomes in efficacy and safety:

- Kishi et. al. 2024 conducted a SLR and meta-analysis of brexpiprazole, aripiprazole, and placebo for **Japanese patients** with MDD. Brexpiprazole showed similar utility to aripiprazole for Japanese patients. Brexpiprazole 1 mg showed a good risk–benefit balance for Japanese patients with MDD although it had a risk of weight gain. Brexpiprazole 2 mg was efficacious but carried risks of discontinuation due to AEs, akathisia, and weight gain. However, the risk of akathisia may be reduced by an initial dose of 0.5 mg/day rather than 1.0 mg/day *(167)*.
- Scott et. al. 2023 conducted a SLR and meta-analysis of augmentation and combination treatments for **early-stage TRD** and concluded that both pharmacological and psychological therapies show larger treatment effects than placebo *(168)*.
- Yan et. al. 2022 conducted a SLR and NMA of the efficacy and acceptability of second-generation antipsychotics with ADTs in **unipolar depression** augmentation. The study concluded that the administration of adjunctive antipsychotics is associated with high effectiveness and low acceptability. Risperidone and aripiprazole were more efficacious and accepted than other AAPs. Quetiapine, brexpiprazole, and cariprazine had a moderate response rate compared to the placebo *(169)*.
- Furukawa et. al. 2022 conducted a SLR and **dose-effect** meta-analysis of the optimal dose of brexpiprazole for augmentation therapy of ADT-refractory depression and reported that 1 to 2 mg brexpiprazole may achieve an optimal balance between efficacy, tolerability and acceptability as acute augmentation treatment of ADT-refractory depression *(170)*.
- Antoun Reyad et. al. 2020 conducted a meta-analysis of RCTs to analyse the efficacy and safety of **only brexpiprazole** in acute management of psychiatric disorders (schizophrenia and MDD). The study concluded that brexpiprazole demonstrated significant improvements in schizophrenia and MDD and is well-tolerated; however, there is an association with akathisia and somnolence *(171)*.
- Kishi et. al., conducted a SLR and meta-analysis of double-blind, randomised, placebo-controlled trials of **only brexpiprazole adjunctive treatment** (vs. placebo) (0.5 to 3 mg/d) for MDD where ADTs had failed. The study concluded that brexpiprazole is a useful adjunctive treatment for patients with MDD who have experienced at least 1 failure of ADT. Brexpiprazole at doses ≤2 mg/d seemed to provide a better risk/benefit balance than >2 mg/d *(172)*.
- Demyttenaere et. al. 2019 conducted a SLR and meta-analysis of the **risk of akathisia for all newly approved antipsychotics**, as monotherapy or adjunctive treatment, in patients with schizophrenia, bipolar disorder, or MDD. The study concluded that the severity of akathisia with these agents generally is mild to moderate, only in a minority of cases (<5%) leading to treatment discontinuation, meaning that this adverse effect appears to be manageable *(173)*.

Table 9: Publications on comparative effectiveness and safety of brexpiprazole vs. other antipsychotics

First Author, Study design	Study population	Treatments	Key efficacy outcomes	Key safety outcomes	Authors conclusions
Kishi 2024 *(167)* SLR and meta-Analysis	Japanese patients with MDD Inclusion criteria was published and unpublished, double-blind, randomised, placebo-controlled trials of brexpiprazole or aripiprazole (ARI) as an adjunctive treatment for Japanese patients with AR-MDD; studies in which at least 70% of the participants were Japanese	For primary meta-analysis: BRE, ARI, and the placebo Secondary meta-analysis, the drugs were divided by dose so there were five treatment arms: brexpiprazole1 (BRE1), brexpiprazole2 (BRE2), aripiprazole 3 mg/day (ARI3), aripiprazole flexible dose (ARI-F), and the placebo	Primary meta-analysis: • Both BRE and ARI were superior to the placebo in their improvement of MADRS scores, CGI-S scores, and social function scale scores • ARI but not BRE had the lower non-response and non-remission rates than the placebo Secondary meta-analysis: • All active-treatment arms (BRE1, BRE2, ARI3, and ARI-F) outperformed the placebo in the improvement of MADRS scores, CGI-S scores, and social function scale scores • ARI3 and ARI-F, but not BRE1 and BRE2, also had a lower non-response and non-remission rates compared with the placebo	Primary meta-analysis: • BRE but not ARI had a higher rate of discontinuation due to adverse events than the placebo, ARI but not BRE had a higher incidence of at least one adverse event compared with the placebo • BRE and ARI had higher risk of both akathisia and weight gain compared to the placebo Secondary meta-analysis: • BRE2 was associated with a higher rate of discontinuation because of adverse events than the placebo and BRE1 • ARI-F was associated with a higher incidence of at least one adverse event than the placebo • RE2 and ARI-F were associated with higher incidences of akathisia than the placebo • BRE1, BRE2, ARI3, and ARI-F were associated with higher incidences of weight gain than the placebo	• Local heterogeneity was evaluated for ARI only. Consequently, confidence in the evidence in the primary NMA was evaluated as low or very low (for both primary and secondary analysis) • BRE showed similar utility to ARI for Japanese patients with AR-MDD • BRE1 showed a good risk–benefit balance for Japanese patients with AR-MDD although BRE1 had a risk of weight gain. • BRE2 was efficacious but carried risks of discontinuation due to adverse events, akathisia, and weight gain. However, the risk of akathisia may be reduced by an initial dose of 0.5 mg/day rather than 1.0 mg/day
Scott 2023 *(168)* SLR and meta-analysis	Patients with early-stage TRD. (The term 'early-stage TRD' in reference to a non-response to one adequate pharmacological or psychological	ADTs (SSRIs, TCA, NaSSA, others), antipsychotics (typical and atypical), mood stabilisers, stimulants, hormones,	ADTs: • These showed a wide range of effect sizes (ESs), with only desipramine (k: 2; ES: 0.69; 95% CI: 0.26, 1.12; I2: 0%), mirtazapine (k: 2; ES: 1.19; 95% CI: 1.02, 1.36; I2: 0%) and bupropion (k: 4; ES: 1.19; 95% CI: 0.45, 1.93; I2: 98%)	• Tolerability data were recorded by 79% of included studies (k: 91). The specific measures used were too heterogeneous to allow for meaningful comparison. Data on acceptability were available for 84% of studies (k: 97). The most commonly used measure to assess tolerability was dropout	• Both pharmacological and psychological therapies show larger treatment effects than placebo. • Findings firstly support lithium, aripiprazole and quetiapine as current

First Author, Study design	Study population	Treatments	Key efficacy outcomes	Key safety outcomes	Authors conclusions
	therapy for depression) Inclusion criteria was RCTs that assessed at least one augmentation or combination treatment (with sample sizes of 10 or more) and adults (aged ⩾18 years old) with MDD who had failed to remit despite at least one adequate ADT monotherapy trial were included	NMDA, vitamins, psychological, and others **Note:** Data for pharmacological augmentation strategies will be presented in the key outcomes and safety columns since these are key comparators	assessed in more than one study Atypical antipsychotics: • All AAPs had been assessed in more than one study, with the most common being aripiprazole (k: 12; ES: 1.28; 95% CI: 1.10, 1.46; I2: 86%), brexpiprazole (k: 5; ES: 0.95; 95% CI: 0.85, 1.05; I2: 58%) and quetiapine (k: 6; ES: 1.23; 95% CI: 1.01, 1.44; I2: 80%). Heterogeneity was substantial for nearly all atypical antipsychotics Lithium: • The most utilised active treatment in the included studies (k: 13), forming the vast bulk of mood stabiliser augmentation studies (lamotrigine k: 2, sodium valproate k: 1). The effect of lithium was found with moderate heterogeneity (ES: 1.13; 95% CI: 0.90, 1.35; I2: 50%) NMDA: • Modulator ketamine was moderately well investigated (k: 8: ES: 1.48; 95% CI: 1.23, 1.73; I2: 74%). The substantial heterogeneity was explained by the esketamine studies (which recruited participants with less severe treatment resistance); the remaining were one oral and three IV ketamine studies, of which four recruited patients with more severe TRD (k: 5: ES: 1.50; 95% CI: 1.30, 1.71; I2: 0%), whereas the four intranasal esketamine studies	due to any cause, which was reported in 28% of active treatment patients, compared to 12% of those receiving placebo • Dropouts due to adverse events were recorded in 23 articles, returning a dropout rate approximately twice as high in active treatment conditions compared to placebo (9.2% vs. 4%). Other, less commonly used, measures included treatment-emergent adverse events, dropout due to intolerance and mean retention time in weeks	first-line augmenters for TRD; findings do not show support for brexpiprazole over these agents, although it is a second-line augmenter in some guidelines

First Author, Study design	Study population	Treatments	Key efficacy outcomes	Key safety outcomes	Authors conclusions
			retained considerable heterogeneity (ES = 1.49; I2 = 87%) Others • The other pharmacological intervention assessed in >3 studies were thyroid hormones (triiodothyronine and thyroxine) (k: 4: ES: 1.24; 95% CI: 0.80, 1.68; I^2: 62%) Additional analyses stratifying between early-stage and substantive TRD: • For all treatments studied, ES 95% CI had large overlap when comparing between studies defining TRD as 1 failed therapy and 2 failed therapies, suggesting treatment efficacy was not sensitive to TRD definition. The exception to this rule was buspirone, for which the ES and 95% CIs were considerably higher when TRD was defined as 2 failed therapies (although this consisted of only one small study)		
Yan 2022 *(169)* SLR and meta-analysis	Patients with unipolar non-psychotic depression (according to any version of the Diagnostic and Statistical Manual of Mental Disorders) Included double-blind RCTs comparing antipsychotics with	Placebo Antipsychotics: aripiprazole, olanzapine, brexpiprazole, quetiapine, cariprazine, risperidone, ziprasidone	• In terms of efficacy, risperidone and aripiprazole were the best among all seven antipsychotics in terms of response or remission rates Response rate: • All active antipsychotics except for ziprasidone (OR: 2.10; 95% CI: 0.98, 4.50) were more efficacious than the placebo, with OR ranging from 1.34 for olanzapine and cariprazine (95% CI: 1.04, 1.73 and 1.07,	• In terms of acceptability and tolerability, olanzapine, aripiprazole, and risperidone ranked as the first three, in that order. Discontinuation due to AEs: • Except for olanzapine and risperidone, all antipsychotics caused AEs more frequently than the placebo, with ORs ranging from 0.04 (95% CI: 0.00, 0.87) for	• Combining adjunctive antipsychotics with antidepressants induces a high response rate but low acceptability and safety. • Risperidone and aripiprazole are more efficacious and acceptable than other commonly used atypical antipsychotics

First Author, Study design	Study population	Treatments	Key efficacy outcomes	Key safety outcomes	Authors conclusions
	a placebo or another antipsychotic augmenting the action of antidepressants as oral administration		1.67, respectively) to 2.17 for risperidone (95% CI: 1.38, 3.42) • Among active antidepressants, aripiprazole was better than olanzapine (OR: 1.36; 95% CI: 1.00, 1.86), brexpiprazole (OR: 1.28; 95% CI: 1.00, 1.64), and cariprazine (OR: 1.37; 95% CI: 1.03, 1.82) Remission rates • Besides ziprasidone (OR: 1.37; 95% CI: 0.68, 2.77), cariprazine showed no significant result (OR: 1.21; 95% CI: 0.96, 1.54) • Olanzapine (OR: 0.51; 95% CI: 0.26, 0.98), brexpiprazole (OR: 0.49; 95% CI 0.26, 0.90), and cariprazine (OR: 0.41; 95% CI: 0.22,0.78) were less efficacious than risperidone	ziprasidone to 0.43 (95% CI: 0.22, 0.82) for aripiprazole • No significant differences were found in the comparison of active antipsychotics All-cause drop-out rate (for acceptability): • Quetiapine (OR: 0.68; 95% CI: 0.50, 0.91), brexpiprazole (OR: 0.69; 95% CI: 0.55, 0.86), and cariprazine (OR: 0.61; 95% CI: 0.46, 0.82) were worse than the placebo	• Olanzapine had relatively low efficacious indices and dropout rates • Quetiapine, brexpiprazole, and cariprazine had a moderate response rate compared to the placebo, while they were the only three drugs worse than the placebo in all-cause dropout rates
Furukawa 2022 *(170)* SLR and dose-effect meta-analysis	Adults 18 years or older, with a primary diagnosis of MDD according to any of the standard operationalised diagnostic criteria with inadequate response to at least one trial of ADT Included all double-blind RCTs that compared two or more doses of brexpiprazole as augmentation of ADT within a trial	Brexpiprazole augmentation with the continuation of ADT with placebo augmentation In the primary analysis, we located the knots at 1, 2, and 3 mg. The dose-effect curve of the primary analysis to estimate the 50% effective dose (ED50) and 95% effective dose (ED95), as it is customary in	• The dose-efficacy curve showed an increase up to doses around 2 mg, and then a flat to decreasing trend through the higher licensed dose up to 3 mg. ED50 was 0.88 mg (OR: 1.24; 95% CI: 1.04, 1.46) and ED95 was 1.79 mg (OR: 1.49; 95% CI: 1.10, 2.02). • The shape of the dose-tolerability curve was comparable to that of the efficacy. The dose-acceptability curve showed a monotonic increasing trend. Both had wide CI bands. Sensitivity analyses excluding trials with overall high risk of bias, including flexible dose arms using maximum target dose (for efficacy: eight trials, 12 active treatment arms,	• The incidence of akathisia and restlessness showed a monotonic increasing trend, whereas the incidence of weight gain peaked off around 2 mg and the dose-effect curve of insomnia was almost flat (post-hoc) • The rate of dropout for adverse events of 1% (six arms, 751 participants), and the rate of dropout for any reason of 12% (six arms, 751 participants) in placebo augmented arms, brexpiprazole augmentation with the maximum target dose of 1.79 mg (ED95) would translate into a rate of dropouts due to adverse events of 1% (95% CI: 0, 4), and a rate of dropout for any reason of 14% (95% CI: 10, 20)	• Augmentation with brexpiprazole in the acute treatment of ADT-refractory depression may achieve most of its efficacy within 1 to 2 mg, whilst additional benefits may be unlikely beyond 2 mg. • The drop-outs due to adverse events may not increase further beyond 2 mg, but the overall drop-out rate seems to increase at greater dosages. • Thus, 1 to 2 mg brexpiprazole may achieve an optimal balance between

First Author, Study design	Study population	Treatments	Key efficacy outcomes	Key safety outcomes	Authors conclusions
		dose-effect analyses. ED50 and ED95 indicate the mean dose that produces 50% and 95%, respectively, of the maximum effect compared with placebo augmentation, expressed in log-OR	3555 participants) generally confirmed the primary analyses • In the primary analysis, we located the knots at 1, 2, and 3 mg. We used the dose-effect curve of the primary analysis to estimate the ED50 and ED95, as it is customary in dose-effect analyses. ED50 and ED95 indicate the mean dose that produces 50% and 95%, respectively, of the maximum effect compared with placebo augmentation, expressed in log-OR. • The average response rate of 18% in the placebo augmented arms at 6 weeks (five arms, 746 participants), brexpiprazole augmentation with the maximum target dose of 1.79 mg (ED95) would translate into a response rate of 25% (95% CI: 20%, 31%)	• According to the GRADE framework, the certainty of evidence for dose-effect relationship was moderate for efficacy (due to some concerns in imprecision), low for tolerability (due to serious concern in imprecision), and moderate for acceptability (due to some concerns in imprecision)	efficacy, tolerability and acceptability as acute augmentation treatment of ADT-refractory depression
Antoun Reyad 2020 *(171)* Meta-analysis of RCTs	Adult patients (18 to 65 years old) taking part in Phase 2/3 RCT's assigned to either brexpiprazole 1 to 4 mg/day, or placebo or active control second generation antipsychotic (quetiapine, aripiprazole) for the management of schizophrenia and MDD	Brexpiprazole vs. placebo, aripiprazole, or quetiapine **Note:** Data for pharmacological augmentation strategies only for MDD are presented in the key outcomes and safety columns	Brexpiprazole vs. placebo: • The mean change from baseline in MADRS score was significantly greater for brexpiprazole compared to placebo (MD: -1.25; 95% CI: -1.74, -0.76; favouring brexpiprazole; P<0.00001) • All studies individually favour brexpiprazole, with low heterogeneity between the studies (X2: 4.82; I2: 0%). SDS mean change was significantly greater for brexpiprazole compared to placebo (MD: -0.37; 95% CI: -0.52, -0.21;(P<0.00001)	Brexpiprazole vs. placebo: • In a total of 3401 patients treated with brexpiprazole compared to 3514 patients who received placebo, the overall RR for trial discontinuation due to adverse effects is 0.90 (95% CI: 0.74 to 1.10; P=0.30) • There was variation among the studies with some favouring brexpiprazole, while others favouring placebo; with a moderate to high heterogeneity (I2: 53%) • Brexpiprazole was associated with some side effects including akathisia (RR: 1.72; 95% CI: 1.38, 2.14; P<0.00001); weight	• Brexpiprazole demonstrated significant improvements in schizophrenia and MDD and is well-tolerated; however, there is an association observed with akathisia and somnolence. These findings will guide psychiatrists and pharmacists in their clinical role for supporting psychiatric patients care

First Author, Study design	Study population	Treatments	Key efficacy outcomes	Key safety outcomes	Authors conclusions
			• Similar positive outcomes for brexpiprazole are highlighted as changes in CGI-S score (MD: -0.19; 95% CI: -0.27, -0.11), HDRS17 (MD: -1.28; 95% CI: -1.79, -0.76), CGI score (MD: -0.21; 95% CI: -0.30, -0.12), MADRS response (MD: 1.36; 95% CI: 1.20, 1.55) , CGI-I response (MD: 1.29; 95% CI: 1.18, 1.41) and MADRS remission (MD: 1.36; 95% CI: 1.16, 1.61)	increase (RR: 2.74; 95% CI: 2.16, 3.48; P<0.00001 and somnolence (RR: 1.87; 95% CI: 1.30, 2.71; P=0.0008) • Brexpiprazole was also associated with restlessness: (RR: 4.11; 95% CI: 2.19, 7.71; P<0.000010) and increased appetite: (RR: 3.88; 95% CI 1.47, 10.3; P=0.006) • Compared to brexpiprazole 4 mg, brexpiprazole lower dose (2 mg) was associated with less risk of akathisia 22/501 compared to 32/496 (RR: 0.68); Somnolence 7/387 vs. 13/383 (RR: 0.53) and trial withdrawal due to adverse events 38/482 vs. 48/477 (RR: 0.78) Brexpiprazole vs. aripiprazole or quetiapine: • One trial was identified comparing brexpiprazole with active control (quetiapine) in MDD • Brexpiprazole compared with quetiapine was associated with less risk of somnolence (RR: 0.25; 95% CI: 0.15, 0.43; P<0.00001), dry mouth (RR:=0.16; 95% CI: 0.05, 0.48; P=0.001) and weight increase (RR: 0.59; 95% CI: 0.32, 1.08; P=0.09) and higher risk of akathisia (RR: 1.73; 95% CI: 0.79, 3.79; P=0.17)	
Kishi 2019 *(172)* SLR and meta-analysis	Patients with MDD with a history of depression and at least 1 ADT failure in the current episode	Adjunctive brexpiprazole concomitantly with an ADT vs. placebo	Compared with placebo, brexpiprazole (at any dose) showed • Higher response rates at all the time points except week 1 (week 6: RR: 0.93; 95% CI: 0.89,	Compared with placebo, brexpiprazole (at any dose) showed • Compared with placebo, brexpiprazole (at all the doses) was associated with higher all-cause discontinuation and	The results of this analysis suggest that brexpiprazole is a useful adjunctive treatment for patients with MDD who have experienced at least 1 failure of ADT. Brexpiprazole at doses ≤2 mg/d seemed to

First Author, Study design	Study population	Treatments	Key efficacy outcomes	Key safety outcomes	Authors conclusions
	The analysis included only double-blind, randomised, placebo-controlled trials that investigated brexpiprazole treatment in patients with MDD and that lasted ≥4 weeks		0.97; P=0.0005; I2: 34%; NNT: 17; 95% CI: 11, 33) • Higher remission rates at weeks 3, 4, and 6 (week 6: RR: 0.95; 95% CI: 0.93, 0.98; P=0.003; I2: 24%: NNT: 25; 95% CI: 14, 50) • Greater improvements in the MADRS total score at all time points (week 6: SMD: −0.20;95% CI: −0.29, −0.11; P<0.00001; I2: 33%) • Greater improvement in SDS total score at week 6 (SMD: −0.12; 95% CI: −0.21, 0.04; P=0.003; I2: 25%) • 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 Subgroup analysis • 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 • 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,	discontinuation due to adverse events as well as with higher incidences of akathisia, insomnia, restlessness, somnolence, and weight increase Subgroup analysis • 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 • Further subgroup meta-analysis compared brexpiprazole doses >2 mg/d and ≤2 mg/d to investigate the dose dependency of these safety outcomes. Both dose levels were associated with a higher incidence of akathisia compared with placebo, but only doses >2 mg/d were associated with a higher incidence of somnolence compared with placebo. The difference compared with placebo in weight increase was marginal for doses >2 mg/d but significant for doses ≤2 mg	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

First Author, Study design	Study population	Treatments	Key efficacy outcomes	Key safety outcomes	Authors conclusions
			brexpiprazole was superior to placebo for the 6-week remission rate and SDS total score in only the fixed-dose studies subgroup. There were no significant subgroup differences in the subgroup analyses		
Demyttenaere 2019 *(173)* SLR and meta-analysis	Placebo as well as active-controlled clinical trials, including subjective (percentage of patients spontaneously reporting akathisia) and/or scale-defined medication-induced akathisia rates with newly approved antipsychotics (NAP) (as monotherapy or as adjunctive treatment) in adult patients with schizophrenia, bipolar disorder or MDD	NAP: asenapine, iloperidone, lurasidone, brexpiprazole, and cariprazine	NR	• The estimated prevalence rates (with 95% CI) of akathisia, ordered from low to high, are respectively 3.9% (2.4, 6.3) for iloperidone, 6.8% (5.1, 9.0) for asenapine, 10% (7.4, 13.5), for brexpiprazole, 12.7% (10.1, 16.1) for lurasidone, and 17.2% (13.4, 22.1) for cariprazine. After Tukey-adjustment for multiple testing, the prevalence rate of akathisia was significantly (P<0.05) lower in iloperidone compared to brexpiprazole, lurasidone, and cariprazine. The prevalence rate of akathisia was significantly (P<0.05) lower in asenapine compared to lurasidone and cariprazine. Finally, the prevalence rate of akathisia was significantly (P<0.05) lower for brexpiprazole compared to cariprazine • With respect to diagnosis, the estimated prevalence of akathisia (with 95%CIs) is respectively 6.6% (5.7, 7.7) in schizophrenia, 9.2% (6.8, 12.5) in bipolar mania, and 11.7% (8.2, 16.8) in MDD • Akathisia was predominantly reported as mild to moderate and generally time limited. Treatment	The meta-analysis showed different prevalence rates of akathisia for different NAP. These differences disappeared when prevalence rates of akathisia were compared under medication vs. placebo conditions after correction for multiple comparisons. This may be due to the fact that patients under placebo condition also spontaneously report akathisia. Iloperidone probably has a very low propensity to cause akathisia, that is generally similar to or even lower than with placebo, while the other NAP have a less benign akathisia profile, varying from a moderate (asenapine and brexpiprazole) to a higher (lurasidone and cariprazine) akathisia risk. Nevertheless, the severity of akathisia with these agents generally is mild to moderate, only in a minority of cases (<5%) leading to treatment discontinuation, meaning that this adverse effect with the NAP appears to be manageable

First Author, Study design	Study population	Treatments	Key efficacy outcomes	Key safety outcomes	Authors conclusions
				discontinuation rates with the NAP were low (<5%) • However, there was evidence for publication bias • Based on a meta-analysis involving 48 (placebo-controlled) studies with 7,132 unique patients in the placebo condition and 12,722 unique patients in the active medication condition, an estimated weighted OR of 2.24 [95% CI:1.93, 2.62] was found, indicating that the odds of akathisia are 2.24 times higher for patients receiving a NAP, compared to those in the placebo condition • The OR (95% CI) of akathisia are, respectively, 1.20 (0.42, 3.45) for iloperidone, 2.04 (1.09, 3.83), for brexpiprazole, 2.37 (1.32, 4.27) for asenapine, 3.47 (2.32, 6.02) for lurasidone, and 4.35 (2.80, 6.75) for cariprazine. However, after Tukey-adjustment for multiple testing, there were no significant (P<0.05) differences between these ORs	

Abbreviations: ADT: antidepressant treatment; ARI-F: Aripiprazole Flexible Dose; ARI3: Aripiprazole 3 mg/day; AR-MDD: Antidepressant-Resistant Major Depressive Disorder; AEs: Adverse Events; BRE1: Brexpiprazole (lower dose); BRE2: Brexpiprazole (higher dose); CI: confidence interval; CGI: Clinical Global Impression; CGI-S: Clinical Global Impression - Severity; ED: effective dose; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HAM-D-17: Hamilton Rating Scale for Depression-17; MADRS: Montgomery-Åsberg Depression Rating Scale; MD: median deviation; MDD: Major Depressive Disorder; NAP: newly approved antipsychotics; NaSSA: noradrenergic and specific serotonergic antidepressants; NMDA: N-methyl-d-aspartate; NR: not reported; OR: odds ratio; PBO: Placebo; RCT: randomised controlled trial; RR: response rate; SDS: Sheehan Disability Scale; SMD: standard median deviation; TCA: tricyclic antidepressant

A.7 Forest Plots/Certainity of Evidence for SLRs and NMAs

Wang 2023: Comparison and ranking of the efficacy and safety of four AAPs (aripiprazole, quetiapine XR, brexpiprazole, and quetiapine) in the adjunctive treatment compared to placebo + ADT of MDD. The key findings of this study are presented in section 8.2.2. The GRADE rating and SUCRA probability ranking for efficacy and AE rate are presented below (Table 10, Table 11, Table 12, Table 13).

Table 10: Summary of GRADE for response rate

Comparison	Study design (number of studies)	Study bias	Heterogeneity and inconsistency	Publication bias	Quality
BRE + ADT vs. ADT	RCT (6)	Not serious	Not serious	Undetected	Moderate
OLA + ADT vs. ADT	RCT (15)	Serious[a]	Not serious	Undetected	Low
ARI + ADT vs. ADT	RCT (8)	Serious[a]	Not serious	Undetected	Low
QUE + ADT vs. ADT	RCT (8)	Serious[a]	Not serious	Undetected	Low
BRE + ADT vs. QUE + ADT	RCT (1)	Serious[a]	NA	Undetected	Very low

Source: *(147)*
Abbreviations: ADT: antidepressant therapy; ARI: aripiprazole; BRE: brexpiprazole; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; NA: not applicable; OLA: olanzapine; PBO: placebo; QUE: quetiapine; RCT: randomised controlled trial; RoB: risk of bias
Note: [a] Authors downgraded by one level when the contributions from low RoB comparisons were less than 30% and contributions from moderate RoB comparisons were 70% or greater

Table 11: Summary of GRADE for adverse event rate

Comparison	Study design (number of studies)	Study bias	Heterogeneity and inconsistency	Publication bias	Quality
BRE + ADT vs. ADT	RCT (6)	Serious[a]	Serious[b]	Undetected	Very low
OLA + ADT vs. ADT	RCT (14)	Serious[a]	Serious[b]	Undetected	Very low
ARI + ADT vs. ADT	RCT (8)	Not serious	Not serious	Undetected	Moderate
QUE + ADT vs. ADT	RCT (11)	Serious[a]	Not serious	Undetected	Very low
BRE + ADT vs. QUE + ADT	RCT (1)	Serious[a]	NA	Undetected	Very low

Source: *(147)*
Abbreviations: ADT: antidepressant therapy; ARI: aripiprazole; BRE: brexpiprazole; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; NA: not applicable; OLA: olanzapine; PBO: placebo; QUE: quetiapine; RCT: randomised controlled trial; RoB: risk of bias
Note: [a] Downgrade because >70% from moderate RoB comparisons; [b] Downgrade because $I^2 > 50\%$

Table 12: SUCRA probability ranking of efficacy outcome indicators

Comparison	Mean change in MADRS total score from baseline to endpoint		Remission rate		Response rate	
	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank
BRE + ADT	45.1	4	48.5	3	73.6	2
OLA + ADT	70.5	2	74.6	2	52.4	3
ARI + ADT	54.6	3	81.0	1	96.6	1
QUE + ADT	79.6	1	45.3	4	27.3	4
PBO + ADT	0.2	5	0.5	5	0.0	5

Source: *(147)*
Abbreviations: ADT: antidepressant therapy; ARI: aripiprazole; BRE: brexpiprazole; MADRS: Montgomery-Åsberg Depression Rating Scale; OLA: olanzapine; PBO: placebo; QUE: quetiapine; SUCRA: surface under the cumulative ranking curve

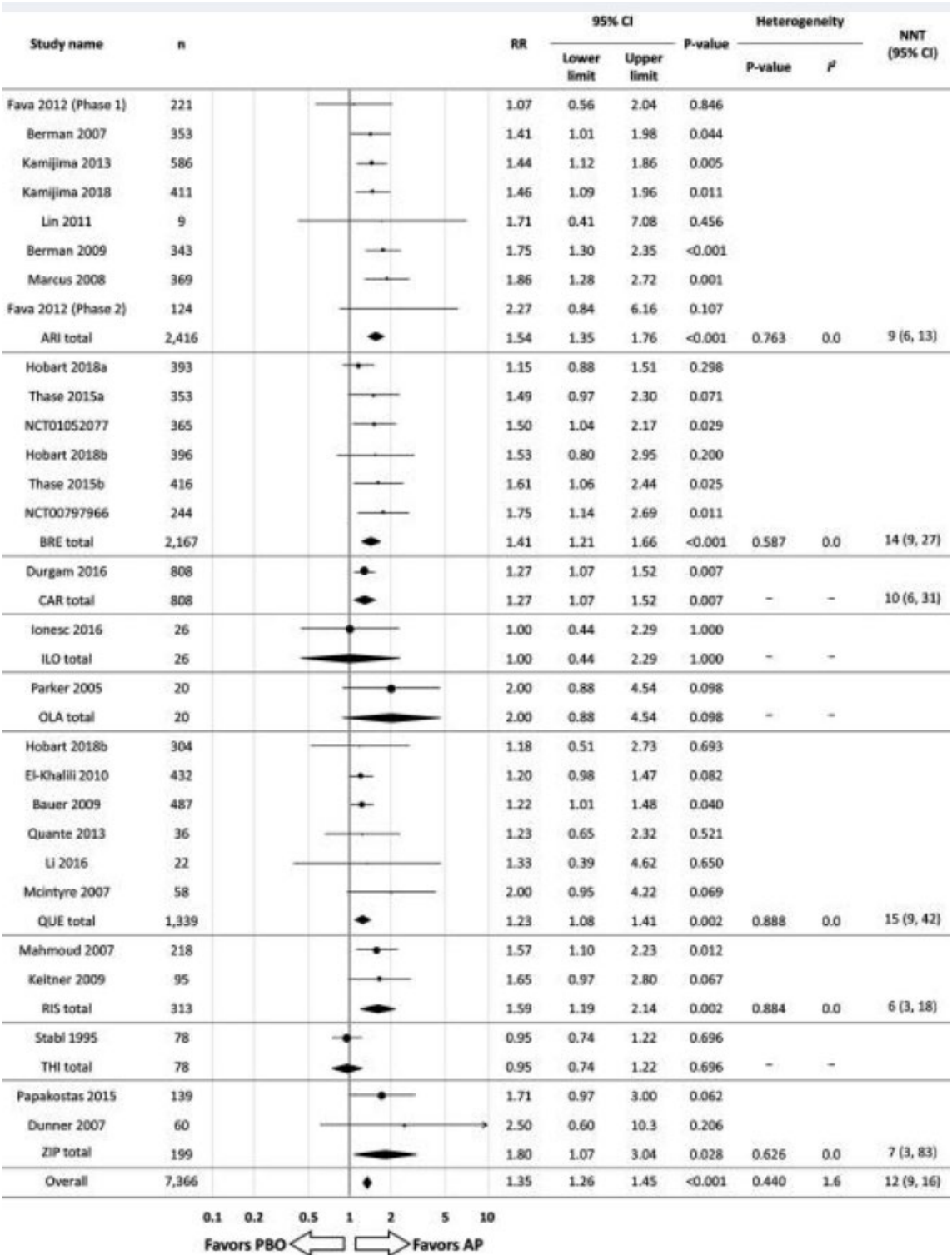
Table 13: SUCRA probability ranking of safety outcome indicators

Comparison	All-cause discontinuation		Adverse events: discontinuation		Adverse events: incidence rate	
	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank
BRE + ADT	68.1	1	47.6	3	22.6	4
OLA + ADT	42.6	3	31.6	4	98.4	1
ARI + ADT	41.0	4	52.9	2	9.6	5
QUE + ADT	40.5	5	18.0	5	43.9	3
PBO + ADT	57.8	2	99.9	1	75.5	2

Source: *(147)*
Abbreviations: ADT: antidepressant therapy; ARI: aripiprazole; BRE: brexpiprazole; Rating Scale; OLA: olanzapine; PBO: placebo; QUE: quetiapine; SUCRA: surface under the cumulative ranking curve

Kishimoto 2023: A SLR and a meta-analysis were conducted on RCTs that reported on the efficacy and safety/tolerability of antipsychotics as adjunctive treatment for adults with MDD. Data of both monotherapy and adjunctive antipsychotic use were extracted but analysed separately using a random-effects model**.** The key findings of this study are presented in section 8.2.2. Forest plots (Figure 8 and Figure 9) of the SLR and NMA have are presented below:

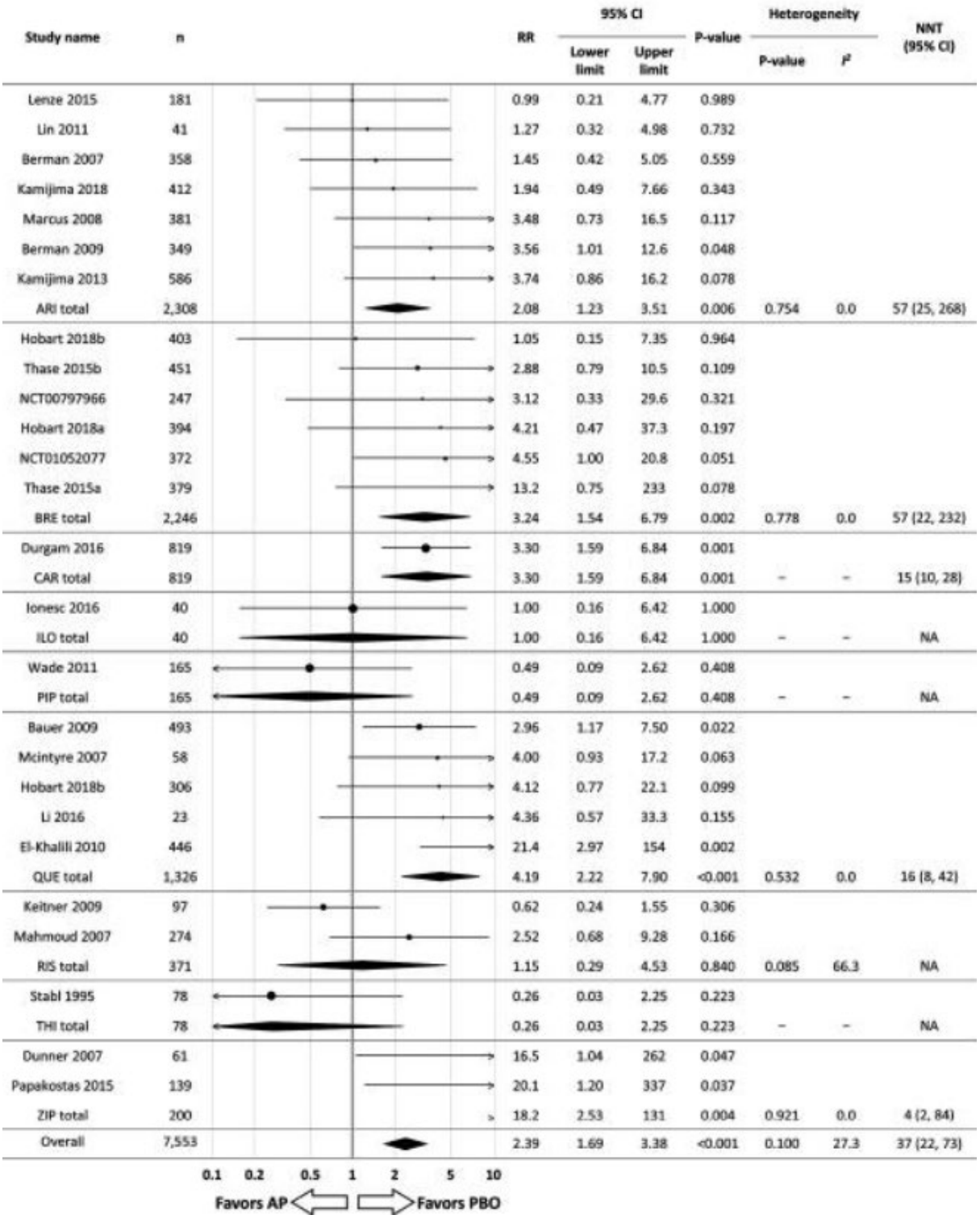
Figure 8: Antipsychotic drug adjunctive therapy vs. placebo for treatment response



Study name	n	RR	95% CI		P-value	Heterogeneity		NNT (95% CI)
			Lower limit	Upper limit		P-value	I^2	
Fava 2012 (Phase 1)	221	1.07	0.56	2.04	0.846			
Berman 2007	353	1.41	1.01	1.98	0.044			
Kamijima 2013	586	1.44	1.12	1.86	0.005			
Kamijima 2018	411	1.46	1.09	1.96	0.011			
Lin 2011	9	1.71	0.41	7.08	0.456			
Berman 2009	343	1.75	1.30	2.35	<0.001			
Marcus 2008	369	1.86	1.28	2.72	0.001			
Fava 2012 (Phase 2)	124	2.27	0.84	6.16	0.107			
ARI total	2,416	1.54	1.35	1.76	<0.001	0.763	0.0	9 (6, 13)
Hobart 2018a	393	1.15	0.88	1.51	0.298			
Thase 2015a	353	1.49	0.97	2.30	0.071			
NCT01052077	365	1.50	1.04	2.17	0.029			
Hobart 2018b	396	1.53	0.80	2.95	0.200			
Thase 2015b	416	1.61	1.06	2.44	0.025			
NCT00797966	244	1.75	1.14	2.69	0.011			
BRE total	2,167	1.41	1.21	1.66	<0.001	0.587	0.0	14 (9, 27)
Durgam 2016	808	1.27	1.07	1.52	0.007			
CAR total	808	1.27	1.07	1.52	0.007	-	-	10 (6, 31)
Ionesc 2016	26	1.00	0.44	2.29	1.000			
ILO total	26	1.00	0.44	2.29	1.000	-	-	
Parker 2005	20	2.00	0.88	4.54	0.098			
OLA total	20	2.00	0.88	4.54	0.098	-	-	
Hobart 2018b	304	1.18	0.51	2.73	0.693			
El-Khalili 2010	432	1.20	0.98	1.47	0.082			
Bauer 2009	487	1.22	1.01	1.48	0.040			
Quante 2013	36	1.23	0.65	2.32	0.521			
Li 2016	22	1.33	0.39	4.62	0.650			
Mcintyre 2007	58	2.00	0.95	4.22	0.069			
QUE total	1,339	1.23	1.08	1.41	0.002	0.888	0.0	15 (9, 42)
Mahmoud 2007	218	1.57	1.10	2.23	0.012			
Keitner 2009	95	1.65	0.97	2.80	0.067			
RIS total	313	1.59	1.19	2.14	0.002	0.884	0.0	6 (3, 18)
Stabl 1995	78	0.95	0.74	1.22	0.696			
THI total	78	0.95	0.74	1.22	0.696	-	-	
Papakostas 2015	139	1.71	0.97	3.00	0.062			
Dunner 2007	60	2.50	0.60	10.3	0.206			
ZIP total	199	1.80	1.07	3.04	0.028	0.626	0.0	7 (3, 83)
Overall	7,366	1.35	1.26	1.45	<0.001	0.440	1.6	12 (9, 16)

Source: *(148)*
Abbreviations: AP: antipsychotic drug; ARI: aripiprazole; BRE: brexpiprazole; CAR: cariprazine; CI: confidence interval; ILO: iloperidone; n: number of patients; NNT: number needed to treat; OLA: olanzapine; PBO: placebo; PIP: pipamperone; QUE: quetiapine; RIS: risperidone; RR: risk ratio; THI: thioridazine; ZIP: ziprasidone
Note: RR values >1 indicate superiority of antipsychotics compared to placebo for treatment response. NNTs for treatment response was calculated

Figure 9: Antipsychotic drug adjunctive therapy vs. placebo for discontinuation due to AE



Study name	n	RR	95% CI		P-value	Heterogeneity		NNT (95% CI)
			Lower limit	Upper limit		P-value	I^2	
Lenze 2015	181	0.99	0.21	4.77	0.989			
Lin 2011	41	1.27	0.32	4.98	0.732			
Berman 2007	358	1.45	0.42	5.05	0.559			
Kamijima 2018	412	1.94	0.49	7.66	0.343			
Marcus 2008	381	3.48	0.73	16.5	0.117			
Berman 2009	349	3.56	1.01	12.6	0.048			
Kamijima 2013	586	3.74	0.86	16.2	0.078			
ARI total	2,308	2.08	1.23	3.51	0.006	0.754	0.0	57 (25, 268)
Hobart 2018b	403	1.05	0.15	7.35	0.964			
Thase 2015b	451	2.88	0.79	10.5	0.109			
NCT00797966	247	3.12	0.33	29.6	0.321			
Hobart 2018a	394	4.21	0.47	37.3	0.197			
NCT01052077	372	4.55	1.00	20.8	0.051			
Thase 2015a	379	13.2	0.75	233	0.078			
BRE total	2,246	3.24	1.54	6.79	0.002	0.778	0.0	57 (22, 232)
Durgam 2016	819	3.30	1.59	6.84	0.001			
CAR total	819	3.30	1.59	6.84	0.001	-	-	15 (10, 28)
Ionesc 2016	40	1.00	0.16	6.42	1.000			
ILO total	40	1.00	0.16	6.42	1.000	-	-	NA
Wade 2011	165	0.49	0.09	2.62	0.408			
PIP total	165	0.49	0.09	2.62	0.408	-	-	NA
Bauer 2009	493	2.96	1.17	7.50	0.022			
Mcintyre 2007	58	4.00	0.93	17.2	0.063			
Hobart 2018b	306	4.12	0.77	22.1	0.099			
Li 2016	23	4.36	0.57	33.3	0.155			
El-Khalili 2010	446	21.4	2.97	154	0.002			
QUE total	1,326	4.19	2.22	7.90	<0.001	0.532	0.0	16 (8, 42)
Keitner 2009	97	0.62	0.24	1.55	0.306			
Mahmoud 2007	274	2.52	0.68	9.28	0.166			
RIS total	371	1.15	0.29	4.53	0.840	0.085	66.3	NA
Stabl 1995	78	0.26	0.03	2.25	0.223			
THI total	78	0.26	0.03	2.25	0.223	-	-	NA
Dunner 2007	61	16.5	1.04	262	0.047			
Papakostas 2015	139	20.1	1.20	337	0.037			
ZIP total	200	18.2	2.53	131	0.004	0.921	0.0	4 (2, 84)
Overall	7,553	2.39	1.69	3.38	<0.001	0.100	27.3	37 (22, 73)

Source: *(148)*
Abbreviations: AE: adverse events; AP: antipsychotic drug; ARI: aripiprazole; BRE: brexpiprazole; CAR: cariprazine; CI: confidence interval; ILO: iloperidone; n: number of patients; NNH: number needed to harm; OLA: olanzapine; PBO: placebo; PIP: pipamperone; QUE: quetiapine; RIS: risperidone; RR: risk ratio; THI: thioridazine; ZIP: ziprasidone
Note: RR values >1 indicate inferiority of antipsychotics compared to placebo for discontinuation due to adverse event. NNHs for discontinuation due to adverse event were calculated

Mishra 2022: A meta-analysis evaluating the effect of augmentation with SDAM drugs (aripiprazole and brexpiprazole) in patients with MDD with 15 RCTs identified and included in the meta-analysis. Primary analysis was presented with pooled results across SDAMs with subgroup analysis by each type of treatment. The key findings of the study are presented in section 8.2.2.The certainty of for the SLR and NMA is presented in evidence (Figure 10).

Figure 10: Summary of evidence and certainty of evidence for adjunctive SDAM drugs compared to placebo for MDD

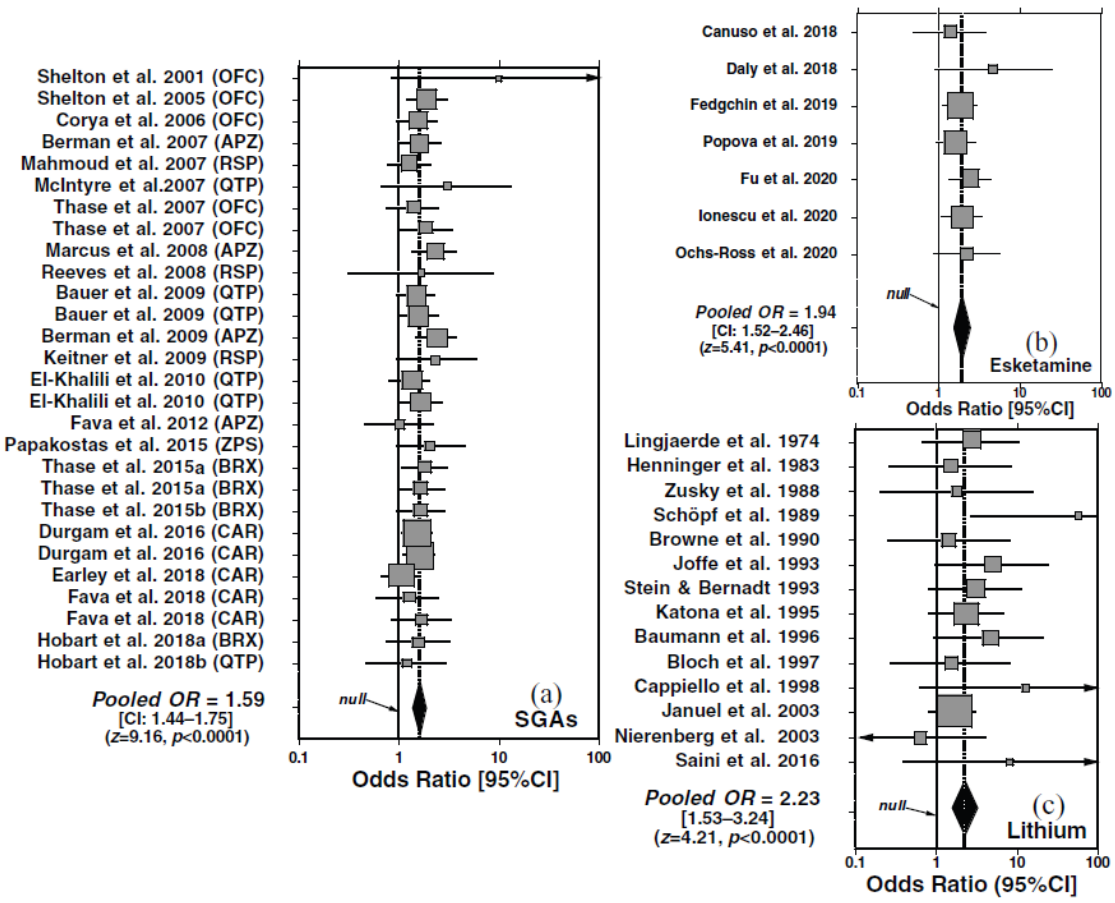
Patient or Population: Major Depressive Disorders; Setting: Clinical; Intervention: Serotonin-Dopamine Activity Modulators (Aripiprazole/Brexpiprazole); Comparison: Placebo

	Anticipated Absolute Effects[a] (95%CI)					
Outcomes	Risk With Placebo	Risk With SDAM	Relative Effect (95%CI)	No. of Participants (Studies)	Certainty of the Evidence (GRADE)	Comments
Remission	166 per 1000	236 per 1000(209 to 269)	OR 1.55(1.32- 1.84)	6570(15 RCTs)	⊕⊕⊕⊕HIGH	SDAM augmentation therapy increases remission when compared with ADT alone.
Remission—aripiprazole	183 per 1000	289 per 1000(254-329)	OR 1.82(1.52-2.19)	2671(8 RCTs)	⊕⊕⊕⊕HIGH	
Remission—brexpirazole	155 per 1000	201 per 1000(167-241)	OR 1.37(1.09-1.73)	3899(7 RCTs)	⊕⊕⊕⊕HIGH	
Response	203 per 1000	291 per 1000(268-316)	OR 1.62(1.44- 1.82)	6386(14 RCTs)	⊕⊕⊕⊕HIGH	SDAM augmentation therapy increases response in patients with MDD.
Response—aripiprazole	241 per 1000	369 per 1000(329-411)	OR 1.84(1.54-2.19)	2490(7 RCTs)	⊕⊕⊕⊕HIGH	
Response—brexpiprazole	177 per 1000	239 per 1000(211-269)	OR 1.46(1.24-1.71)	3896(7 RCTs)	⊕⊕⊕⊕HIGH	
MADRS		MD 2.01 higher(1.46 higher to 2.56 higher)	…	6555(14 RCTs)	⊕⊕⊕⊕HIGH	Adjunctive SDAM therapy causes an increased reduction in MADRS scores.
MADRS—aripiprazole		MD 2.65 higher(2.12 higher to 3.17 higher)	…	2659(7 RCTs)	⊕⊕⊕⊕HIGH	
MADRS—brexpiprazole		MD 1.56 higher(0.88 higher to 2.24 higher)	…	3896(7 RCTs)	⊕⊕⊕⊕HIGH	
CGI-S		MD 0.23 higher(0.1 higher to 0.36 higher)	…	6341(14 RCTs)	⊕⊕⊕⊕HIGH	Adjunctive SDAM therapy causes an increased reduction in CGI-S slightly.
CGI—aripiprazole		MD 0.32 higher(0.17 higher to 0.48 higher)	…	2483(7 RCTs)	⊕⊕⊕⊕HIGH	
CGI—brexpiprazole		MD 0.16 higher(0.08 higher to 0.24 higher)	…	3858(7 RCTs)	⊕⊕⊕⊕HIGH	
AE	469 per 1000	583 per 1000(548-618)	OR 1.58(1.37-1.83)	6794(14 RCTs)	⊕⊕⊕⊕HIGH	Adjunctive SDAM therapy has slightly increased chances of AEs.
AE—aripiprazole	514 per 1000	673 per 1000(616-726)	OR 1.95(1.52-2.51)	2796(7 RCTs)	⊕⊕⊕⊕HIGH	
AE—brexpiprazole	437 per 1000	516 per 1000(485-548)	OR 1.37(1.21-1.56)	3998(7 RCTs)	⊕⊕⊕⊕HIGH	
SAEs	18 per 1000	13 per 1000(9-20)	OR 0.72(0.48-1.08)	6452(13 RCTs)	⊕⊕⊕⊕HIGH	Adjunctive SDAM therapy results in little to no difference in SAEs.
SAEs—aripiprazole	12 per 1000	11 per 1 000(5-23)	OR 0.94(0.43-2.03)	2443(6 RCTs)	⊕⊕⊕⊕HIGH	
SAEs—brexpiprazole	22 per 1000	15 per 1000(9-24)	OR 0.65(0.40-1.05)	4009(7 RCTs)	⊕⊕⊕⊕HIGH	

Source: *(149)*
Abbreviations: AE: adverse event; CGI-S: clinical global impression–severity; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; MADRS: Montgomery-Asberg Depression Rating Scale; MD: mean difference; MDD: major depressive disorder; OR: odds ratio; RCT: randomised controlled trial; SAE: serious adverse event; SDAM: serotonin-dopamine activity modulator
Note: GRADE working group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. [a] The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

Vazquez 2021: SLR and NMA to compare efficacy and tolerability of combination treatments for MDD: ADTs + second-generation antipsychotics vs. ADTs + esketamine vs. ADT + lithium. The assessments and comparisons are based on meta-analysis to estimate and compare OR as well as NNT to indicate efficacy, and NNH arising from commonly clinically encountered adverse effects. The key findings of the study can be found in section 8.2.2. Forest plots of the SLR and NMA are presented in Figure 11.

Figure 11: Forest plots of random-effects meta-analyses for clinical trials testing the efficacy of supplementing antidepressants with active agents or placebo for major depression: (a) second-generation antipsychotics (SGAs, 28 trials), (b) intranasal esketamine, (c) lithium carbonate (13 trials)



Source: *(150)*
Abbreviations: APZ: aripiprazole; BRX: brexpiprazole; CAR: cariprazine; OFC: olanzapine + fluoxetine combination; QUE: quetiapine; OR: odds ratio; RSP: risperidone; SGA: second-generation antipsychotics; ZPS: ziprasidone

A.8 Clinical Guidelines and Recommendations

Clinical guidelines and Recommendation	Strength of recommendation
American Psychiatric Association (127) For those who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the ADT with a depression-focused psychotherapy [I] or with other agents [II] or changing to another non-MAOI ADT [I] Assessing the adequacy of treatment response augmentation of ADT medications can utilise another non-MAOI ADT [II], generally from a different pharmacological class, or a non-ADT medication such as lithium [II], thyroid hormone [II], or a second-generation antipsychotic [II]	[I] Recommended with substantial clinical confidence [II] Recommended with moderate clinical confidence [III] May be recommended on the basis of individual circumstances
American College of Physicians (156) ACP suggests one of the following options for patients in the acute phase of moderate to severe major depressive disorder who did not respond to initial treatment with an adequate dose of a second-generation ADT: • Switching to or augmenting with cognitive behavioural therapy (conditional recommendation; low-certainty evidence) • Switching to a different second-generation ADT or augmenting with a second pharmacologic treatment (second generation ADT augmentation, atypical antipsychotics, psychostimulants, levothyroxine, lithium) (conditional recommendation; low-certainty evidence) The informed decision on the options should be personalised and based on discussion of potential treatment benefits, harms, adverse effect profiles, cost, feasibility, patients' specific symptoms (such as insomnia, hypersomnia, or fluctuation in appetite), comorbidities, concomitant medication use, and patient preferences	**Certainty of evidence** Low: Confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Clinical guidelines and Recommendation	Strength of recommendation
British Association for Psychopharmacology (154) Consider adding a second agent especially if: -there is partial/insufficient response on the current antidepressant (D) and, -there is good tolerability of current antidepressant (D), -switching antidepressant has been unsuccessful (D). Consider adding quetiapine (A), aripiprazole (A) or lithium (A) as first-line treatments	**Strength of recommendation** A: directly based on category I evidence B: directly based on category II evidence or extrapolated recommendation from category I evidence C: directly based on category III evidence or extrapolated recommendation from category I or II evidence D: directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence S: standard of good practice

Clinical guidelines and Recommendation	Strength of recommendation
Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines *(128)* Strategies for poor response to an initial ADT include optimising the dose, switching to another ADT, adding an adjunctive medication, and incorporating psychological and/or neuromodulation treatments Adjunctive strategies, especially with atypical antipsychotic agents (serotonin and dopamine activity modulators), have greater evidence for efficacy and shorter time to response or remission, but they generally have a greater side effect burden than ADT monotherapy Brexpiprazole (1mg to 3 mg) is recommended as a first line adjunct treatment option nonresponse or partial response to an ADT (Level of evidence: Level 1)	**Criteria for level of evidence and line of treatment** Level of evidence: 1: Meta-analysis with narrow confidence intervals and/or 2 or more RCTs with adequate sample size, preferably placebo controlled 2: Meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size 3: Small-sample RCTs or non-randomised, controlled prospective studies or case series or high-quality retrospective studies 4: Expert opinion/consensus Line of treatment: First line: Level 1 or Level 2 Evidence, plus clinical support Second line: Level 3 Evidence or higher, plus clinical support Third line: Level 4 Evidence or higher, plus clinical support (Note that Level 1 and 2 Evidence refer specifically to treatment studies in which randomised comparisons are available. Recommendations involving epidemiological or risk factors primarily arise from observational studies, and hence the highest level of evidence is usually Level 3. Higher order recommendations (e.g., principles of care) reflect higher level judgement of the strength of evidence from various data sources and therefore are primarily Level 4 Evidence. Clinical support refers to application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are feasible and relevant to clinical practice. Therefore, treatments with higher levels of evidence may be downgraded to lower lines of treatment due to clinical issues such as side effects or safety profile)

Clinical guidelines and Recommendation	Strength of recommendation
NICE guidelines *(129)* If a person whose depression has had no response or a limited response to ADT medication does not want to try a psychological therapy, and instead wants to try a combination of medications, explain the possible increase in their side-effect burden If a person with depression wants to try a combination treatment and is willing to accept the possibility of an increased side-effect burden, consider referral to a specialist mental health setting or consulting a specialist. Treatment options include: Adding an additional ADT medication from a different class (for example, • adding mirtazapine or trazodone to an SSRI) • combining an ADT medication with a second-generation antipsychotic (for example, aripiprazole, olanzapine, quetiapine or risperidone) or lithium • augmenting ADTs with electroconvulsive therapy (see the recommendations on electroconvulsive therapy for depression), lamotrigine, or triiodothyronine (liothyronine) In June 2022, this was an off-label use for some antipsychotics, lamotrigine, and triiodothyronine (liothyronine)	NR

Clinical guidelines and Recommendation	Strength of recommendation
World Federation of Societies of Biological Psychiatry guidelines *(155)* The augmentation of ADTs with antipsychotics (quetiapine or aripiprazole) represents an alternative to lithium augmentation and is recommended in case monotherapy failed. Potential unwanted effects include sedation (quetiapine), weight gain (quetiapine, and to a lesser extent aripiprazole) and akathisia (aripiprazole) (CE: A, RG: 2) In patients with psychotic depression a combination of an ADT with an antipsychotic medication is recommended when treatment is initiated (CE: B, RG: 3)	**Category of Evidence (CE)** A: Full evidence from controlled studies is based on: 2 or more double-blind, parallel-group, RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo" in a study with adequate blinding) and 1 or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists) In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 2 more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment Recommendation Grade (RG) 1: Category A evidence and good risk – benefit ratio 2: Category A evidence and good risk – benefit ratio 3: Category B evidence 4: Category 5 evidence 5: Category D evidence
Royal Australian and New Zealand College of Psychiatrists *(157)* Second/third generation antipsychotics (Grade: consensus-based recommendation [CBR]) remain preferred options for augmentation in TRD Recommended AAPs with potent 5HT2A/2C receptor blockade: Aripiprazole, brexpiprazole, lurasidone, quetiapine, olanzapine, risperidone	CBRs: 1) The existing intervention evidence base was absent, ambiguous, or of doubtful clinical impact in the Australian and New Zealand context; and 2) The mood disorders committee (based on collective clinical and research knowledge and experience) reached consensus on the clinical utility of the recommendations

Clinical guidelines and Recommendation	Strength of recommendation
Malaysian clinical practice guidelines *(158)* In treatment treatment-resistant MDD the following strategies may be considered: • switching ADTs to a different class (Level I) • combination of ADTs (Level I) • augmentation with AAP/lithium/AED (Level I) Combination of ADT and antipsychotic should be considered in major depressive disorder with psychotic features (Level I)	**Levels of evidence:** I: Evidence from at least one properly randomised controlled trial II-1: Evidence obtained from well-designed controlled trials without randomisation II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group II-3: Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence III: Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

Abbreviations: AAP: atypical antipsychotics; ACP: American College of Physicians; ADT: antidepressant treatment; AED: antiepileptic drugs; BAP: British Association for Psychopharmacology; CANMAT: Canadian Network for Mood and Anxiety Treatments; CBR: consensus-based recommendation; CE: category of evidence; EML: Essential Medicines List; FDA: Food and Drug Administration; HRQoL: health-related quality of life; LMICs: low- and middle-income countries; MaHTAS: Malaysian Health Technology Assessment Section; MDD: major depressive disorder; MAOI: monoamine Oxidase Inhibitors; mhGAP: Mental Health Gap Action Programme; NICE: National Institute for Health and Care Excellence; NR: not reported; RCT: randomised controlled trial; RG: recommendation grade; SDS: Sheehan Disability Scale; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression; WFSBP: World Federation of Societies of Biological Psychiatry