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## Brazilian Psychiatric Association Guidelines for pharmacological treatment of Major Depressive Disorder: An overview of systematic reviews and meta-analyses

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# Brazilian Psychiatric Association Guidelines for pharmacological treatment of major depressive disorder: an overview of systematic reviews and meta-analyses

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## Abstract

**Objective:** To synthesize evidence on pharmacological treatments for major depressive disorder (MDD) to inform updated Brazilian clinical guidelines.

**Methods:** This overview included systematic reviews and meta-analyses published in the last 10 years, identified through MEDLINE, Cochrane Library, and SciELO. Eligible studies involved adults with MDD receiving pharmacological interventions. Risk of bias was assessed using ROBIS,

methodological quality using AMSTAR 2, and certainty of evidence using the GRADE approach.

**Results:** Forty studies were included. In acute treatment, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, mirtazapine, and vortioxetine showed consistent evidence across efficacy and tolerability outcomes. For adjunctive treatment, atypical antipsychotics demonstrated the highest certainty of evidence, with short-term support for benzodiazepines. In treatment-resistant depression, ketamine, esketamine, and atypical antipsychotic augmentation showed moderate certainty for response outcomes. In the maintenance phase, SSRIs and SNRIs were associated with the most consistent evidence for relapse prevention and acceptability.

**Conclusion:** These findings support a hierarchy of pharmacological strategies across different stages of MDD. Although consistent with international guidelines, their implementation should consider local healthcare context and resource availability.

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## Introduction

Depressive disorder is a highly prevalent mental condition, affecting approximately 280 million individuals worldwide. In Brazil, data from the most recent National Health Survey indicate a lifetime prevalence of 10.8%.[1] This disorder results from a complex interplay of social, psychological, and biological factors,[2] and is frequently characterized by a chronic or recurrent course that profoundly compromises daily functioning, social relationships, self-perception, and the individual's understanding of the surrounding world.[3-6] Consequently, depressive disorder represents one of the leading global public health challenges, constituting a major cause of work absenteeism and disability, as well as one of the most significant risk factors for suicide.[3-6]

Although several internationally recognized clinical practice guidelines are currently available, such as those developed by the American Psychiatric Association (APA),[7] the National Institute for Health and Care Excellence (NICE)[8], the Canadian Network for Mood and Anxiety Treatments (CANMAT)[9], the Royal Australian and New Zealand College of Psychiatrists (RANZCP)[10], and the World Federation of Societies of Biological Psychiatry (WFSBP),[11] their direct transposition across different health systems remains limited.

Methodological heterogeneity, sociocultural variability, inequalities in access to therapeutic resources, and the continuous emergence of new scientific evidence underscore the need for contextual adaptation to ensure clinical relevance and feasibility in specific settings.

In Brazil, national guidelines for the management of depressive disorders were initially published in 2001.[12] Subsequently they were updated in 2003 and 2009.[13,14] However, substantial advances in psychopharmacology, psychotherapy research, neurobiological understanding, and methodological approaches to evidence synthesis have occurred since these publications. Given the high prevalence of depressive disorders and their considerable burden on public health, it is imperative to develop updated national guidelines that not only incorporate contemporary evidence but also address gaps and limitations identified in previous recommendations.

Furthermore, the expanding body of knowledge regarding treatment efficacy, safety profiles, and integrated or augmented therapeutic strategies demands systematic review and rigorous synthesis. Such efforts are essential to support more precise clinical decision-making, reduce variability in clinical practice, and ultimately improve outcomes for individuals affected by depressive disorders. Beyond convergence with international guidelines, the development of truly national recommendations requires the explicit incorporation of the sociocultural and structural specificities of the Brazilian healthcare system. In this context, adaptation to the realities of the SUS, including medication availability within RENAME, regional inequalities, and organizational barriers to implementation, is a decisive step to ensure the applicability, equity, and effective clinical translatability of guidelines in Brazil.

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## Methods

### Eligibility criteria

Only meta-analyses and systematic reviews were included. Exclusion criteria encompassed observational studies, case series, editorials, research protocols, pooled analyses, randomized clinical trials, and non-systematic reviews. All searches were restricted to studies published within the last 10 years, in English, Portuguese, or Spanish, involving adult populations (≥18 years).

The study selection was guided by the PICO framework: population (adults with major depressive disorder), intervention (pharmacological treatments), comparator (placebo or other drugs), outcomes (response, remission, tolerability, adverse effects, and dropout rates), and study design (systematic reviews and meta-analyses).

Studies involving bipolar depression, pseudodementia, dysthymia, and depression in special situations were also excluded.

The review protocol was registered in PROSPERO (CRD 420250656413).

**Subjects**

Adults over 18 years diagnosed with major depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria. Male and female participants.[15,16]

**Types of interventions**

The study compared pharmacotherapy to placebo or other drugs.

**Information sources**

A systematic literature search was conducted in MEDLINE (via PubMed), the Cochrane Library, and SciELO.

*Selection criteria (screening)*

In MEDLINE, the search strategy combined Medical Subject Headings (MeSH) and free-text terms. The MeSH terms **"**Depressive Disorder, Major**"** and **"**Drug Therapy**"** were used, together with the free-text terms "Depression", "Major Depression"**,** "Unipolar Depression"**,** "Pharmacotherapy**"**, and "Antidepressants". These terms were combined using Boolean operators (OR within concept groups and AND between concept groups). Filters were applied to restrict results to systematic reviews and meta-analyses**,** human studies**,** adult populations (≥18 years)**,** and publications from the last 10 years**.**

In the Cochrane Library, searches were performed using the terms "depression", "major depressive disorder" OR "unipolar depression", combined

with **"**pharmacotherapy" OR **"**antidepressants", with results limited to review articles involving adult populations.

In SciELo, searches were conducted using the Portuguese terms "depressão","transtorno depressivo maior" OR "depressão maior"**,** combined with "tratamento farmacológico" OR "antidepressivos"**,** with filters applied for systematic reviews and meta-analyses published within the last 10 years.

*Selection process*

Three independent authors (MPMA, JDG, and MVL) screened titles and abstracts for relevance. Discrepancies were resolved through consultation with a fourth author (LB). For details of the flow diagram see figure S1.

**Risk of bias assessment**

The Risk of Bias in Systematic Reviews (RoBIS) tool was applied to assess bias risk, supplemented by conflict of interest analyses. Studies with high bias risk were excluded.[17] For details see figure S2.

**Quality assessment**

The remaining studies were evaluated using A Measurement Tool to Assess Systematic Reviews (AMSTAR 2), with studies of critically low quality excluded. [18]

**Data items (outcomes and measures)**

The main outcome measure was the treatment effectiveness (rates of response and remission symptoms as measured by the scale adopted during the proposed treatment). The most commonly used scales were the Hamilton Rating Scale for Depression (HDRS) and the Montgomery–Åsberg Depression Rating Scale (MADRS). Response was generally defined as a ≥50% reduction in baseline depression scale scores (HDRS or MADRS), while remission was most commonly defined as HDRS ≤7 or MADRS ≤10, although definitions varied across studies.

The secondary outcomes measured included tolerability, side effects, and rates of dropout.[19,20]

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**Data collection process (eligibility)**

A total of 905 articles were identified for screening; 826 were excluded after assessing titles or abstracts. 79 articles were assessed for eligibility and fully read; 19 were excluded because they did not meet the criteria. The remaining 60 articles were assessed using the ROBIS, and 12 were excluded due to a high risk of bias, while studies with moderate risk were retained and considered in the certainty of evidence assessment. Subsequently, the remaining 48 studies were assessed using the AMSTAR2 tool, excluding 8 due to a critically low level of quality. The final analysis included 40 articles.

The study selection flowchart, designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, is presented in Supplementary Figure S1.21

Studies excluded after full-text assessment, including those excluded due to high risk of bias (ROBIS) and critically low methodological quality (AMSTAR 2), are detailed in Supplementary Table S2 with reasons for exclusion.

**Synthesis and evidence**

During the evidence synthesis process, authors MPMA, JDG, and MVL conducted a full-text review of the eligible studies, critically appraised the evidence, extracted key findings, and assessed the strength of the available data.

The certainty of evidence and the strength of recommendations were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach**,** considering the methodological quality of the included studies, consistency and magnitude of effect estimates, precision of the results, and clinical relevance of outcomes.

Although no formal quantitative assessment of overlap (e.g., corrected covered area) was performed, potential overlap between included meta-analyses was considered during data interpretation. A qualitative synthesis approach was adopted to minimize double counting of evidence and avoid overestimation of treatment effects.

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## Results

We identified and included 40 articles in the final review, addressing different pharmacological interventions. Supplementary Table S1 presents the description of the included studies, while Supplementary Table S2 lists the studies excluded after full-text analysis. Figure S2 presents the risk of bias assessment using the ROBIS tool. All included studies and supplementary materials were cross-checked to ensure full consistency in study classification across the manuscript.

### 1. Monotherapy

About antidepressants, 17 studies were selected, Cipriani et al. 2018 (AMSTAR 2 High), Jakobsen et al. 2017 (AMSTAR 2 High), Wagner et al. 2018 (AMSTAR 2 Moderate), Guo et al. 2020 (AMSTAR 2 Low), Maneeton et al. 2013 (AMSTAR 2 Low), Wang et al. 2013 (AMSTAR 2 Low), Berhan et al. 2014 (AMSTAR 2 Low),Thase et al. 2016 (AMSTAR 2 Low), Meeker et al. 2015 (AMSTAR 2 Low), Koester et al. 2017 (AMSTAR 2 High), Llorca et al. 2014 (AMSTAR 2 Low), Yang X et al. 2024 (AMSTAR 2 Low), Koesters M et al. 2013 (AMSTAR 2 High), Guaiana G et al.2013 (AMSTAR 2 High), Huang KL et al. 2014 (AMSTAR 2 Moderate), Thase et al. 2017 (AMSTAR 2 Low) and Kamp CB et al.2024 (AMSTAR 2 Low).[22-38] For more details see Table S1.

The GRADE classification was used to create the recommendation hierarchy. In terms of response, the best options were SSRIs, venlafaxine (which includes desvenlafaxine), mirtazapine, vortioxetine and agomelatine. Regarding remission, the recommended improvement was moderate for mirtazapine and vortioxetine.

In terms of tolerability, most antidepressants showed moderate certainty of evidence, particularly SSRIs, venlafaxine, mirtazapine, vortioxetine, agomelatine, desvenlafaxine, bupropion, vilazodone, trazodone, duloxetine, milnacipran, levomilnacipran, reboxetine and nefazodone, whereas tricyclic antidepressants showed lower certainty.

Regarding side effects, the certainty of evidence was predominantly low across antidepressants, with moderate-low certainty observed for mirtazapine and low certainty for most other agents, including SSRIs, SNRIs and multimodal antidepressants.

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In terms of dropout rates, moderate certainty was observed for SSRIs, venlafaxine, mirtazapine, vortioxetine, agomelatine and several newer antidepressants, while tricyclic antidepressants and some individual agents such as bupropion and levomilnacipran showed lower certainty.

Considering all variables together response, remission, tolerability, side effects and dropout the moderate to high certainty of evidence was observed for mirtazapine, vortioxetine and SSRIs across multiple clinically relevant outcomes.

For non-antidepressant agents, 5 studies were included, Yao et al. 2020 (AMSTAR 2 Low), Galizia et al. 2016 (AMSTAR 2 High), Appleton et al. 2016; 2021 (AMSTAR 2 High) and Luo et al. 2020 (AMSTAR 2 Low).[39-43] For more details see Table S1.

The certainty of evidence was generally lower across outcomes. Riluzole showed low certainty for response and remission, with moderate certainty for tolerability, side effects and dropout rates, indicating some consistency in safety outcomes but limited confidence in efficacy measures. S-Adenosyl-L-Methionine (SAMe) demonstrated low certainty across all evaluated domains, including response, remission, tolerability, side effects and dropout. Omega-3 fatty acids presented low certainty for response and remission and very low certainty for tolerability, adverse effects and dropout rates.

Overall, when considering all evaluated variables, these non-antidepressant agents showed lower certainty of evidence across efficacy outcomes compared with standard antidepressants.

Table 1 presents the GRADE assessment of primary and secondary clinical outcomes for pharmacological monotherapy in major depressive disorder.

**Table 1.** Certainty of evidence (GRADE) for primary and secondary clinical outcomes for pharmacological monotherapy in MDD

| Drug Class / Medication | Response | Remission | Tolerability | Side effects | Drop outs |
|---|---|---|---|---|---|
| SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) | High | Low | Moderate | Low | Moderate-Low |
| Venlafaxine | High | Low | Moderate | Low | Moderate |
| Mirtazapine | High | Moderate | Moderate | Moderate-Low | Moderate |
| Vortioxetine | High | Moderate- | Moderate | Low | Moderate |



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| | | | | | |
|---|---|---|---|---|---|
| | | Low | | | |
| Agomelatine | High-moderate | Low | Moderate | Low | Moderate |
| Desvenlafaxine | Moderate-Low | Low | Moderate | Low | Moderate |
| TCAs (amitriptiline/clomipramine) | Moderate-Low | Low | Low | Low | Low |
| Bupropion | Moderate-Low | Low | Moderate | Low | Low |
| Vilazodone | Moderate-Low | Low | Moderate | Low | Moderate |
| Trazodone | Moderate-Low | Low | Moderate | Low | Moderate |
| Duloxetine | Moderate-Low | Low | Moderate | Low | Moderate |
| Milnacipran | Low | Low | Moderate | Low | Moderate |
| Levomilnacipran | Low | Low | Moderate | Low | Low |
| Reboxetine | Low | Low | Moderate | Low | Moderate |
| Nefazodone | Low | Low | Moderate | Low | Moderate |
| Riluzole | Low | Low | Moderate | Moderate | Moderate |
| SAMe | Low | Low | Low | Low | Low |
| Omega-3 | Low | Low | Very Low | Very Low | Very Low |

**2. Adjunctive treatments (add-on):**

Regarding adjunctive treatment, 5 studies were included, Köhler-Forsberg O et al. 2019 (AMSTAR 2 Low), Jeuring HW et al. 2023 (AMSTAR 2 Low), Kishi et al. 2017 (AMSTAR 2 Low), Ogawa et al. 2019 (AMSTAR 2 High), and Wen XJ et al. 2014 (AMSTAR 2 High).[44-48] For more details see Table S1.

In terms of response, the moderate certainty of evidence was observed for atypical antipsychotics and short-term benzodiazepine use (early phase ≤ 4 weeks), both with moderate certainty, while Z-drugs, anti-inflammatory agents and dopamine-stimulating agents showed low certainty.

Regarding remission, moderate certainty was observed for atypical antipsychotics and Z-drugs, whereas benzodiazepines showed low certainty and dopamine-stimulating agents showed very low certainty. However, all Z-drug studies included in the analysis had short trial durations (mean approximately 10.5 weeks), and it was not possible to determine whether Z-drugs have sustained long-term effects on depressive symptoms, including insomnia.

In terms of tolerability, moderate certainty was found only for early-phase benzodiazepine use, while atypical antipsychotics, Z-drugs, anti-inflammatory agents and dopamine-stimulating agents showed low certainty of evidence.

Regarding side effects, moderate certainty was observed for benzodiazepines in early-phase use, whereas all other adjunctive classes demonstrated low certainty and in terms of dropout rates, moderate certainty

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was again limited to early-phase benzodiazepines, with low certainty across the remaining adjunctive treatment classes.

Following the application of the GRADE framework to establish a recommendation hierarchy for adjunctive pharmacological treatment, and considering all variables together response, remission, tolerability, side effects and dropout the moderate certainty of evidence was observed for atypical antipsychotics and short-term benzodiazepines (for anxiety and insomnia) across efficacy and safety outcomes, whereas Z-drugs (for insomnia) showed intermediate recommendation strength and anti-inflammatory and dopamine-stimulating agents showed the lowest overall recommendation levels.

Table 2 presents the GRADE assessment of primary and secondary clinical outcomes for pharmacological adjunctive treatments in major depressive disorder (MDD).

**Table 2.** Certainty of evidence (GRADE) for primary and secondary clinical outcomes of pharmacological adjunctive treatments in MDD

| Drug Class / Medication | Response | Remission | Tolerability | Side effects | Drop outs |
|---|---|---|---|---|---|
| Atypical antipsychotics (aripiprazole, quetiapine, olanzapine, risperidone) | Moderate | Moderate | Low | Low | Low |
| Benzodiazepines* Early phase (≤ 4 weeks) | Moderate | Low | Moderate | Moderate | Moderate |
| Z-drugs** | Low | Moderate | Low | Low | Low |
| Anti-inflammatory agents | Low | Low | Low | Low | Low |
| Dopamine-stimulating agents | Low | Very Low | Low | Low | Low |

* For insomnia and anxiety in short-term. ** For insomnia in short-term.

## 3. Treatment-resistant depression

A total of 12 studies evaluating pharmacological augmentation strategies in treatment-resistant depression were identified and included in the analysis, Terao et al. 2024 (AMSTAR 2 High), Caddy et al. 2015 (AMSTAR 2 High), Dean et al. 2021 (AMSTAR 2 High), Ng J et al. 2021 (AMSTAR 2 Low), Edwards et al. 2021 (AMSTAR 2 High), Furukawa et al. 2022[a], Furukawa et al. 2022[b] (AMSTAR 2 Moderate), Zhou et al. 2015 (AMSTAR 2 High), Seshadri et al. 2021 (AMSTAR 2 Low), Goh et al. 2019 (AMSTAR 2 High), Liu et al. 2015 (AMSTAR 2 Moderate), and Nunes et al. 2022 (AMSTAR 2 High).[49-60] Further details are provided in Table S1.

BJP PRE-PROOF

In terms of response, moderate certainty of evidence was observed for ketamine (IV racemic), intranasal esketamine, aripiprazole, brexpiprazole, quetiapine (both dosage ranges), olanzapine/fluoxetine combination, lithium, liothyronine (T3), lamotrigine and modafinil (moderate–low). In contrast, risperidone, lisdexamfetamine, pindolol and adjunctive antidepressants demonstrated low certainty.

Regarding remission, moderate certainty was observed for aripiprazole, brexpiprazole, both quetiapine dose ranges and olanzapine/fluoxetine, whereas ketamine, esketamine, lithium, T3, lamotrigine and pindolol showed low certainty. Remission outcomes were not reported (NR) for modafinil and lisdexamfetamine.

In terms of tolerability, moderate certainty was observed for aripiprazole, brexpiprazole, both quetiapine dose ranges, olanzapine/fluoxetine, lamotrigine and pindolol, while most other agents demonstrated low certainty.

Regarding side effects, moderate certainty was found for lamotrigine and pindolol, whereas the remaining augmentation strategies showed low certainty and in terms of dropout rates, moderate certainty was observed for quetiapine (250–350 mg/day), lamotrigine and pindolol, while most other agents demonstrated low certainty of evidence.

Considering all evaluated variables together response, remission, tolerability, side effects and dropout the moderate certainty of evidence was observed for aripiprazole, brexpiprazole, quetiapine (particularly in both evaluated dose ranges) and the olanzapine/fluoxetine combination across efficacy and tolerability outcomes. Ketamine and esketamine showed moderate certainty for response but lower certainty across safety and remission outcomes, while lithium, T3, lamotrigine and other agents demonstrated more variable or lower overall certainty.

Table 3 presents the GRADE assessment of primary and secondary clinical outcomes for pharmacological treatments in treatment resistant depression (TRD).

BJP PRE-PROOF

**Table 3.** Certainty of evidence (GRADE) for primary and secondary clinical outcomes of pharmacological augmentation strategies in treatment-resistant depression (TRD)

| Drug Class / Medication | Response | Remission | Tolerability | Side effects | Drop outs |
|---|---|---|---|---|---|
| Ketamine (IV, racemic) | Moderate | Low | Low | Low | Low |
| Esketamine (intranasal) | Moderate | Low | Low | Low | Low |
| Aripiprazole | Moderate | Moderate | Moderate | Low | Low |
| Brexpiprazole | Moderate | Moderate | Moderate | Low | Low |
| Quetiapine (150–250 mg/day) | Moderate | Moderate | Moderate | Low | Low |
| Quetiapine (250–350 mg/day) | Moderate | Moderate | Moderate | Low | Moderate |
| Olanzapine/fluoxetine | Moderate | Moderate | Moderate | Low | Low |
| Risperidone | Low | Low | Low | Low | Low |
| Lithium | Moderate | Low | Low | Low | Low |
| T3 (liothyronine) | Moderate | Low | Low | Low | Low |
| Lamotrigine | Moderate | Low | Moderate | Moderate | Moderate |
| Modafinil | Moderate-Low | NR | Low | NR | Low |
| Lisdexamfetamine | Low | NR | Low | NR | Low |
| Pindolol | Low | Low | Moderate | Moderate | Moderate |
| Antidepressants (amitriptyline, nortriptyline, bupropion, mirtazapine, buspirone) | Low | Low | Low | Low | Low |
| Long-term aripiprazole augmentation (≥ 6 months) | Low | Low | Low | Low | Low |

NR = not reported.

## 4. Maintenance Phase

A 2023 network meta-analysis by Kishi et al. 2023 (AMSTAR 2 Moderate), evaluated 6-month relapse prevention across 15 antidepressants, including amitriptyline, citalopram, desvenlafaxine, duloxetine, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, reboxetine, sertraline, tianeptine, venlafaxine, and vortioxetine.[61] For more details see Table S1.

Overall, the strongest evidence for relapse prevention was observed for SSRIs, SNRIs and atypical antidepressants, all of which reached moderate certainty, whereas tricyclic antidepressants, melatonergic antidepressants and other less established antidepressant agents showed lower certainty levels.

A similar pattern was observed for acceptability outcomes, with SSRIs and SNRIs presenting moderate certainty and atypical antidepressants showing low- moderate certainty, while the remaining classes were supported only by low-certainty evidence.

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When tolerability and side-effect profiles were examined, the certainty of evidence was uniformly low across all antidepressant classes, indicating limited confidence in comparative safety differences during long-term use.

Regarding treatment discontinuation, SSRIs and SNRIs again demonstrated more favorable evidence, with moderate certainty, whereas atypical antidepressants reached low–moderate certainty and the remaining classes remained supported by low certainty evidence.

Taken together, the overall GRADE profile suggests that SSRIs and SNRIs represent the most consistently supported options for maintenance treatment, combining moderate certainty for relapse prevention and acceptability with more stable dropout outcomes. Atypical antidepressants occupy an intermediate position, while tricyclic antidepressants, melatonergic antidepressants and other agents with limited evidence demonstrated lower overall recommendation strength.

Table 4 presents the GRADE assessment of clinical outcomes for antidepressants classes in the maintenance treatment in major depression disorder.

**Table 4.** Certainty of evidence (GRADE) for antidepressant classes in the maintenance treatment of major depressive disorder

| Drug Class/Medication | Relapse prevention | Acceptability | Tolerability | Side effects | Drop outs |
|---|---|---|---|---|---|
| SSRIs<br>citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline | Moderate | Moderate | Low | Low | Moderate |
| SNRIs<br>desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine | Moderate | Moderate | Low | Low | Moderate |
| Atypical antidepressants<br>bupropion, mirtazapine, nefazodone, reboxetine, tianeptine, vortioxetine, vilazodone | Moderate | Low-Moderate | Low | Low | Low-Moderate |
| Tricyclic antidepressants (TCAs)<br>amitriptyline | Low | Low | Low | Low | Low |
| Melatonergic antidepressant<br>agomelatine | Low | Low | Low | Low | Low |
| Other antidepressants<br>agents with limited or inconsistent maintenance data | Very Low | Low | Low | Low | Low |

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## Discussion

This review applied the GRADE framework to evaluate the certainty of evidence across acute treatment, adjunctive strategies, treatment-resistant depression, and maintenance phase interventions, aiming to support the update of Brazilian clinical guidelines for the pharmacological treatment of major depressive disorder. The findings demonstrate substantial concordance with major international clinical guidelines, including NICE (2022), CANMAT (2023), RANZCP (2020), WFSBP (2013), and APA (2010) recommendations.[7-11] However, important nuances emerge when certainty of evidence across multiple clinically relevant outcomes when efficacy, tolerability, safety and treatment discontinuation is considered simultaneously.

Importantly, the presence of moderate to high risk of bias in several included systematic reviews, particularly in the domains of data collection and synthesis, may have influenced the certainty of evidence and should be considered when interpreting the strength of recommendations.

In the acute treatment phase, the higher recommendation strength observed for SSRIs and selected newer antidepressants, such as mirtazapine and vortioxetine, aligns with international guidance emphasizing antidepressants as first-line biological treatments for moderate to severe depressive episodes. The WFSBP[11] guideline identifies antidepressants as the cornerstone pharmacological intervention and highlights that no single antidepressant class consistently demonstrates clear superiority in efficacy, while differences in tolerability and safety frequently guide clinical decision-making. Similarly, NICE [8] adopts a patient-centered and shared decision-making model, emphasizing treatment selection based on effectiveness, adverse-event profile and individual preference rather than strict class hierarchy. This approach is consistent with the present GRADE findings, in which several agents demonstrate comparable efficacy but differ in tolerability and dropout outcomes, ultimately influencing their overall recommendation strength.

Regarding adjunctive pharmacological treatment, the GRADE hierarchy favoring atypical antipsychotic augmentation is coherent with contemporary recommendations. The RANZCP[10] framework describes augmentation and switching as key strategies following insufficient response to first-line therapy,

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integrating dose optimization, switching and augmentation within a structured clinical pathway. Likewise, NICE[8] recommends consideration of oral antipsychotics or lithium as augmentation options in individuals who fail to achieve adequate response. The current findings reinforce these recommendations by demonstrating higher certainty across response and remission outcomes for antipsychotic augmentation compared with other adjunctive strategies. Importantly, although short-term evidence suggested potential benefits for hypnotic agents such as Z-drugs, the limited duration of available studies and lack of long-term data support a cautious interpretation, consistent with guideline recommendations emphasizing short-term and symptom-targeted use rather than sustained augmentation strategies.

In treatment-resistant depression, the evidence synthesis showed stronger recommendations for glutamatergic modulation, particularly ketamine and esketamine, as well as for atypical antipsychotic augmentation, reflecting recent developments in international guidelines. The RANZCP[10] guideline recognizes ketamine as a rapid-acting intervention in resistant depression, particularly for acute symptom reduction, while also emphasizing limitations related to durability of effect, safety considerations and long-term outcomes. The observed superiority of intravenous ketamine for short-term antidepressant response compared with intranasal esketamine or some augmentation strategies supports this emerging clinical positioning, characterized by robust acute efficacy but limited certainty regarding long-term benefit. Findings related to antipsychotic augmentation further parallel NICE[8] recommendations that include oral antipsychotics and lithium among further-line interventions for resistant depression. In addition, WFSBP[11] guidelines acknowledge that a substantial proportion of patients fail to achieve remission with first-line therapy and therefore support optimization strategies including augmentation and switching, reinforcing the relevance of multi-step treatment algorithms in clinical practice.

During the maintenance phase, SSRIs and SNRIs demonstrated the most consistent certainty across relapse prevention and acceptability outcomes. This pattern closely reflects guideline consensus emphasizing continuation and maintenance treatment to prevent relapse and recurrence. NICE[8] explicitly frames relapse prevention as a core component of long-term depression

BJP PRE-PROOF

management, recommending continued treatment and monitoring based on individual risk and previous illness course. Similarly, WFSBP[11] distinguishes acute, continuation and maintenance phases, highlighting maintenance treatment as essential to reduce recurrence and preserve long-term functioning. The predominance of SSRIs and SNRIs in the present GRADE synthesis likely reflects their favorable balance between efficacy, acceptability and long-term tolerability, factors consistently prioritized in guideline-based treatment planning.

From a broader clinical perspective, the comparison between GRADE-based evidence synthesis and international guideline recommendations highlights a largely convergent treatment framework across different stages of major depressive disorder.

While guidelines provide algorithmic and clinically pragmatic recommendations, the GRADE approach offers an additional quantitative dimension by integrating efficacy, tolerability, safety and treatment discontinuation into a unified hierarchy of recommendation. This multidimensional assessment helps clarify why some interventions widely used in clinical practice may receive lower overall recommendation strength when broader clinical outcomes are considered.

Overall, the findings reinforce the role of SSRIs and SNRIs as foundational pharmacological treatments across acute and maintenance phases, support the use of atypical antipsychotic augmentation in cases of insufficient response or resistance, and position ketamine-based approaches as promising yet primarily short-term interventions requiring further long-term evaluation.

Although the present findings demonstrate substantial concordance with major international clinical guidelines, their direct applicability to the Brazilian context requires careful considerations. In the Brazilian Unified Health System (SUS), the availability of pharmacological treatments for major depressive disorder is primarily guided by the National List of Essential Medicines (RENAME). Based on the results of this guideline, new medications may be incorporated into that list.

First-line antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are widely accessible and therefore represent the most feasible initial treatment options in public healthcare settings. In contrast, newer

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antidepressants and augmentation strategies, including agents such as vortioxetine, agomelatine, and esketamine, have limited availability in the public system, which may restrict their real-world applicability despite favorable evidence profiles. Additionally, regional disparities in healthcare access, differences in prescribing practices, and socioeconomic factors may further influence treatment selection and adherence.

Therefore, the translation of GRADE-based recommendations into clinical practice in Brazil should be adapted to local resource availability, healthcare infrastructure, and patient-specific factors.

Beyond reproducing existing guideline recommendations, the present study contributes by integrating a multidimensional GRADE-based synthesis across efficacy, tolerability, safety, and treatment discontinuation outcomes, allowing a more comprehensive and clinically applicable hierarchy of pharmacological strategies.

**Limitations**

This study has several limitations. First, potential overlap between included meta-analyses may have resulted in partial redundancy of evidence, which is a recognized limitation of umbrella reviews and may lead to overestimation of treatment effects. Second, although studies with high risk of bias and critically low methodological quality were excluded, several included studies presented moderate risk of bias, particularly in data synthesis and reporting domains, which may influence the certainty of the findings. Third, variability in outcome definitions and reporting across studies may limit comparability between interventions. Additionally, the narrative nature of the synthesis, although structured by the GRADE framework, may introduce interpretative bias when compared to fully quantitative pooled analyses.

Finally, the applicability of findings to the Brazilian context is influenced by differences in healthcare access, medication availability, and system-level constraints, which may limit the direct implementation of some recommendations.

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## Conclusion

This study provides a comprehensive GRADE-based synthesis of pharmacological treatments for major depressive disorder across different stages of illness. The findings reinforce the central role of antidepressants, particularly SSRIs and SNRIs, while supporting the use of adjunctive strategies, especially atypical antipsychotics and ketamine and esketamine in cases of insufficient response or treatment resistance.

Although overall effect sizes remain modest, the integration of efficacy, tolerability, safety, and treatment discontinuation outcomes provides a more clinically relevant framework for individualized treatment selection.

Importantly, the translation of these findings into clinical practice requires adaptation to local healthcare systems. In Brazil, factors such as medication availability within the public health system and regional disparities must be considered when applying evidence-based recommendations.

Future research should prioritize high-quality studies with standardized outcomes, longer follow-up periods, and approaches that incorporate biological and clinical stratification to support precision psychiatry.

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BJP PRE-PROOF

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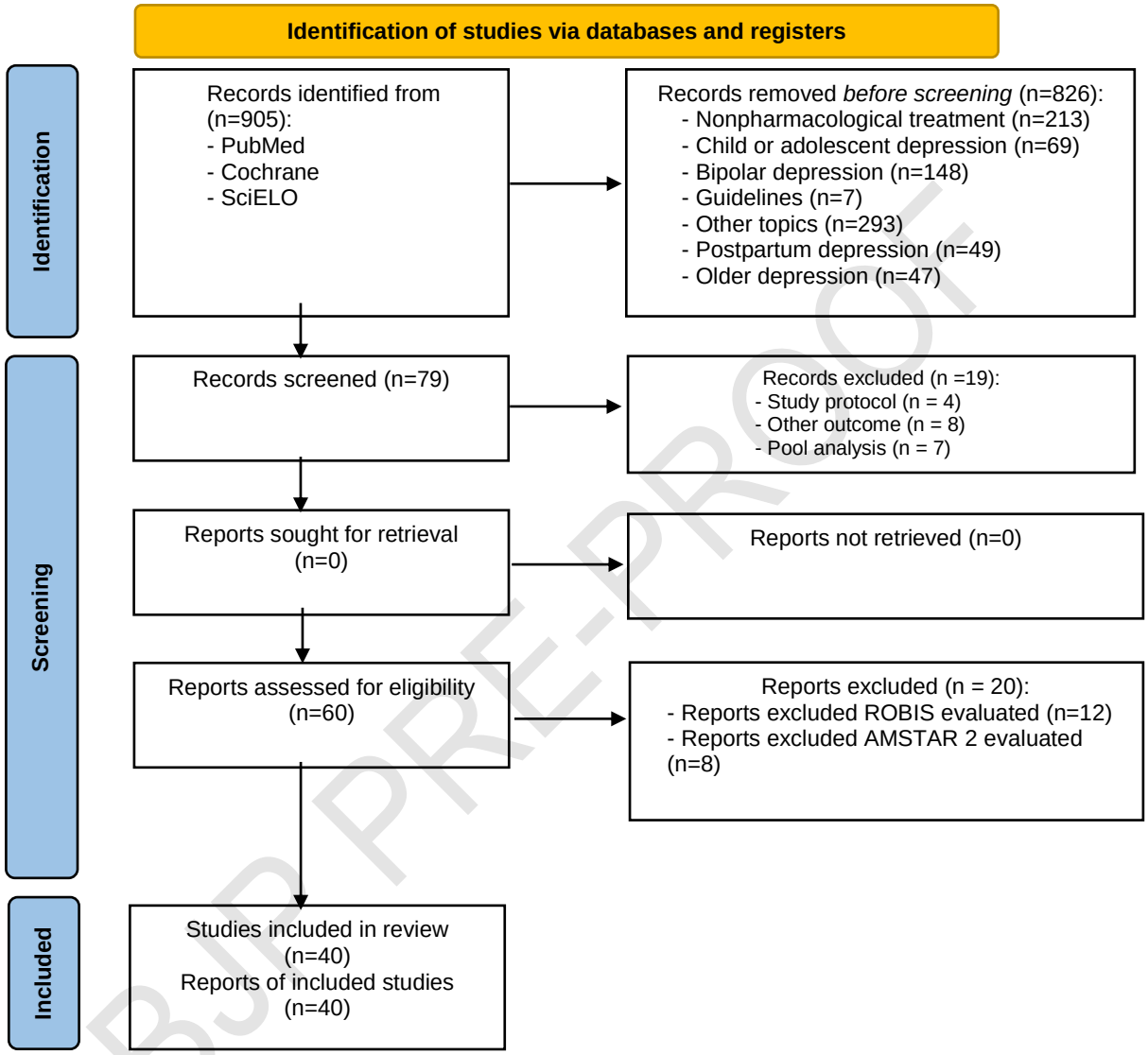
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## Supplementary material

**Supplementary Figure S1** Flow diagram of study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)




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**Supplementary Figure S2** Presents the results of the risk-of-bias assessment conducted using the ROBIS tool



**Supplementary Table S1** Assessed articles and their level of evidence

| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| 1. Appleton KM et al., 2021 | 25 studies involving a total of 1438 participants investigated the impact of n-3PUFA supplementation compared to placebo, and one study involving 40 participants investigated the impact of n-3PUFA supplementation compared to antidepressant treatment. participants with a primary diagnosis of major or unipolar depressive disorder | n-3 polyunsaturated fatty acids (n-3PUFAs) | Systematic review and meta-analysis | Depressive symptomology, assessed using any continuous validated measure of depressive symptomology, and adverse events, assessed using number of individuals experiencing adverse events | Depressive symptomology remission or response, quality of life, and failure to complete | For the placebo comparison, n-3PUFA supplementation results in a small to modest benefit for depressive symptomology, compared to placebo: standardized mean difference (SMD) -0.30 (95% confidence interval (CI) -0.10 to -0.50; 25 studies, 1373 participants, very low quality evidence), but this effect is unlikely to be clinically meaningful (an SMD of 0.30 represents a difference between groups in scores on the HDRS (17-item) of approximately 2.1 points (95% CI 0.7 to 3.5)) Only one study was available for the antidepressant comparison, involving 40 participants. This study found no differences between treatment with n-3PUFAs and treatment with antidepressants in depressive symptomology (mean difference (MD) -0.70 (95% CI - 5.88 to 4.48) | High | n-3PUFAs were more effective than placebo: SMD = -0.30 (95% CI -0.50 to -0.10) | The number of individuals experiencing adverse events was similar in n-3PUFA and placebo groups: OR = 1.24 (95% CI 0.95 to 1.62) |
| 2. Appleton KM et al., 2016 | 26 RCTs, total 1498 MDD adults patients | ω-3 Fatty acids | Systematic review and meta-analyses | Depressive symptomology, assessed using any continuous validated measure of depressive symptomology, and adverse events, assessed using number of individuals experiencing adverse events | Depressive symptomology remission or response, quality of life, and failure to complete | n-3PUFA supplementation resulted in a small-to-modest benefit for depressive symptomology: SMD=−0.32 (95% CI −0.52 to −0.12; 25 studies, 1373 participants, very low-quality evidence), but this effect is unlikely to be clinically meaningful, is very imprecise and, based on funnel plot inspection, sensitivity analyses and comparison with large well-conducted trials, is likely to be biased. For n-3PUFAs versus antidepressants, no differences were found between treatments | High | Depressive symptomology was lower after n-3PUFAs compared with placebo: SMD=−0.32 (95% CI −0.52 to −0.12), 25 studies, 1373 participants. A SMD of 0.32 represents a difference between groups in scores on the Hamilton Depression Rating Scale (HDRS; 17 items) of approximately 2.2 (0.8 to 3.6 (95% CI)) points (based on the SDs | Number of individuals experiencing adverse events were similar in n-3PUFA and placebo groups—OR=1.24 (95% CI 0.95 to 1.62), 19 studies, 1207 participants |

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| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | in depressive symptomology (MD=−0.70 (95% CI −5.88 to 4.48); 1 study, 40 participants, very low-quality evidence) | | reported in the trials included) | |
| 3. Berhan A et al., 2014 | 7 RCTs (n=3934) in adult patients with Major Depressive Disorder (MDD) | Vortioxetine | Meta-analysis | Change in MADRS and/or in HAM-D24 total score from baseline, proportion of patients who achieved a ≥50% MADRS and/or HAMD24 score reduction from baseline, and number of patients with adverse events | None. | Demonstrated a statistically significant reduction in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score from baseline among patients who were on vortioxetine (WMD = −3.92; 95% CI, −5.258 to −2.581). Furthermore, a statistically significant number of patients with MDD who were on vortioxetine have achieved a greater than or equal to 50% reduction in depression symptoms from baseline. However, a significant number of patients who were on vortioxetine therapy reported more adverse events than patients who were on placebo (overall OR = 1.21; 95% CI, 1.06 to 1.38) | Low | At the end of interventions, there was a statistically significant reduction in the MADRS total score from baseline among patients who were on vortioxetine as compared with placebo treated patients (WMD = −3.92; 95% CI, −5.258 to −2.581). Treatment with vortioxetine was significantly associated with a mean decline in HAM-D24 total score from baseline (WMD = −2.67; 95% CI, −3.96 to −1.38) | Comparison based on treatment related adverse events demonstrated that a significantly large number of patients treated with vortioxetine experienced more adverse events than patients who were on placebo (overall OR = 1.21; 95% CI, 1.06 to 1.38) |
| 4. Caddy C et al., 2015 | Aged 18 years or older with a primary diagnosis of unipolar major depressive, total number of participants 1242 from the 25 RCTs | Ketamine and other glutamate receptor modulators | Systematic review and meta-analysis | Efficacy outcome (dichotomous): number of participants who respond to treatment, where treatment response is defined as a reduction of at | Efficacy outcome (dichotomous): number of participants who achieve remission. Efficacy outcome (continuous): Mean endpoint scores or mean change scores in | Among all glutamate receptor modulators, only ketamine (administered intravenously) proved to be more efficacious than placebo, though the quality of evidence was limited by risk of bias and small sample sizes. There was low quality evidence that treatment with ketamine increased the likelihood of | High | Significant difference in response in favour of ketamine over placebo at 24 hours (random-effects OR 10.77, 95% CI 2.00 to 58.00; P = 0.006; I2 = 0%; NNTB = 3; 3 studies, 56 participants), at 72 hours (random-effects OR 12.59, 95% CI 2.38 | Significant difference in favour of placebo over ketamine in terms of confusion (random-effects OR 3.76, 95% CI 1.13 to 12.47; P = 0.03; I2 = 4%; NNTH = 4; 2 studies, 76 participants; Analysis |

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| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| | | | | least 50% compared to baseline on the Hamilton Rating Scale for Depression (HRSD), Montgomery-Åsberg Depression Rating Scale (MADRS), or any other depression scale, depending on the study authors' definition, or 'much or very much improved' (score 1 or 2) on the Clinical Global Impression Improvement scale. Adverse events outcome | depression severity from baseline to the time point in question Suicidality, cognition, loss of hope and other health-related quality of life measures, costs to healthcare services, acceptability | response after 24 hours (odds ratio (OR) 10.77, 95% confidence interval (CI) 2.00 to 58.00; 3RCTs, 56participants), 72 hours (OR 12.59, 95% CI 2.38 to 66.73; 3 RCTs, 56 participants), and one week (OR 2.58, 95% CI 1.08 to 6.16; 4 RCTs, 131 participants). The effect of ketamine was even less certain at two weeks, as data were available from only one trial (OR 0.93, 95% CI 0.31 to 2.83; 51 participants, low quality evidence). This was consistent across all efficacy outcomes. Ketamine caused more confusion and emotional blunting compared to placebo. One RCT with 72 participants reported higher numbers of responders on ketamine than midazolam at 24 hours (OR 0.36, 95% CI 0.14 to 0.58), 72 hours (OR 0.37, 95% CI 0.16 to 0.59), and one week (OR 0.29, 95% CI 0.08 to 0.49). However, midazolam was better tolerated than ketamine. e Found better efficacy of sarcosine over citalopram at four weeks (OR 6.93, 95% CI 1.53 to 31.38; 1 study, 40 participants), but not at two weeks (OR: 8.14, 95% CI 0.88 to 75.48); fewer participants in the sarcosine group experienced adverse events (OR 0.04, 95% CI 0.00 to 0.68; P = 0.03, 1 study, 40 participants). In one study with 18 participants, ketamine was more effective than ECT at 24 hours (OR 28.00, 95% CI 2.07 to 379.25) and 72 hours (OR | | to 66.73; P = 0.003; I2 = 0%; NNTB = 3; 3 studies, 56 participants) and at one week (random-effects OR 2.58, 95% CI 1.08 to 6.16; P = 0.03; NNTB = 6; 4 studies, 131 participants. We found no significant difference in response between ketamine and placebo at two weeks (OR 0.93, 95% CI 0.31 to 2.83; P = 0.90; 1 study, 51 participants) | 1.2) and emotional blunting (OR 23.40, 95% CI 1.12 to 489.52; P = 0.04; NNTH = 3; 1 study, 30 participants. We found no significant difference in terms of other adverse events |

BJP PRE-P

| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
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| | | | | | | 12.25, 95% CI 1.33 to 113.06), but not at one week (OR 3.35, 95% CI 0.12 to 93.83), or two weeks (OR 3.35, 95% CI 0.12 to 93.83).No differences in terms of adverse events were found between ketamine and ECT. | | | |
| 5. Cipriani A et al., 2018 | 522 RCTs comprising 116 477 participants. Adults (≥18 years old and of both sexes) with major depressive disorder diagnosed according to standard operationalized criteria | Antidepressants | Systematic review and network meta-analysis | Efficacy (response rate measured by the total number of patients who had a reduction of ≥50% of the total score on a standardized observer-rating scale for depression) and acceptability (treatment discontinuation measured by the proportion of patients who withdrew for any reason). | Endpoint depression score, remission rate, and the proportion of patients who dropped out early because of adverse events. | In terms of efficacy, all antidepressants were more effective than placebo, with ORs ranging between 2·13 (95% credible interval [CrI] 1·89–2·41) for amitriptyline and 1·37 (1·16–1·63) for reboxetine. For acceptability, only agomelatine (OR 0·84, 95% CrI 0·72–0·97) and fluoxetine (0·88, 0·80–0·96) were associated with fewer dropouts than placebo, whereas clomipramine was worse than placebo (1·30, 1·01–1·68). When all trials were considered, differences in ORs between antidepressants ranged from 1·15 to 1·55 for efficacy and from 0·64 to 0·83 for acceptability. In head-to-head studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (range of ORs 1·19–1·96), whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were the least efficacious drugs (0·51–0·84). For acceptability, agomelatine, citalopram, escitalopram, | High | The random-effects summary SMD for all antidepressants was 0·30 | In terms of dropouts due to adverse events, all active drugs were associated with higher withdrawal rates than placebo with ORs ranging between 1·64 and 4·44, and 95% CrI excluding the null, except agomelatine (OR 1·21, 95% CrI 0·94–1·56 |

BJP PRE-PROOF

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| | | | | | | fluoxetine, sertraline, and vortioxetine were more tolerable than other antidepressants (range of ORs 0·43–0·77), whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine had the highest dropout rates (1·30–2·32) | | | |
| 6. Dean RL et al., 2021 | Thirty-one new studies were identified for inclusion in this updated review. Overall, we included 64 studies (5299 participants), Double- or single-blinded randomized controlled trials (RCTs) | Ketamine and other glutamate receptor modulators | Meta-analysis | Response rate (50% reduction on a standardized rating scale) and adverse events | Acceptability and tolerability | The evidence suggests that ketamine may result in an increase in response and remission compared with placebo at 24 hours odds ratio (OR) 3.94, 95% confidence interval (CI) 1.54 to 10.10; n = 185, studies = 7, very low-certainty evidence). Ketamine may reduce depression rating scale scores over placebo at 24 hours, but the evidence is very uncertain (standardized mean difference (SMD) -0.87, 95% CI -1.26 to -0.48; n = 231, studies = 8, very low-certainty evidence). When compared with midazolam, the evidence showed that ketamine increases remission rates at 24 hours (OR 2.21, 95% CI 0.67 to 7.32; n = 122,studies = 2, low-certainty evidence). The evidence is very uncertain about the response efficacy of ketamine at 24 hours in comparison with midazolam, and its ability to reduce depression rating scale scores at the same time point (OR 2.48, 95% CI 1.00 to 6.18; n = 296, studies = 4,very low-certainty evidence). Esketamine treatment likely results in a large | High | Ketamine was more efficacious than placebo in terms of the number of participants who responded to treatment at 24 hours (random-effects odds ratio (OR) 3.94, 95% confidence interval (CI )1.54 to 10.10; P = 0.004; participants = 185; studies = 7; $I^2$ = 14%), very low-certainty evidence,, at 72 hours (random-effects OR 15.84, 95% CI 3.68 to 68.12; P = 0.0002; participants = 83; studies = 4; $I^2$ = 0%), and at one week (random-effects OR 3.76, 95% CI 0.98 to 14.42; P = 0.05; participants = 196; studies = 5; I2 = 43%). Results at two weeks, four weeks, and three months had high levels of heterogeneity, so no conclusions could be made about the response efficacy of ketamine versus placebo at these time points: two | Participants assigned to treatment with ketamine were more likely to report the following adverse events than those who received placebo: agitation/anxiety (random-effects OR 3.44, 95% CI 1.07 to 11.04; P = 0.04; participants = 143; studies = 3; I2 = 9%, confusion (random-effects OR 3.76, 95% CI 1.13 to 12.47; P = 0.03; participants = 76; studies = 2; I2 = 4%; Analysis 1.6), dissociative symptoms (random-effects OR 7.72, 95% CI 1.31 to 45.51; P = 0.02; participants = 145; studies = 3; I2 = 0% |

BJP PRE-PROOF

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| | | | | | | increase in participants achieving remission at 24 hours compared with placebo (OR 2.74, 95% CI 1.71 to 4.40; n = 894, studies = 5, moderate-certainty evidence). Esketamine probably results in decreases in depression rating scale scores at 24 hours compared with placebo (SMD -0.31, 95% CI -0.45 to -0.17; n = 824, studies = 4, moderate-certainty evidence). The findings show that esketamine increased response rates, although this evidence is uncertain (OR 2.11, 95% CI 1.20 to 3.68; n = 1071, studies = 5, low-certainty evidence). Found very little evidence for the remaining glutamate receptor modulators | | weeks (random-effects OR 2.92, 95% CI 0.48 to 17.78; P = 0.24; participants = 206; studies = 4; I2 = 83%); four weeks (random-effects OR 1.37, 95% CI 0.50 to 3.77; P = 0.54; participants = 202; studies = 4; I2 = 59%); three months (random-effects OR 1.95, 95% CI 0.24 to 15.69; P = 0.53; participants = 117; studies = 3; I2 = 80%) | |
| 7. Edwards SJ et al., 2013 | 12 RCTs were included l adults ≥ 18 years l people with unipolar depression l TRD defined as failure to respond to at least two previous antidepressants in the current episode of depression | Lithium and Atypical antipsychotic drugs | Systematic review and meta-analysis | Response (measured by a reduction of at least 50% in HAMD or MADRS score | QoL as reported using a validated QoL rating scale25 (e.g. SF-36) l adverse events (total number of events, individual adverse events for which comparable data were available for both augmentation with AAP and with lithium, and withdrawal rates due to an adverse event) l withdrawals (all cause) as a surrogate outcome for adherence to medication l | Five RCTs reported response based on the MADRS and the remaining RCT used the Hamilton Depression Rating Scale. The results of the meta-analysis (fixed effects) demonstrated a statistically significant benefit for fluoxetine + olanzapine over fluoxetine alone [odds ratio (OR) 1.48; 95% confidence interval (CI) 1.13 to 1.94] with a moderate level of statistical heterogeneity (I 2 = 53%; p = 0.07). Five RCTs reported the outcome of remission. Fixed-effects meta-analysis demonstrated a statistically significant increase in remissions in patients treated with olanzapine + fluoxetine compared with fluoxetine alone (OR 1.77; 95% CI 1.27 to 2.47) | High | The results of the meta-analysis (fixed effects) demonstrated a statistically significant benefit for fluoxetine + olanzapine over fluoxetine alone [odds ratio (OR) 1.48; 95% confidence interval (CI) 1.13 to 1.94] with a moderate level of statistical heterogeneity (I2 = 53%; p = 0.07). The single trial comparing fluoxetine + lithium with fluoxetine alone used two definitions of response, one prespecified primary analysis and one post hoc analysis. Results of the primary and post hoc analyses for response | Fixed-effects meta-analysis of five trials found that olanzapine augmentation therapy was associated with a non-statistically significant increase in discontinuations (OR 1.25; 95% CI 0.91 to 1.71) with no statistical heterogeneity (I2 = 0%; p = 0.51). Data on all-cause withdrawals demonstrated fewer withdrawals with a lithium augmentation strategy than with fluoxetine alone, although this difference was |

BJP PRE-PR

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| | | | | | relapse rate l mortality (all cause). | with no statistical heterogeneity (I 2 = 0%; p = 0.75). Data on relapse rates were not available for analysis. Four RCTs reported least square mean difference (MD) from baseline in MADRS score at study end point. Fixed-effects meta-analysis resulted in a statistically significant MD of − 2.04 (95% CI − 3.25 to − 0.82) in favor of fluoxetine + olanzapine. However, there was a high level of heterogeneity that was statistically significant (I 2 = 73%; p = 0.01). Fixed-effects meta-analysis of five trials found that olanzapine augmentation therapy was associated with a non-statistically significant increase in discontinuations (OR 1.25; 95% CI 0.91 to 1.71) with no statistical heterogeneity (I 2 = 0%; p = 0.51) The single trial comparing fluoxetine + lithium with fluoxetine alone used two definitions of response, one prespecified primary analysis and one post hoc analysis. Results of the primary and post hoc analyses for response data indicated a non-significant trend in favor of lithium augmentation compared with SSRI alone (OR 1.48; 95% CI 0.37 to 5.95 and OR 3.85; 95% CI 0.80 to 18.62, respectively). Data on remission or relapse rates were not available. The MD in change in MADRS score from baseline between fluoxetine + lithium compared with fluoxetine alone was − 3.79 (95% CI − 11.25 to | | data indicated a non-significant trend in favor of lithium augmentation compared with SSRI alone (OR 1.48; 95% CI 0.37 to 5.95 and OR 3.85; 95% CI 0.80 to 18.62, respectively). Data on remission or relapse rates were not available. | statistically non-significant (OR 0.68; 95% CI 0.15 to 3.16) |

BJP PRE-P

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| | | | | | | 3.67) − a non-significant improvement from baseline score with fluoxetine + lithium compared with fluoxetine alone. Data on all-cause withdrawals demonstrated fewer withdrawals with a lithium augmentation strategy than with fluoxetine alone, although this difference was statistically non-significant (OR 0.68; 95% CI 0.15 to 3.16). Seven RCTs were included in the MTC: six for SSRI + AAP compared with SSRI alone and one RCT for SSRI + lithium compared with SSRI alone. Analyses of response (random-effects model) using the lithium primary analysis and the lithium post hoc analysis data showed a non-significant trend in favor of treatment with lithium [OR 1.29; 95% credible interval (CrI) 0.11 to 5.32 and OR 4.15; 95% CrI 0.25 to 20.34, respectively]. Five trials were included in the analysis for mean change in MADRS (four RCTs were AAPs and one was a lithium RCT). The random-effects model resulted in a weighted MD of −1.47 (95% CrI − 9.10 to 6.41) for the mean change in MADRS score from baseline for fluoxetine + lithium compared with fluoxetine + olanzapine, which suggests a statistically non-significant trend in favor of lithium augmentation. Six trials reported data on all-cause withdrawals. The fixed-effects model results suggested a statistically non-significant trend in favor of augmentation with | | | |

BJP PRE-P

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| | | | | | | lithium (OR 0.74; 95% CrI 0.10 to 2.66) compared with augmenting with AAP | | | |
| 8. Furukawa Y et al., 2022 | Ten RCTs studies including 2625 participants, evaluating aripiprazole augmentation therapy in adults (≥18 years old, both genders) with major depressive disorder showing inadequate response to at least one antidepressant treatment | Aripiprazole | Systematic review and dose–effect meta-analysis | Efficacy | Tolerability and acceptability | The maximum target dose–efficacy curve showed an increase up to doses between 2 mg (odds ratio OR = 1.46, 95% CI 1.15–1.85) and 5 mg (OR = 1.93, 95% CI 1.33–2.81), and then a non-increasing trend through the higher licensed doses up to 20 mg (OR = 1.90, 95% CI 1.52–2.37) | Moderate | The ED50 was 1.7 mg (OR = 1.39, 95% CI 1.13–1.72) and the ED95 was 4.0 mg (OR = 1.88, 95% CI 1.29–2.73) | Given the average response rate at 8 weeks among the placebo augmentation arm of 23% (274/1197), the rate of drop-out because of adverse events of 1% (16/1261) and the rate of drop- out for any reason of 9% (110/1197), aripiprazole augmentation with a maximum target dose of 4.0 mg (ED95) would translate into a response rate of 36% (95% CI 28–45%), a rate of drop-out because of adverse events of 4% (95% CI 1–12%) and a rate of drop-out for any reason of 10% (95% CI 5–17%). Titrating up further while balancing side-effects seems safe, but does not seem to add more benefit |

BJP PRE-PROOF

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| 9. Furukawa Y et al., 2022. | Six studies, including 1671 participants in total, aged 18 years or older of both genders, with a primary diagnosis of MDD, with inadequate response to at least one trial of antidepressant | Brexipiprazole | Systematic review and dose-effect meta-analysis | Efficacy | Tolerability and acceptability | The dose-efficacy curve showed an increase up to doses around 2 mg (odds ratio [OR] 1.52, 95% confidence interval [CI] 1.12–2.06) and then a decreasing trend through the higher licensed dose up to 3 mg (OR 1.40, 95% CI 0.95–2.08) | Moderate | 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 (odds ratio [OR] 1.24, 95% confidence interval [CI] 1.04– 1.46) and ED95 was 1.79 mg (OR 1.49, 95% CI 1.10–2.02) | Given an average response rate of 18% in the placebo augmented arms at 6 weeks (five arms, 746 participants), 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), brexpiprazole augmentation with the maximum target dose of 1.79 mg (ED95) would translate into a response rate of 25% (95% I: 20%–31%), 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%) |
| 10. Galizia I et al., 2016 | Eight studies with 934 participants, men and women aged from 18 to 80 years. Diagnosis Participants with a diagnosis of major depression Participants with a diagnosis of major depression, with or without psychotic symptoms, according to Diagnostic and | S-adenosyl methionine (SAMe) | Systematic review and meta-analysis | Efficacy: Change in mean scores from baseline to end of treatment on the depression rating scale used, such as the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Åsberg Depression Rating Scale | Efficacy: response to treatment, defined as a 50% reduction or greater in depression score from baseline to end of treatment. Remission: defined as a depression rating scale score within normal range at end of the study. Acceptability: | There was no strong evidence of a difference in terms of change in depressive symptoms from baseline to end of treatment between SAMe and placebo as monotherapy (standardized mean difference (SMD) -0.54, 95% confidence interval (CI) -1.54 to 0.46; P = 0.29; 142 participants; 2 studies; very low-quality evidence). There was also no strong evidence of a difference in terms of drop-out rates due to any reason between SAMe and | High | There was no strong evidence of a difference in terms of change in depressive symptoms from baseline to end of treatment between SAMe and placebo as monotherapy (standardized mean difference (SMD) -0.54, 95% confidence interval (CI) -1.54 to 0.46; P = 0.29; 142 participants; 2 studies; very low quality evidence). Low quality | There was also no strong evidence of a difference in terms of drop-out rates due to any reason between SAMe and placebo, when used as monotherapy (risk ratio (RR) 0.88, 95% CI 0.61 to 1.29; P = 0.52; 142 participants; 2 studies; low quality evidence). There was also no strong evidence of a |

BJP PRE-PROOF

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| | Statistical Manual of Mental Disorders (DSM)-III/II-R), DSM-IV/IV-TR, or International Classification of Diseases (ICD)-9, ICD-10 | | | (MADRS) Acceptability: participants dropping out of treatment during study period for any reason | participants experiencing trouble some adverse effects of any nature. Specific adverse effects | placebo, when used as monotherapy (risk ratio (RR) 0.88, 95% CI 0.61 to 1.29; P = 0.52; 142 participants; 2 studies; low quality evidence). Low quality evidence showed that the change in depressive symptoms from baseline to end of treatment was similar between SAMe and imipramine, both as monotherapy (SMD -0.04, 95% CI -0.34 to 0.27; P = 0.82; 619 participants; 4 studies). There was also no strong evidence of a difference between SAMe and a tricyclic antidepressant in terms of drop-outs due to any reason (RR 0.61, 95% CI 0.28 to 1.31; P = 0.2; 78 participants; 3 studies; very low quality evidence). There was little evidence of a difference in terms of change in depressive symptoms from baseline to end of treatment between SAMe and escitalopram, both as monotherapy (MD 0.12, 95% CI -2.75 to 2.99; P = 0.93; 129 participants; 1 study; low quality evidence). There was no strong evidence of a difference between SAMe and escitalopram in terms of drop-outs due to any reason (RR 0.81, 95% CI 0.57 to 1.16; P = 0.26; 129 participants; 1 study; low quality evidence). There was low quality evidence that SAMe is superior to placebo as add-on to SSRIs in terms of change in depressive symptoms from baseline to end oftreatment(MD -3.90, 95% CI - | | evidence showed that the change in depressive symptoms from baseline to end of treatment was similar between SAMe and imipramine, both as monotherapy (SMD -0.04, 95% CI -0.34 to 0.27; P = 0.82; 619 participants; 4 studies) | difference between SAMe and a tricyclic antidepressant in terms of drop-outs due to any reason (RR 0.61, 95% CI 0.28 to 1.31; P = 0.2; 78 participants; 3 studies; very low quality evidence) |

BJP PRE-P

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| | | | | | | 6.93 to -0.87; P = 0.01; 73 participants; 1 study). There was no strong evidence of a difference between SAMe and placebo as adjunctive therapy to an SSRI in terms of drop-outs due to any reason (RR 0.70, 95% CI 0.31 to 1.56; P = 0.38; 73 participants; 1 study; very low quality evidence) | | | |
| 11. Goh KK et al., 2019 | Eight double-blinded randomized controlled trials, a total of 677 patients treatment-resistant unipolar depression | Lamotrigine | Systematic review and meta-analysis | Change of depressive severity and response rate among the patients | Safety profile of the intervention, including reported discontinuation rate and adverse events. | Significant improvements in Hamilton Rating Scale for Depression scores and response rates were shown in lamotrigine augmentation groups compared with control groups, of which the pooled result of six Chinese studies showed positive effects of Hamilton Rating Scale for Depression improvement while the pooled result of two non-Chinese studies was statistically non-significant. Patients with more severe illness and longer duration of illness were more effectively treated with lamotrigine augmentation. The magnitude of depression improvement after lamotrigine augmentation was higher in patients treated with selective serotonin reuptake inhibitors than those treated with serotonin-norepinephrine reuptake inhibitor | High | Significant improvement in HAMD scores was shown in the lamo-trigine augmentation group (trials=8; n=677; (MD=−6.06; 95% confidence interval (CI), –9.58 to −2.53; p<0.001; I2=98%); (SMD=−1.71; 95% CI, –2.74 to −0.69; p<0.01; I2=97%)) com-pared with the control group in patients with treatment-resistant unipolar depression, | No differences between the lamotrigine augmentation group and the control group were found regarding all-cause treatment discontinuation (trials=8; n=677; (RR=0.75; 95% CI, 0.45–1.24; p=0.26; I2=0%)) and discontinuation due to adverse event (trials=8; n=677; (RR=0.96; 95% CI, 0.37–2.53; p=0.27; I2=7%)). Overall, lamotrigine augmentation was well-tolerated as there was no statistical difference between the lamotrigine augmentation group and the control group on the adverse events reported (trials=8; n=677; (RR=1.08; 95% CI, 0.97–1.20; |

BJP PREPROOF

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| | | | | | | | | | p=0.18; I2=0%)) |
| 12. Guaiana G et al., 2013 | Participants of both sexes, aged 18 years or older, with a primary diagnosis of major depressio13 studies (4495 participants) | Agomelatine | Systematic review and meta-analysis | Efficacy: the number of participants who responded to treatment, showing a reduction of at least 50% on the Hamilton Rating Scale for Depression (HAM-D) the Montgomery Asberg Depression Rating Scale (MADRS), or any other depression scale or the CES-D scale or were 'much or very much improved' (score 1 or 2) on the Clinical Global Impression-Improvement (CGI-I) | The number of participants who achieved remission as defined by: a score of 7 or less on the 17-item HAM-D, or 8 or less on the longer version of HAM-D; 10 or less on the MADRS; not ill or borderline mentally ill' on the CGI-S. Group mean scores at endpoint on HAM-D, MADRS, CGI-S or any other depression rating scale score. Acceptability. Tolerability. | Agomelatine did not show any advantage or disadvantage over the other antidepressants for our primary outcome, response to treatment(risk ratio (RR) 1.01, 95% confidence interval (CI) 0.95 to 1.08, P value 0.75 compared to SSRIs, and RR 1.06; 95% CI 0.98 to 1.16, P value 0.16 compared to venlafaxine). Also, agomelatine showed no advantage or disadvantage over other antidepressants for remission (RR 0.83; 95% CI 0.68 to 1.01, P value 0.07 compared to SSRIs, and RR 1.08; 95% CI 0.94 to 1.24, P value 0.73 compared to venlafaxine). Overall, agomelatine appeared to be better tolerated than venlafaxine in terms of lower rates of dropouts (RR 0.40; 95% CI 0.24 to 0.67, P value 0.0005), and showed the same level of tolerability as SSRIs (RR 0.95; 95% CI 0.83 to 1.09, P value 0.44). Agomelatine induced a lower rate of dizziness than venlafaxine (RR 0.19, 95% CI | High | There was no evidence that agomelatine was less or more effective than SSRIs as a whole (Mantel-Haenszel risk ratio (RR) 1.01, 95% confidence interval (CI) 0.95 to 1.08, P value 0.75; 10 trials, 3826 participants), statistical heterogeneity was moderate (I2 = 31%). Considering each comparator, there was no evidence that agomelatine was less or more effective than: paroxetine (RR 0.92, 95% CI 0.77 to 1.09, P value 0.33, I2 = 56%; three trials, 1189 participants); fluoxetine (RR 1.01, 95% CI 0.92 to 1.11, P value 0.80, I2 = 31%; four trials, 1862 participants); sertraline (RR 1.11, 95% CI 0.94 to 1.30, P value 0.23, one trial, 313 participants); or escitalopram (RR 1.05, | There was no evidence that agomelatine was associated with a lower or higher total drop-out rate than SSRIs as a whole (RR 0.95, 95% CI 0.83 to 1.09, P value 0.44, I2 = 0%; ten trials, 3826 participants). There was no evidence that agomelatine was associated with a higher total drop-out rate than: paroxetine (RR 1.01, 95% CI 0.80 to 1.28, P value 0.94; three trials, 1189 participants); fluoxetine (RR 0.96, 95% CI 0.74 to 1.26, P value 0.78, I2 = 43%; four trials, 1862 participants); sertraline (RR 0.72, 95% CI 0.43 to 1.21, P value 0.21; one trial, 313 participants); |

BJP PRE-PROOF

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| | | | | | | 0.06 to 0.64, P value 0.007) | | 95% CI 0.95 to 1.16, P value 0.33, I2 = 0%; two trials, 462 participants) | and escitalopram (RR 0.81, 95% CI 0.50 to 1.32, P value 0.76, I2 = 0%; two trials, 462 participants) |
| 13. Guo X et al., 2020 | Adults with a primary diagnosis of major depressive disorder according to standard, operationalized diagnostic criteria, 134 studies (30,644 patients treated with antidepressants and 16,002 treated with placebo) | Antidepressants | Meta-analysis | Mean and variance (standard deviation (SD), standard error, or confidence intervals) of symptom change for depression symptoms ratings from each study for the active and placebo groups | None. | Antidepressant-treated patients showed a significantly greater magnitude (g = 0.28, 95% CI 0.25–0.30, p < .0001) and lower variability (CVR = 0.94, 95% CI 0.93–0.95, p < .0001) of change in symptom severity relative to placebo-treated patients. Compared to placebo antidepressant-related improvement was more uniform in older studies (z = 3.01, p = .003) and in studies where antidepressants showed greater efficacy (z = −7.21, p < .0001). \| Imipramine, moclobemide, amitriptyline and mirtazapine showed significantly lower CVR than several other antidepressants. However, no difference in CVR exists between multiple and single-neurotransmitter profile antidepressants (z = −0.01, p = .99) | Low | Significantly lower variability in the antidepressant treated groups compared to placebo treated groups (CVR = 0.94, 95% CI 0.93–0.95, p < .0001, Fig. 3). Efficacy difference (SMD) between antidepressant and placebo. Antidepressants showed significantly greater improvements in symptoms than placebo (g = 0.28, 95%CI 0.25-0.30, p<.0001) | - |

BJP PRE-PROOF

| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
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| 14. Huang KL et al., 2014 | Six RCTs used a double-blind design involving 1871 patients, age 18 years or older and a primary diagnosis of MDD | Agomelatine | Meta-analysis | Efficacy | Acceptability, Tolerability | In the acute phase, agomelatine had higher response rates (relative risk (RR) 1.08, 95% confidence interval (CI) 1.02–1.15) compared to SSRIs and SNRIs. In the remission analysis, only acute remission rates (RR 1.12, 95% CI 1.01–1.24) significantly differed. The action of agomelatine was superior on the Leeds Sleep Evaluation Questionnaire-Quality of Sleep score (mean difference 4.05, 95% CI 0.61–7.49). Discontinuation due to inefficacy did not differ between agomelatine and SSRIs/SNRIs (RR 0.74, 95% CI 0.42–1.28). Compared to SSRIs and SNRIs, however, agomelatine revealed a lower rate of discontinuation due to side effects (RR 0.38, 95% CI 0.25–0.57) | Moderate | Despite the use of different effect measures in this study (RRs vs. between-group difference), the findings of this study were consistent with the literature. The pooled response rates in the acute phase were 75.3% for agomelatine and 69.5% for other SSRIs and SNRIs (between-group difference (standard error (SE)) = 5.83 (2.06), 95% CI 1.78–9.87, p = 0.005). the SMD of our pooled estimate was -0.14 (95% CI from -0.25 to -0.03). | Agomelatine has been shown to have better acceptability than SSRIs and SNRIs in MDD patients. There were significantly fewer dropouts owing to adverse events from agomelatine (RR 0.38, 95% CI 0.25–0.57). The proportion of patients who had experienced at least one adverse event related to treatment was significantly lower with agomelatine compared with SSRIs and SNRIs (RR 0.68, 95% CI 0.50–0.92) |
| 15. Jakobsen JC et al., 2017 | 131 randomized placebo-controlled trials enrolling a total of 27, 422 participants. Participants had to be 18 years or older and have a primary diagnosis of major depressive disorder | Selective serotonin reuptake inhibitors | Systematic review with meta-analysis and Trial Sequential Analysis | Depressive symptoms measured on the 17-item or 21-item Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), or the Beck's Depression Inventory (BDI) . Remission (Hamilton < 8 points; BDI <10 points; MADRS < | Suicides, suicide attempts, and suicide ideation during the intervention period. Quality of life. | SSRIs significantly reduced the Hamilton Depression Rating Scale (HDRS) at end of treatment (mean difference −1.94 HDRS points; 95% CI −2.50 to −1.37; P < 0.00001; 49 trials; Trial Sequential Analysis-adjusted CI −2.70 to −1.18); Bayes factor below predefined threshold (2.01*10−23). The effect estimate, however, was below our predefined threshold for clinical significance of 3 HDRS points. SSRIs significantly decreased the risk of no remission (RR 0.88; 95% CI 0.84 to 0.91; P < 0. 00001; 34 trials; Trial Sequential Analysis adjusted CI 0.83 to 0.92); Bayes factor (1426.81) | High | SSRIs versus placebo significantly reduced the HDRS score (mean difference −1.94 points; 95% CI −2.50 to −1.37; P < 0.00001 Using standardized mean difference, random-effects meta-analysis showed that SSRI versus placebo significantly decreased the standardized mean difference score (trials reporting mean scores: −0.23; 95% CI −0.31 to −0.14; P < 0.00001; trials reporting mean change scores: −0.26; 95% CI −0.35 to −0.17; P < | Random-effects meta-analysis showed that SSRIs versus placebo significantly increased the risk of a serious adverse event (OR 1.37; 95% CI 1.08 to 1.75; P = 0.009 |

BJP PRE-P

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| | | | | 10 points) Adverse events during the intervention period which were classified as serious and non-serious adverse events | | did not confirm the effect) | | 0.00001). The standardised mean difference was below our predefined threshold for clinical significance | |
| 16. Jason NG et al., 2021 | Four RCTs, two prospective open-label trials (n=1727).Adult subjects with MDD as defined by DSM .Adult subjects with Treatment Resistant Depression (i.e., resistant to ≥ 2 ADs) | ketamine and esketamine | Systematic review | Measures of general functioning | None | Overall, mixed results were reported with respect to the effect across disparate functional measures (e.g., Sheehan Disability Scale [SDS]) using ketamine/esketamine. A single study demonstrated a significant decrease (i.e., improvement) in SDS total scores in TRD with esketamine treatment; most studies, however, did not report on functional outcomes and have functional outcomes as a (co)-primary outcome measure | Low | When comparing both esketamine/AD groups to the AD/placebo group, there were also no significant between-group differences (p>0.05) in SDS total scores (56mg/oral AD: LSMD = -2.5 [95%CI = -5.25, 0.20]; 84mg/ oral AD: LSMD = -2.2 [95%CI = -4.91; 0.53]). All three groups reported a decrease in SDS total scores (i.e., improvement), respectively (56mg/ oral AD: mean change [SD] = -11.0 [9.32]; 84mg/oral AD: mean change [SD] = -11.1 [10.04]; AD/placebo: mean change [SD] = -8.4 [9.70]; level of significance not reported) | - |

BJP PRE-PROOF

| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
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| 17. Jeuring H W et al., 2023. | The 27 RCTs included a total of 3387 patients | Dopamine stimulating agents (DSA) | Systematic review and meta-analysis | Severity of depressive symptoms before and after exposure to the selected medications. Different validated measurement types of depression were included: most commonly the Hamilton Depression Rating Scale (HAM-D) and Montgomery Asberg Depression Rating Scale (MADRS) | None. | DSA were found to reduce depressive symptoms (SMD=-0.26, 95%CI[-0.43;-0.10]) It can be concluded that off-label DSA are overall effective in reducing depressive symptoms. However, the evidence is weak | Low | The model showed a significant effect of DSA on reducing depressive symptoms (SMD = − 0.26, 95% CI [− 0.43; − 0.10]). Augmentation effects were not significant (SMD = − 0.23, 95% CI [− 0.52; 0.06], p = 0.106), but monotherapy effects were (SMD = − 0.31, 95% CI [− 0.53; − 0.09], p = 0.012) | - |
| 18. Kamp C B et al., 2024 | Adults with a primary diagnosis of major depressive disorder, as defined by standardized diagnostic criteria such as the *Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases.* A total of 103 studies randomized 10.590 participant | **Tricyclic Antidepressants** | Systematic review with meta-analysis and trial sequential analysis. | Depressive symptoms measured by the 17-item Hamilton Depression Rating Scale (HDRS-17) Serious adverse events Quality of life | Proportion of participants with suicides or suicide attempts Non-serious adverse events | Beneficial effect of tricyclic antidepressants, with a mean difference of −3.77 points on the HDRS-17 (95% CI: −5.91 to −1.63; p < 0.01; 17 studies; Bayes factor: 0.003). Evidence of a harmful effect of tricyclic antidepressants, with an odds ratio (OR) of 2.78 (95% CI: 2.18 to 3.55; p < 0.01; 35 studies; Bayes factor: 1.72 × $10^{-5}$). T-tests did not reveal significant differences between the tricyclic antidepressants and placebo groups (p = 0.35 and p = 0.07, respectively). The meta-analysis did not show evidence of a difference between groups (OR 0.52; 95% | Low | Beneficial effect of tricyclic antidepressants, with a mean difference of −3.77 points on the HDRS-17 (95% CI: −5.91 to −1.63; p < 0.01; 17 studies; Bayes factor: 0.003). Evidence of a harmful effect of tricyclic antidepressants, with an odds ratio (OR) of 2.78 (95% CI: 2.18 to 3.55; p < 0.01; 35 studies; Bayes factor: 1.72 × $10^{-5}$). The meta-analysis did not show evidence of a difference between groups (OR 0.52; 95% CI: 0.16 to 1.67; p = 0.27; | Evidence of a harmful effect of tricyclic antidepressants, with an odds ratio (OR) of 2.78 (95% CI: 2.18 to 3.55; p < 0.01; 35 studies; Bayes factor: 1.72 × $10^{-5}$). T-tests did not reveal significant differences between the tricyclic antidepressants and placebo groups (p = 0.35 and p = 0.07, respectively). Evidence of a harmful effect of tricyclic antidepressants, with a relative risk (RR) of 2.10 (95% CI: 1.78 to |

BJP PRE-PROOF

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| | | | | | | CI: 0.16 to 1.67; p = 0.27; 5 studies; Bayes factor: 0.71). Evidence of a harmful effect of tricyclic antidepressants, with a relative risk (RR) of 2.10 (95% CI: 1.78 to 2.48; p < 0.01; 58 studies; Bayes factor: 6.32 × $10^{-8}$) | | 5 studies; Bayes factor: 0.71) | 2.48; p < 0.01; 58 studies; Bayes factor: 6.32 × $10^{-8}$) |
| 19. Kishi T et al., 2017 | 5 double blind randomized trials 1 study did not report whether the patients in the group control received placebo 2089 patients MDD diagnosis | Z drugs | Systematic review and meta-analysis | Measures for efficacy and safety were remission rate defined by HAMD scale and all-cause discontinuation | Measures were response rate, HAMD total score improvement, discontinuation due to inefficacy and adverse events, and individual adverse effects | Pooled Z-drug + antidepressants was superior to placebo + antidepressants regarding the remission rate (RR = 0.85, NNT = 10). Although pooled Z-drug + antidepressants was also superior to placebo + antidepressants/antidepressants alone regarding HAMD score improvement (SMD = -0.23), there was not significant difference in response rate and discontinuation due to inefficacy between groups | Low | Pooled Z-drug adjunctive therapy was superior to the placebo + antidepressants with respect to the remission rate (RR = 0.85, 95%CI = 0.77–0.94, p = 0.002, I 2 = 0 %, NNT = 10, N = 3, n = 983 Pooled Z-drug adjunctive therapy was also superior to placebo + antidepressants/antidepressants alone with respect to the HAMD total score improvement (SMD = −0.23, 95 % CI = −0.35 to −0.11, p = 0.0002, I 2 = 42 %, N = 5, n = 1964; In addition, pooled Z-drug adjunctive therapy was marginally superior to placebo + antidepressants with respect to the response rate (RR = 0.73, 95 % CI = 0.53–1.00, p = 0.05, N = 3, n = 983); | Although there were no differences in the discontinuation due to adverse events between the treatment groups, a higher incidence of at least one adverse event (RR = 1.09, 95 % CI = 1.03–1.15, p = 0.004, I 2 = 0 %, NNH = 20, N = 5, n = 2023) and dizziness (RR = 1.76, 95 % CI = 1.27–2.45, p = 0.0007, I 2 = 3 %, NNH = 25, N = 5, n = 2023) was observed in the pooled Z-drugs adjunctive therapy group than in the placebo + antidepressants/antidepressants-alone group |

BJP PREPROOF

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| 20. Kishi T et al., 2023 | 34 RCTs studies 9384 patients with MDD diagnosis | Antidepressants | Systematic review and network meta-analysis | 6-month relapse rate (efficacy) | All-cause discontinuation (acceptability) | In terms of the 6-month relapse rate, amitriptyline, citalopram, desvenlafaxine, duloxetine, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, reboxetine, sertraline, tianeptine, venlafaxine, and vortioxetine outperformed placebo. Compared to placebo, desvenlafaxine, paroxetine, sertraline, venlafaxine, and vortioxetine had lower all-cause discontinuation; however, sertraline had a higher discontinuation rate due to adverse events | Moderate | In terms of the 6-month relapse rate, amitriptyline, citalopram, desvenlafaxine, duloxetine, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, reboxetine, sertraline, tianeptine, venlafaxine, and vortioxetine outperformed the placebo with RRs (95% CrIs) ranging from 0.149 (0.018–0.610) for nefazodone to 0.583 (0.410–0.789) for fluoxetine | Acceptability Compared to placebo, desvenlafaxine, paroxetine, sertraline, venlafaxine, and vortioxetine had lower all-cause discontinuation with RRs (95% CrIs) ranging from 0.523 (0.327–0.817) for paroxetine to 0.768 (0.518–0.998) for vortioxetine |
| 21. Koesters M et al., 2017 | 15 studies total 7746 adults with Major Depressive Disorder diagnosis of to DSM-III, DSM- III-R, DSM-IV , DSM-IV-TR, DSM-5 , ICD-10 or Research Diagnostic Criteria, and Chinese Classification of Mental Disorders . Seven studies were placebo controlled; eight studies compared vortioxetine to SNRIs | Vortioxetine. | Systematic review and meta-analysis | Response to treatment, as defined by a reduction of at least 50% on the HAM-D or MADRS or any other depression scale, or score 1 or 2 CGI-I. Total number of dropouts measuring acceptability | Remission defined a priori as: ◦ 7 points or less on the 17-item HAM-D and as 8 points or less for all the other longer versions of HAM-D; ◦ 10 or less points on the MADRS; ◦ “not ill or borderline mentally ill” (score 1 or 2) on Clinical Global Impression . Severity CGI-S at endpoint. Endpoint mean scores, or mean change scores at endpoint on HAM-D, MADRS, or any other depression rating scale score. Dropouts due to | Vortioxetine may be more effective than placebo across the three efficacy outcomes: response (Mantel-Haenszel RR 1.35, 95% CI 1.22 to 1.49; 14 studies, 6220 participants), remission (RR 1.32, 95% CI 1.15 to 1.53; 14 studies, 6220 participants) and depressive symptoms measured using the Montgomery-Åsberg Depression Scale (MADRS) (score range: 0 to 34; higher score means worse outcome: MD -2.94, 95% CI -4.07 to -1.80; 14 studies, 5566 participants. In comparison with other antidepressants, very low-quality evidence from eight studies showed no clinically significant difference between vortioxetine and SNRIs as a class for response (RR 0.91, 95% CI 0.82 to 1.00; 3159 participants) or remission (RR | High | Vortioxetine may be more effective than placebo Response RR 1.35, 95% CI 1.22 to 1.49; 14 studies, 6220 participants), Remission (RR 1.32, 95% CI 1.15 to 1.53; 14 studies, 6220 participants) and Depressive symptoms (MADRS) (score range: 0 to 34; higher score means worse outcome: MD -2.94, 95% CI -4.07 to -1.80; 14 studies, 5566 participants comparison with other antidepressants no clinically significant difference between vortioxetine and SNRIs as a class for response (RR 0.91, 95% CI 0.82 to 1.00; 3159 participants) or remission (RR 0.89, | Dropout rates (RR 1.05, 95% CI 0.93 to 1.19; 14 studies, 6220 participants) discontinued vortioxetine than placebo because of adverse effects (RR 1.41, 95% CI 1.09 to 1.81; 14 studies, 6220 participants) but fewer discontinued due to inefficacy (RR 0.56, 95% CI 0.34 to 0.90, P = 0.02; 14 studies, 6220 participants) no significant differences between vortioxetine and the SNRIs as a class for total dropout rates (RR 0.89, 95% CI 0.73 to 1.08), dropouts due to adverse events (RR |

BJP PRE-PROOF

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| | | | | | adverse events, due to inefficacy. Tolerability. | 0.89, 95% CI 0.77 to 1.03; 3155 participants). There was a small difference favoring SNRIs for depressive symptom scores on the MADRS (MD 1.52, 95% CI 0.50 to 2.53; 8 studies, 2807 participants). Against individual antidepressants, analyses suggested that vortioxetine may be less effective than duloxetine in terms of response rates (RR 0.86, 95% CI 0.79 to 0.94; 6 studies, 2392 participants) and depressive symptoms scores on the MADRS scale (MD 1.99, 95% CI 1.15 to 2.83; 6 studies; 2106 participants). Against venlafaxine, meta-analysis of two studies found no statistically significant differences (response: RR 1.03, 95% CI 0.85 to 1.25; 767 participants; depressive symptom scores: MD 0.02, 95% CI -2.49 to 2.54; 701 participants) | | 95% CI 0.77 to 1.03; 3155 participants. There was a small difference favoring SNRIs for depressive symptom scores on the MADRS (MD 1.52, 95% CI 0.50 to 2.53; 8 studies, 2807 participants) Vortioxetine may be less effective than duloxetine in terms of response rates (RR 0.86, 95% CI 0.79 to 0.94; 6 studies, 2392 participants) and depressive symptoms scores on the MADRS scale (MD 1.99, 95% CI 1.15 to 2.83; 6 studies; 2106 participants). Against venlafaxine, meta-analysis of two studies found no statistically significant differences (response: RR 1.03, 95% CI 0.85 to 1.25; 767 participants; depressive symptom scores: MD 0.02, 95% CI -2.49 to 2.54; 701 participants) | 0.74, 95% CI 0.51 to 1.08) and dropouts due to inefficacy (RR 1.52, 95% CI 0.70 to 3.30) |
| 22. Koesters M et al., 2013 | 13 studies included adults patients (≥ 18 years) with a primary diagnosis of unipolar major depression according to DSM-IV,DSM-IV-TR or ICD-10 | Agomelatine | Systematic review and meta-analysis | For acute-phase studies was the group mean score on the Hamilton Rating Scale for Depression (HRSD) at the end of the trial, or group mean change from | For efficacy: (a) Group mean scores at the end of the trial, or group mean change from baseline to end-point, on any depression rating scale or Clinical Global Impression | Acute treatment with agomelatine was associated with a statistically significant superiority over placebo of –1.51 HRSD points (99% CI –2.29 to –0.73, nine studies). Data extracted from three relapse prevention studies failed to show significant effects of agomelatine over placebo (relative risk 0.78, 99% CI 0.41– | High | Acute-phase studies indicated that acute treatment with agomelatine is associated with a statistically significant difference over placebo of -1.51 points on the HRSD (99% CI -2.29 to -0.73 Data extracted from the | Whereas discontinuation because of inefficacy significantly favored agomelatine, discontinuation because of adverse events did not differ between agomelatine and placebo |

BJP PRE-PROOF

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| | | | | baseline to end-point. For long-term studies was the proportion of patients who relapsed during the follow-up treatment period. | Rating scale (CGI); (b) Treatment responders, that is proportion of patients showing a reduction of at least 50% on the HRSD or MADRS or any other depression scale; (c) Treatment remitters, that is the proportion of patients with a score of seven or less on the 17-item HRSD, or eight or less on the longer versions of the HRSD; ten or less on the MADRS; 'not ill or borderline mentally ill' on the CGI – Severity scale (CGI-S); or any other equivalent value on a depression scale defined by the authors. For acceptability: (a) Total number of participants who dropped out during the trial as a proportion of the total number of randomized participants: total drop-out rate. (b) Number of | 1.48). Secondary efficacy analyses showed a significant advantage of agomelatine over placebo in terms of response (with no effect for remission). | | 10 acute-phase studies (2896 patients) indicated that acute treatment with agomelatine is associated with an SMD over placebo of -0.18 (99% CI -0.27 to -0.08) | |

BJP PREPROOF

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| | | | | | participants who dropped out as a result of inefficacy during the trial as a proportion of the total number of randomized participants. (c) Number of participants who dropped out as a result of adverse events during the trial as a proportion of the total number of randomized participants. (d) Total number of participants experiencing adverse events | | | | |
| 23. Köhler-Forsberg O et al., 2019 | 36 RCTs 10000 Patients MDD diagnosis Patients with somatic diseases+MDD symptoms | Anti-inflammatory drugs | Meta-analysis | Reduction in depressive symptoms measured by HAMD scale Responde in each intervention group serious adverse effects | Non serious adverse effects depressive symptoms measured at maximum follow-up remission at maximum follow-up | Anti-inflammatory agents improved depressive symptoms compared to placebo as add-on in patients with MDD (SMD = -0.64; 95%-CI = -0.88, -0.40; $I^2$ = 51%; N = 597) and as monotherapy (SMD = -0.41; 95%-CI = -0.60, -0.22; $I^2$ = 93%, N = 8825). Anti-inflammatory add-on improved response (RR = 1.76; 95%-CI = 1.44-2.16; $I^2$ = 16%; N = 341) and remission (RR = 2.14; 95%-CI = 1.03-4.48; $I^2$ = 57%; N = 270). | Low | Efficacy of anti-inflammatory intervention pharmacological anti-inflammatory treatment was superior compared to placebo with an antidepressant effect by a SMD of - 0.49 (95%-CI = - 0.64 to - 0.33;),anti-inflammatory treatment as add on improved the chance of response (RR = 1.76; 95%-CI = 1.44 to 2.16; I 2 = 16%; N = 341) and remission (RR = 2.14; 95%-CI = 1.03 to 4.48) Specific anti-inflammatory drugs compared to placebo. NSAIDs (SMD = -0.40; | No increased risks for gastrointestinal symptoms (RR = 1.18; 95%-CI = 0.86 to 1.61; I 2 = 0%), pain/muscle aching (RR = 0.83; 95%-CI = 0.47 to 1.49; I 2 = 25%), or cardiovascular events (RR = 1.37; 95%-CI = 0.49 to 3.77; I 2 = 0%) as compared to placebo. The risk for infections was non-significantly increased (OR = 1.14; 95%- CI = 0.99 to 1.31; P = 0.06; I 2 = 0%) |

BJP PREPROOF

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| | | | | | | | | 95%-CI = -0.62 to -0.18; I 2 = 82%), cytokine inhibitors (SMD = -0.56; 95%-CI = -0.93 to -0.19; I 2 = 95%), statins (SMD = -0.26; 95%- CI = -0.48 to -0.04; I 2 = 65%), glucocorticoids (SMD = -0.90; 95%-CI = -1.44 to -0.36; I 2 = 0%), and minocycline (SMD = -0.87; 95%- CI = -1.45 to -0.29; I 2 = 63%), whereas the antidepressant for pioglitazone was not significant (SMD = -0.43; 95%-CI = -1.56 to 0.70; I 2 = 83%)Regarding add-on treatment in MDD, NSAIDs (all trials investigated celecoxib; SMD = -0.82; 95%-CI = -1.17 to -0.46; I 2 = 0%; N = 132), glucocorticoids (SMD = -0.90; 95%-CI = -1.44 to -0.36; I 2 = 0%; N = 59), and statins (SMD = -0.73; 95%-CI = -1.05 to -0.42; I 2 = 0%; N = 164) showed significant better antidepressant effects as compared to antidepressants + placebo | |

BJP PRE-PROOF

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| 24. Liu Y et al., 2015 | Five RCTs consisting of 154 patients, adults with a primary diagnosis of unipolar TRD (treatment resistant depression) who had failed to respond to at least one SSRI | Pindolol | Systematic review and meta-analysis | Standardized mean difference (SMD) in changes of depression rating scores from baseline to endpoint | The proportion of patients who responded to treatment (a decrease of ≥50% or similar criterion in depression rating scores) was estimated. Tolerability outcome was assessed by the proportion of patients failing to complete the study. Safety outcome was assessed by the proportion of subjects who complained of side effects | The overall pooled effect size in the primary and secondary efficacy analysis showed no significant effects of pindolol plus SSRI therapy (standardized mean difference = - 0.43, p = 0.24; OR = 1.92, p = 0.39, respectively). In terms of acceptability, there was no statistical difference in either tolerability or safety between the two groups (OR = 0.46, p = 0.40; OR = 0.90, p = 0.94, respectively). | Moderate | The overall pooled effect size showed no significant effect of pindolol plus SSRI therapy with an SMD of - 0.43 (95% CI, - 1.14 to 0.29; p= 0.24). The secondary efficacy analysis found that pindolol plus SSRI therapy was not associated with a significant increase in OR The pooled OR value from the random effects model was 1.92 (95% CI, 0.44 to 8.44; p= 0.39) | Tolerability the OR value was 0.46 (95% CI, 0.08 to 2.81; p= 0.40) Safety, there was no significant difference with an OR value of 0.90 (95% CI, 0.05 to 15.49; p= 0.94). |
| 25. Llorca PM, et al., 2014 | 117 RCTs in included a total of 18 326 MDD patients | Vortioxetine | Meta-analysis and Meta-regression analysis | Efficacy and tolerability. To enable comparisons between studies using different primary scales, MADRS or HAM-D (either HAM-D 17, 21 or 24) scores. | Tolerability, was defined as the proportion of total patients in each treatment group that withdrew from the study before completion due to adverse events (AEs) during the first 2 months (6–12 weeks) of treatment | For efficacy, estimates of treatment effect (negative estimates favor vortioxetine) for vortioxetine versus comparators were: agomelatine, –0.16 (p = 0.11); desvenlafaxine, 0.03 (p = 0.80); duloxetine, 0.09 (p = 0.42); escitalopram, –0.05 (p = 0.70); sertraline, –0.04 (p = 0.83); venlafaxine IR/XR, 0.12 (p = 0.33); and vilazodone, –0.25 (p = 0.11). For tolerability, all but one combination was numerically in favor of vortioxetine (odds ratio < 1), although not all differences were statistically significant: agomelatine, 1.77 (p = 0.03); desvenlafaxine, 0.58 (p = 0.04); duloxetine, 0.75 (p = 0.26); escitalopram, 0.67 (p = 0.28); | Low | For efficacy, estimates of treatment effect (negative estimates favor vortioxetine) for vortioxetine versus comparators were: agomelatine, –0.16 (p = 0.11); desvenlafaxine, 0.03 (p = 0.80); duloxetine, 0.09 (p = 0.42); escitalopram, –0.05 (p = 0.70); sertraline, –0.04 (p = 0.83); venlafaxine IR/XR, 0.12 (p = 0.33); and vilazodone, –0.25 (p = 0.11). | The differences in tolerability between vortioxetine and the first group were statistically significant in favor of vortioxetine (OR 0.58 [p < 0.05] versus desvenlafaxine; OR 0.30 [p < 0.01] versus sertraline; OR 0.4 [p < 0.01] versus venlafaxine IR/XR). Agomelatine, with a mean incidence of withdrawals due to any AE of 4.4%, had a statistically significant advantage compared to vortioxetine (OR 1.77 |

BJP PREPROOF

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| | | | | | | sertraline, 0.30 (p = 0.01); venlafaxine, 0.47 (p = 0.01); and vilazodone, 0.64 (p = 0.18) | | | [p < 0.05]) |
| 26. Luo XD et al., 2020 | 910 MDD patients in 10 Randomized controlled trials (RCTs) | Omega-3 polyunsaturated fatty acid | Network meta-analysis | None | None | Results of pairwise meta-analysis showed that n-3 PUFAs were superior to placebo (SMD: 1.243 ± 0.596; 95% CI: 0.060 ~ 2.414). Results of the network meta-analysis showed that both the high (SMD: 0.908 ± 0.331; 95% CI: 0.262 ~ 1.581) and the low-dose (SMD: 0.601 ± 0.286; 95% CI: 0.034 ~ 1.18) n-3 PUFAs were superior to placebo, and the efficacy of high-dose n-3 PUFAs is superior to that of low-dose | Low | N 3 PUFAs were superior to placebo (SMD: 0.71; 95% CI: − 1.13 ~ − 0.28). Subgroup analysis showed that, both the high-dose n-3 PUFAs subgroup (SMD: -0.90; 95% CI: − 1.51 ~ − 0.29) and low-dose PUFAs subgroup (SMD: -0.61; 95% CI: − 1.15 ~ − 0.06) were superior to the placebo subgroup Network meta-analysis for all the available data showed that, both high (SMD: 0.908 ± 0.331; 95% CI: 0.262 ~ 1.581) and low dose (SMD: 0.601 ± 0.286; 95% CI: 0.034 ~ 1.18) n-3 PUFAs were superior to placebo | None |
| 27. Maneeton N et al., 2013 | A total of 1,117 participants in three RCTs were included in adult patients with MDD | Bupropion | Meta-analysis | Response rate; remission rate | Overall discontinuation rate;discontinuation rate due to adverse events | The pooled mean changed scores of the bupropion-treated group were comparable to those of the venlafaxine-treated group with standardized mean differences (95% CI) of 0.05 (−0.16 to 0.26). The overall response and remission rates were similar with the RRs (95% CI) of 0.92 (0.79–1.08) and 0.97 | Low | SMD of depression severity had no significant differences between groups (SMD [95% CI] of 0.05 [−0.16 to 0.26].The pooled response rate was comparable (RR [95% CI] of 0.92 [0.79 to 1.08]The pooled | Discontinuation rate and discontinuation rate due to adverse events were not different between groups with the RRs (95% CI) of 1.00 (0.80–1.26) and 0.69 (0.44–1.10), respectively |

BJP PRE-PROOF

| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
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| | | | | | | (0.75–1.24), respectively. The pooled overall discontinuation rate and discontinuation rate due to adverse events were not different between groups with the RRs (95% CI) of 1.00 (0.80–1.26) and 0.69 (0.44–1.10), respectively | | remission rate of the two groups had also no significant difference between groups (RR [95% CI] of 0.97 [0.75 to 1.24] | |
| 28. Meeker AS et al., 2015 | 11 RCTs with 6,145 participants with acute MDD | Vortioxetine | Systematic review and meta-analysis | Response and remission. Response is typically defined by a decrease of ≥50% in the Hamilton Depression Rating Scale (HAMD) or Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline. Remission is defined by a total HAMD (≤7) or MADRS (≤10) score. | Absolute change in HAMD and MADRS scores from baseline. Rates of serious adverse events | The response rate with vortioxetine was significantly higher for 1-mg (relative risk (RR) = 1.91; 95% confidence interval (CI) 1.36 to 2.69), 5-mg (RR = 1.33; 95% CI 1.10 to 1.61), 10-mg (RR = 1.42; 95% CI 1.21 to 1.67), and 20-mg doses (RR = 1.58; 95% CI 1.19 to 2.08) compared to placebo. Remission rates were significantly higher for the 10-mg group (RR = 1.45; 95% CI 1.18 to 1.77) and the 20-mg group (RR = 1.68; 95% CI 1.19 to 2.37) compared to placebo. Meta-regression of dose on the log odds ratio of response was not statistically significant (β = 0.01; P = 0.46). Vortioxetine response rates were lower than active serotonin and norepinephrine reuptake inhibitor (SNRI) comparators for the 5-mg (RR = 0.88; 95% CI 0.80 to 0.98), 15-mg (RR = 0.78; 95% CI 0.68 to 0.90), and 20-mg (RR = 0.82; 95% CI 0.72 to 0.94) doses | Low | In remission rates for the 10-mg (RR 1.45; 95% CI 1.18 to 1.77; I 2 = 35%) and the 20-mg groups (RR 1.68; 95% CI 1.19 to 2.37; I 2 = 67%) compared to placebo, but no difference for the 1-mg (1.57; 95% CI 0.98 to 2.50; I 2 = not applicable), 2.5-mg (RR 0.99; 95% CI 0.77 to 1.28; I 2 = 0%), 5-mg (RR 1.27; 95% CI 0.98 to 1.66; I 2 = 70.4%), and 15-mg groups (RR 1.26; 95% CI 0.86 to 1.84; I 2 = 63.9%) compared to placebo<br>Rates of response were significantly lower than the SNRI for the 5-mg (RR = 0.88; 95% CI 0.80 to 0.98; I 2 = 13%), 15-mg (RR = 0.78; 95% CI 0.68 to 0.90; I 2 = 0%), and 20-mg (RR = 0.82; 95% CI 0.72 to 0.94; I 2 = 0%) doses | AEs were nausea and vomiting. At the 20-mg dose, 20.3% (95% CI 16.5% to 24.2%) and 5.5% (95% CI 1.2% to 9.8%) more patients treated with vortioxetine than placebo experienced nausea and vomiting, respectively |

BJP PRE-PROOF

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| 29. Nuñez NA et al., 2022 | A total of 65 studies (N = 12,415). Adult MDD patients (18–65 years of age) refractory to one or more antidepressant | 19 augmentation agents | A systematic review and network meta-analysis (NMA) | Response rates | Remission rates and all cause discontinuation rates | NMA for response rates, compared to placebo, were significant for: liothyronine, nortriptyline, aripiprazole, brexpiprazole, quetiapine, lithium, modafinil, olanzapine (fluoxetine), cariprazine, and lisdexamfetamine. For remission rates, compared to placebo, were significant for: thyroid hormone(T4), aripiprazole, brexpiprazole, risperidone, quetiapine, and olanzapine (fluoxetine). Compared to placebo, ziprasidone, mirtazapine, and cariprazine had statistically significant higher discontinuation rates | High | Response rates, in order of decreasing efficacy, T3, nortriptyline, aripiprazole, brexpiprazole, quetiapine, lithium, modafinil, olanzapine (fluoxetine), cariprazine and lisdexamfetamine were statistically significant compared to placebo, with RRs ranging from 1.18 (1.03–1.37) for lisdexamfetamine to 1.90 (1.16– 3.11) for T3 Lithium showed a significantly higher response rate than placebo (RR=2.43, 95% CI:1.45–4.07, p <0.0007 Remission rates In order of efficacy, T4, aripiprazole, risperidone, quetiapine, olanzapine(fluoxetine), brexpiprazole were statistically significant compared to placebo with RRs ranging from 1.44 (1.00–2.08) for brexpiprazole to 1.91 (1.04–3.52) for T4. | Discontinuation rates were significantly higher compared to placebo for ziprasidone (RR= 20.12, 95% CI 1.17–344.58), mirtazapine (RR= 4.12, 95% CI, 1.97–8.63), and cariprazine (RR= 1.72 (95% CI 1.09–2.73) |
| 30. Ogawa Y et al., 2019 | 10 randomized controlled trials involving 731 participants, adults with major depression | Benzodiazepines | Systematic review and meta-analysis | Depressive severity was based on the observer-rated scale, preferably the Hamilton Rating Scale for Depression (HRSD), Acceptability of | Response in depression, defined as 50% or greater reduction in depression severity measures, and global response. Anxiety severity, Insomnia severity, | Combined therapy of benzodiazepines plus antidepressants was more effective than antidepressants alone for depressive severity in the early phase (four weeks) (SMD –0.25, 95% CI –0.46 to –0.03; 10 studies, 598 participants; moderate-quality evidence), but there was no | High | (SMD –0.25, 95% CI –0.46 to –0.03; 10 studies, 598 participants; but there was no difference between treatments in the acute phase (five to 12weeks)(SMD–0.18, 95% CI –0.40 to 0.03; 7 studies, 347 participants; or in the continuous | Acceptability of treatment was no difference in the dropouts due to any reason between combined therapy and antidepressants alone (RR 0.76, 95% CI 0.54 to 1.07; 10 studies, 731 |

| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
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| | | | | treatment, as measured by leaving study early for any reason. | Adverse effects: | difference between treatments in the acute phase (five to 12weeks)(SMD–0.18, 95% CI –0.40 to 0.03; 7 studies, 347 participants; low-quality evidence) or in the continuous phase (more than 12 weeks) (SMD–0.21, 95% CI –0.76 to 0.35; 1 study, 50 participants; low-quality evidence). For acceptability of treatment, there was no difference in the dropouts due to any reason between combined therapy and antidepressants alone (RR 0.76, 95% CI 0.54 to 1.07; 10 studies, 731 participants; moderate-quality evidence). For response in depression, combined therapy was more effective than antidepressants alone in the early phase (RR 1.34, 95% CI 1.13 to 1.58; 10 studies, 731 participants), but there was no evidence of a difference in the acute phase (RR 1.12, 95% CI 0.93 to 1.35; 7 studies, 383 participants) or in the continuous phase (RR 0.97, 95% CI 0.73 to 1.29; 1 study, 52 participants). For remission in depression, combined therapy was more effective than antidepressants alone in the early phase (RR 1.39, 95% CI 1.03 to 1.90, 10 studies, 731 participants), but there was no evidence of a difference in the acute phase (RR 1.27, 95% CI 0.99 to 1.63; 7 studies, 383 participants) or in the continuous phase (RR 1.31, 95% CI 0.80 to 2.16; 1 study, 52 participants). There was no | | phase (more than 12 weeks) (SMD–0.21, 95% CI –0.76 to 0.35; 1 study, 50 participants<br>For response in depression, combined therapy was more effective than antidepressants alone In the early phase (RR 1.34, 95% CI 1.13 to 1.58; 10 studies, 731 participants), but there was no evidence of a difference in the acute phase (RR 1.12, 95% CI 0.93 to 1.35; 7 studies, 383 participants) or in the continuous phase (RR 0.97, 95% CI 0.73 to 1.29; 1 study, 52 participants)<br>For remission combined therapy was more effective than antidepressants alone in the early phase (RR 1.39, 95% CI 1.03 to 1.90, 10 studies, 731 participants), but there was no evidence of a difference in the acute phase (RR 1.27, 95% CI 0.99 to 1.63; 7 studies, 383 participants) or in the continuous phase (RR 1.31, 95% CI 0.80 to 2.16; 1 study, 52 participants) | participants |

BJP PRE-PROOF

| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
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| | | | | | | evidence of a difference between combined therapy and antidepressants alone for anxiety severity in the early phase (SMD –0.76, 95% CI –1.67 to 0.14; 3 studies, 129 participants) or in the acute phase (SMD –0.48, 95% CI –1.06 to 0.10; 3 studies, 129 participants) | | | |
| 31. Seshadri A et al., 2021 | 4 studies (2 open label, 1 prospective observational, 1 RCT), total 2632 patients with MDD diagnosis. With inadequate response to an antidepressant after at least 6 weeks of treatment | Aripiprazole | Systematic Review and meta-analysis | Response, remission | Adverse effects | Random effects meta-analysis of 3 studies, revealed a weighted average remission proportion od 0,33 (0,16-0,51) showing trend of improved response with duration treatment. Three studies provided adverse data, weight gain (25%-28%) was higher in studies with patients receiving doses ≥ 5 mg and lower (3,5%) in a study using doses < 5 mg. Akathisia (15%-16%), insomnia (12%-17%), somnolence (14%) and fatigue (18%) were common adverse effects. Tardive dyskinesia risk was low (< 1%) at 1 year follow-up | Low | Random effects meta-analysis of 3 studies, revealed a weighted average remission proportion of 0,33 (0,16-0,51) | Weight gain (25%-28%) was higher in studies with patients receiving doses ≥ 5 mg and lower (3,5%) in a study using doses < 5 mg. Akathisia (15%-16%), insomnia (12%-17%), somnolence (14%) and fatigue (18%) were common adverse effects. Tardive dyskinesia risk was low (< 1%) at 1 year follow-up. |
| 32. Terao I et al., 2024 | 22 RCTs studies, involving a total of 2371 patients were aged 18 to 65 years and diagnosed with TRD, defined as a lack of response to at least two previous antidepressant treatments | Intravenous racemic ketamine, intranasal esketamine, aripiprazole, and lithium | Systematic review and meta-analysis | Response rate, assessed using scales such as the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (HAMD) | Tolerability, evaluated by dropout rates due to adverse events, and acceptability, measured by dropout rates for any reason | All the medications analyzed, including intravenous racemic ketamine, intranasal esketamine, aripiprazole, and lithium, demonstrated significantly greater efficacy than placebo. Intravenous racemic ketamine was significantly more effective than intranasal esketamine (OR 3.20; 95% CI: 1.43-7.16) and compared to aripiprazole also showed superiority (OR 2.90; 95% CI: 1.33-6.27). When | High | Intravenous racemic ketamine was significantly more effective than intranasal esketamine (OR 3.20; 95% CI: 1.43-7.16) and compared to aripiprazole also showed superiority (OR 2.90; 95% CI: 1.33-6.27). When compared to lithium, exhibited a higher OR (1.92; 95% CI: 0.70-5.22), although this difference was not | Both intranasal esketamine and aripiprazole showed significantly higher dropout rates due to side effects compared to placebo. The ORs were 3.03 (95% CI: 1.41-6.53) for intranasal esketamine and 2.24 (95% CI: 1.21-4.14) for aripiprazole. Intravenous racemic |

BJP PRE-PROOF

| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
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| | | | | | | compared to lithium, exhibited a higher OR (1.92; 95% CI: 0.70-5.22), although this difference was not statistically significant. Both intranasal esketamine and aripiprazole showed significantly higher dropout rates due to side effects compared to placebo. The ORs were 3.03 (95% CI: 1.41-6.53) for intranasal esketamine and 2.24 (95% CI: 1.21-4.14) for aripiprazole. Intravenous racemic ketamine and lithium, however, did not differ significantly from placebo in terms of tolerability. Intravenous racemic ketamine demonstrated better outcomes, it was significantly more acceptable than intranasal esketamine (OR 0.19; 95% CI: 0.06-0.59), aripiprazole (OR 0.21; 95% CI: 0.07-0.60), and placebo (OR 0.28; 95% CI: 0.07-1.08). Lithium showed no significant difference compared to intravenous racemic ketamine in terms of acceptability | | statistically significant | ketamine and lithium, however, did not differ significantly from placebo in terms of tolerability. Intravenous racemic ketamine demonstrated better outcomes, it was significantly more acceptable than intranasal esketamine (OR 0.19; 95% CI: 0.06-0.59), aripiprazole (OR 0.21; 95% CI: 0.07-0.60), and placebo (OR 0.28; 95% CI: 0.07-1.08). |

BJP PRE-PROOF

| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
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| 33. Thase M et al., 2017 | 5 double blind RCTs 1087 patients MDD diagnosis. | Venlafaxine ER. | Meta-analysis | Reduction depressive symptoms ≥50% assessed by HAMD 21/HAMD 17 or MADRS scales remission as scores ≤ 7 HAMD7 or ≤ 10 by MADRS scale | Safety and tolerability was assessed based on adverse events (AEs) and discontinuations due to AEs | Statistically significant separation between venlafaxine ER and placebo groups for HAM-$D_{17}$ total score was seen at week 2 and all subsequent assessments (p-values <.0001). There was no significant interaction between treatment and baseline HAM-$D_{17}$ total score. Probability of HAM-$D_{17}$ remission at week 8 decreased with increasing baseline HAM-$D_{17}$ total score (p = .0012; OR: 0.94); however, baseline HAM-$D_{17}$ total score did not predict response | Low | Least squares mean (SE) change from baseline in HAM-D17 total score at week 8 last-observation-carried-forward (LOCF) was −12.23 (0.33) for venlafaxine ER compared with −9.28 (0.35) for placebo (p < 0.0001) Results for MADRS total score were similar and least squares mean (SE) change from baseline at week 8 LOCF of −14.69 (0.52) for venlafaxine ER and −10.52 (0.55) for placebo (p < 0.0001). The NNT was 6 for both response and remission, based on either HAM-D17 or MADRS | The NNH based on discontinuations due to AE was 18 |
| 34. Thase ME et al., 2016 | 11 trials double-blind, placebo controlled, 5128 patients major depressive episode, as described in DSM-IV-TR, MADRS total scores of at least 22, CGI-Score of at least 4 | Vortioxetine | Meta-analysis | MADRS total score, HAM-D24 total score, or a composite z-score of Digit Symbol Substitution Test (DSST) and Rey Auditory Verbal Learning Test (RAVLT) score, with the MADRS total score as a predefined secondary endpoint in those trials that utilized the HAM-D24 total score or DSST/RAVLT | MADRS response and remission, and the CGI-S and CGI-I scores | Vortioxetine 5, 10, and 20mg/day were associated with significant reductions in MADRS total score (Δ-2.27, Δ-3.57, and Δ-4.57, respectively; p<0.01) versus placebo. The effects of 15mg/day (Δ-2.60; p=0.105) were not significantly different from placebo. Vortioxetine 10 and 20mg/day were associated with significant reductions in 9 of 10 MADRS single-item scores. Vortioxetine treatment was also associated with significantly higher rates of response and remission and with significant improvements in other depression-related scores versus placebo. This meta-analysis of vortioxetine (5- | Low | 5, 10, and 20mg/day were associated with significant reductions in MADRS total score (Δ-2.27, Δ-3.57, and Δ-4.57, respectively; p<0.01) versus placebo. The effects of 15mg/day (Δ-2.60; p=0.105) were not significantly different from placebo | None. |

BJP PRE-P

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| | | | | composite score | | 20mg/day) in adults with MDD supports the efficacy demonstrated in the individual studies, with treatment effect increasing with dose | | | |
| 35. Wagner G et al., 2018 | 24 RCTs (seven unique head-to-head studies and 17 placebo- and active controlled trials) outpatient populations with MDD diagnosed by a validated instrument second-generation antidepressant, total 4023 patients | Levomilnacipran, vilazodone, and vortioxetine and other second-generation antidepressants | Systematic review and network meta-analysis | Response to treatment on the Hamilton Depression Rating Scale (defined as a 50 percent improvement of scores from baseline) | Safety and tolerability | Direct comparisons were limited to vilazodone versus citalopram, and vortioxetine versus duloxetine, paroxetine, or venlafaxine XR (extended release). Results of head-to-head trials and network meta-analyses, overall, indicated similar efficacy among levomilnacipran, vilazodone, or vortioxetine and other second-generation antidepressants | Moderate | Vilazodone compared with citalopram. Results from network meta-analyses provided similar results for response (RR 1.01, 95% CI 0.72 to 1.41) Vortioxetine compared with duloxetine r Results from network meta-analyses indicated similar response rates between vortioxetine and duloxetine (RR 1.22, 95% CI 0.95 to 1.56 Vortioxetine compared with venlafaxine XR Results from network meta-analyses provided similar results for response (RR 1.15, 95% CI 0.91 to 1.45; Vortioxetine compared with other second-generation antidepressants network meta-analysis model, the comparison with bupropion lost statistical significance (RR 1.29, 95% CI 0.99 to 1.68). The difference in response rates for the comparison of vortioxetine with fluoxetine, however, remained statistically | Vilazodone compared with citalopram Risks for most specific adverse events were similar between the vilazodone and citalopram treatment groups (Significantly more patients treated with vilazodone experienced diarrhea (26.5% vs. 10.6%; RR 2.49, 95% CI 1.69 to 3.67 and vomiting (6.6% vs. 1.8%; RR 3.73, 95% CI 1.41 to 9.86]) than patients treated with citalopram Vortioxetine compared with paroxetine Overall risks of adverse events were numerically higher in patients treated with vortioxetine than paroxetine (43.8% vs. 31.5%; RR 1.39, 95% CI 0.84 to 2.31 Concerning specific adverse events, statistically significantly more patients treated with vortioxetine |

BJP PRE-PROOF

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| | | | | | | | | significant (RR 1.30, 95% CI 1.02 to 1.67) | experienced nausea (37.5% vs. 16.7%; RR 2.25, 95% CI 1.12 to 4.53 than patients treated with paroxetine Vortioxetine compared with venlafaxine XR overall risks of adverse events vortioxetine in comparison to patients treated with venlafaxine XR (74.0% vs. 75.2%; RR 0.98, 95% CI 0.84 to 1.15 discontinuation was similar between patients treated with vortioxetine or venlafaxine XR (18.8% vs. 18.4%; RR 1.02, 95% CI 0.58 to 1.79 |
| 36. Wang Y et al., 2013 | 17 RCTs studies with 3,110 patients over 18 years of age with major depression | Fluoxetine and paroxetine | Meta-analysis | The response rate to at the end point treatment. Response was defined as at least a 50% reduction in the absolute HDRS or MADRS score from baseline, or significant improvement in the CGI, at the conclusion of therapy | The dropout rate | In the 6-week subgroup, paroxetine was more efficacious than fluoxetine (odds ratio [OR]: 0.74; P < 0.05). In the 8/10-week subgroup, two drugs displayed comparative efficacy (OR, 0.85; P > 0.05). In the 12-week subgroup, fluoxetine was more efficacious than paroxetine (OR: 1.25; P < 0.05). There were no significant differences in acceptability | Low | The OR of fluoxetine versus paroxetine was 1.03 (95% CI: 0.88–1.20), indicating that the treatment efficacies of the two SSRIs in depressed patients were nearly equipotent. In subgroup analysis, in the 6-week subgroup, paroxetine was more efficacious than fluoxetine (odds ratio [OR]: 0.74; P < 0.05). In the 8/10-week subgroup, two drugs displayed comparative efficacy (OR, 0.85; P > 0.05). In | The OR of fluoxetine versus paroxetine was 0.95 (95% CI: 0.81–1.12), demonstrating that there was little difference in the acceptability of the two SSRIs |

BJP PRE-PROOF

| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
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| | | | | | | | | the 12-week subgroup, fluoxetine was more efficacious than paroxetine (OR: 1.25; P < 0.05) | |
| 37. Wen XJ et al., 2014 | 17 trials, involving 3807 participants aged from 18 to 65 years, fitting the diagnostic standard of MDD according to the Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or text revision (DSM-IV TR) diagnosis of MDD, single episode or recurrent MDD | Atypical antipsychotics | Meta-analysis | The remission scale included MADRS and the 17-item Hamilton Rating Scale for Depression (HRSD-17) (15,16). Remission rate was defined according to the primary trials on the MADRS rating scale. As for the HRSD-17 rating scale, a total score of #7 was defined as remission. Response was defined as a 50% decrease on the MADRS score from baseline to the end of study or as a 50% decrease in the HRSD-17 total score to the end of study | The discontinuation rate due to adverse effects was used to assess the safety of AAPs for MDD patients | The remission rate (RR) and overall response rate (ORR) of adjunctive treatment with AAPs were significantly higher than placebo treatment: RR=1.90 (95%CI=1.61-2.23, z=7.74, P,0.00001) and ORR=1.68 (95%CI=1.45-1.94, z=7.07, P,0.00001). We found that the short-term (4 weeks) treatment [ORR=1.70 (95%CI=0.98-2.95, Z=1.89, P=0.06)] was significantly different from the long-term (6-12 weeks) treatment [ORR=1.68 (95%CI=1.45-1.94, z=7.07, P,0.00001)]. No significant difference in ORR was observed between groups with or without sedative drugs. The discontinuation rate due to adverse effects was higher for adjunctive treatment with AAPs: ORR=3.32 (95%CI=2.35-4.70, z=6.78, P,0.00001). These results demonstrate that the augmentation of ATDs with AAPs (olanzapine, quetiapine, aripiprazole, and risperidone) was more effective than a placebo | High | Remission rate ORRs for different AAPs varied from 1.78 to 2.63, with substantial overlap among 95%CI. The ORR for overall remission was 1.90 (95%CI=1.61-2.23), with statistical significance of Z=7.74, P,0.00001. The overall remission rate was 32.6% (676/2074) for adjunctive groups compared with 18.2% (297/1637) for placebo groups. The AR for remission was 0.145, indicating an NNT of 7 (95%CI=6-9) Response rate ORRs for different AAPs varied from 1.40 to 1.99, with substantial overlap among the 95%CI. The ORR for overall response was 1.68 (95%CI=1.45-1.94), with statistical significance of z=7.07, P,0.00001. The ORR was 43.8% (908/2074) for adjunctive groups compared with 28.7% (470/1637) for placebo | The ORR for discontinuation rate was 3.32 (95%CI=2.35-4.70), with statistical significance of P,0.00001. The overall discontinuation rate was 9.1% (194/2127) for AAPs groups, compared with 2.6% (43/1680) for placebo groups. The AR for the discontinuation rate due to adverse effects was 0.07, indicating an NNH of 16 (95%CI=12-20 |

BJP PRE-PROOF

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| | | | | | | | | groups. The AR for response rate was 0.15, indicating an NNT of 7 (95%CI=6-8) | |
| 38. Yang X et al., 2024 | Participants diagnosed with MDD based on the **(DSM)** or the **(SCID I)**. 16 randomized controlled trials comprising a total of 6593 participants aged 18 years and older | Vortioxetine | Systematic review and meta-analysis | Mean change in depression scale scores, such as the **(MADRS)** and the **(HAM-D),** from baseline to the end of the study | Response (defined as a 50% or greater reduction in total depression scale scores), dropout rate for any reason (acceptability), dropout rate due to adverse events (tolerability), occurrence of adverse events (safety) | Vortioxetine demonstrated a small to moderate effect in improving depressive symptoms compared to placebo **(Cohen's d = -0.34; 95% CI: -0.43 to -0.26; $I^2$ = 59.26%; P < 0.01**). The response rate was significantly higher in the vortioxetine group compared to placebo **(RR = 1.37; 95% CI: 1.27 to 1.48; $I^2$ = 53.67%; P < 0.01**). Compared to other antidepressants: **SSRIs:** No significant difference in symptom improvement (**Cohen's d = 0.02; 95% CI: -0.17 to 0.22; $I^2$ = 0%; P = 0.81**). **SNRIs:** Lower efficacy compared to vortioxetine (**Cohen's d = 0.14; 95% CI: 0.06 to 0.22; $I^2$ = 26.46%; P < 0.01**). The dropout rate for any reason was slightly higher in the vortioxetine group compared to placebo (**RR = 1.11; 95% CI: 1.00 to 1.23; $I^2$ = 7.98%; P = 0.04**). The dropout rate due to adverse events was significantly higher in the vortioxetine group (**RR = 1.39; 95% CI: 1.15 to 1.69; $I^2$ =** | Low | Vortioxetine demonstrated a small to moderate effect in improving depressive symptoms compared to placebo (**Cohen's d = -0.34; 95% CI: -0.43 to -0.26; $I^2$ = 59.26%; P < 0.01**). The response rate was significantly higher in the vortioxetine group compared to placebo (**RR = 1.37; 95% CI: 1.27 to 1.48; $I^2$ = 53.67%; P < 0.01**). Compared to other antidepressants: **SSRIs:** No significant difference in symptom improvement (**Cohen's d = 0.02; 95% CI: -0.17 to 0.22; $I^2$ = 0%; P = 0.81**). **SNRIs:** Lower efficacy compared to vortioxetine (**Cohen's d = 0.14; 95% CI: 0.06 to 0.22; $I^2$ = 26.46%; P < 0.01**) | The dropout rate for any reason was slightly higher in the vortioxetine group compared to placebo (**RR = 1.11; 95% CI: 1.00 to 1.23; $I^2$ = 7.98%; P = 0.04**). The dropout rate due to adverse events was significantly higher in the vortioxetine group (**RR = 1.39; 95% CI: 1.15 to 1.69; $I^2$ = 0%; P < 0.01**). The rate of adverse events was slightly higher in the vortioxetine group compared to placebo (**RR = 1.11; 95% CI: 1.07 to 1.14; $I^2$ = 4.13%; P < 0.01**) |

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| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | **0%; P < 0.01**).<br>The rate of adverse events was slightly higher in the vortioxetine group compared to placebo (**RR = 1.11; 95% CI: 1.07 to 1.14; $I^2$ = 4.13%; P < 0.01**) | | | |
| 39. Yao R et al., 2020 | 7 RCTs with a total of 373 patients diagnosed as depressive disorder | Riluzole | Systematic review and meta-analysis | Change in depression severity | Response rate, remission rate, relapse time and rate, adverse events | Showed no antidepressant efficacy compared to placebo in monotherapy or riluzole-ketamine combined therapy, while it might relieve depression severity to some extent in riluzole-citalopram therapy. Furthermore, riluzole showed favorable safety for DD. The longer relapse time of riluzole group might have clinical significance to some extent, although this had no statistical difference | Moderate | Change in depression severity The subgroup analyses indicated that there was no significant difference between riluzole and placebo group when riluzole/placebo monotherapy (P = .512, I 2 = 0%; SMD −0.078, 95% CI −0.335 to 0.178, P = .549) or combination of riluzole/placebo and ketamine (P = .063, I2 = 71%; SMD −0.427, 95% CI −0.968 to 0.115, P = .122) was dosed. While some difference was shown when combined riluzole with citalopram (SMD 0.844, 95% CI 0.315 to 1.374, P = .002). Response rate the results of fixed effects model suggested that there was no significant difference between riluzole and placebo group (RR 1.201, 95% CI 0.908 to 1.587, P = .199 | Adverse events, the difference between riluzole and placebo group was not significant (RR 1.296, 95% CI 0.920 to 1.824, P = .138 |

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| Reference | Population | Intervention | Study type | Primary outcome | Secondary outcome | Main results | Level of evidence (Amstar 2) | Effect size | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| 40. Zhou X et al., 2015 | 18 RCTs (total n = 4422), adult patients (aged more than 18 years) diagnosed with a current episode of major depressive disorder according to standard diagnostic interviews, patients who had an inadequate response to at least one course of conventional antidepressant treatment prior to enrollment in the study | Antipsychotics | Systematic Review and Network Meta-Analysis | Efficacy was mean change scores in depressive symptoms, as measured by the mean change score of depression rating scales from baseline to endpoint | Response and remission in depressive symptoms, as estimated by the proportion of patients who achieved a decrease of a certain percentage or moved below the threshold in depression rating scores | All standard-dose atypical antipsychotics were significantly more efficacious than placebo in the efficacy (standardized mean differences [SMDs] ranged from -0.27 to -0.43). There were no significant differences between these drugs. Low-dose atypical antipsychotics were not significantly more efficacious than the placebo. In terms of tolerability, all standard-dose atypical antipsychotics, apart from risperidone, had significantly more side-effect discontinuations than placebo (odds ratios [ORs] ranged from 2.72 to 6.40). In terms of acceptability, only quetiapine (mean 250–350mg daily) had significantly more all-cause discontinuation than placebo (OR = 1.89). In terms of quality of life/functioning, standard-dose risperidone and standard-dose aripiprazole were more beneficial than placebo (SMD = -0.38; SMD = -0.26, respectively), and standard-dose risperidone was superior to quetiapine (mean 250–350mg daily) | High | Compared with placebo, all standard-dose agents were significantly more effective (SMD ranged from -0.27 to -0.43), while low-dose OFC (olanzapine/fluoxetine) and low-dose aripiprazole were not. In terms of the QoL/functioning outcome, only standard dose risperidone and standard-dose aripiprazole were significantly more beneficial than placebo (SMD = -0.38, 95% CrI -0.65 to -0.12, and SMD = -0.26, 95% CrI -0.40 to -0.11, respectively). Moreover, standard-dose risperidone was significantly more beneficial than quetiapine (mean dosage: 250–350mg daily; SMD = 0.35, 95% CrI 0.02 to 0.70 | All standard-dose agents, except for risperidone, had significantly more side-effect discontinuations than placebo (OR ranged from 2.72 to 6.40). Quetiapine (mean dose 250–350mg daily) and standard-dose OFC had significantly more side-effect discontinuations than low-dose OFC (OR = 5.68, 95% credible interval [CrI] 1.38 to 90.42; OR = 8.53, 95% CrI 1.08 to 36.67, respectively). In terms of acceptability outcome, only quetiapine (mean dose 250–350mg daily) had a significantly higher rate of all cause discontinuation than placebo (OR = 1.89, 95% CrI 1.19 to 3.10) |

BJP PRE-P

**Table S2** Articles excluded after full text analysis.

| Identification | Article | Reason |
|---|---|---|
| 1 | Sheehan DV et al. 2016 | Other outcome |
| 2 | Katzman MA et al. 2017 | Other outcome |
| 3 | Vaccarino SR et al. 2019 | Other outcome |
| 4 | Kamp CB et al. 2024 | Other outcome |
| 5 | Krause M et al. 2019 | Other outcome |
| 6 | Wong S et al. 2024 | Other outcome |
| 7 | Calder CN et al. 2024 | Other outcome |
| 8 | Wiesinger T et al. 2023 | Other outcome |
| 9 | Vieta E et al. 2013 | Pool analysis |
| 10 | Iovieno N et al. 2021 | Pool analysis |
| 11 | Katzman MA et al. 2020 | Pool analysis |
| 12 | Li G et al. 2017 | Pool analysis |
| 13 | Carrasco JL et al. 2016 | Pool analysis |
| 14 | Magid M et al. 2015 | Pool analysis |
| 15 | Pae CU et al. 2014 | Pool analysis |
| 16 | Juul S et al. 2021 | Study protocol |
| 17 | Jia Y et al. 2016 | Study protocol |
| 18 | Jones BDM et al. 2021 | Study protocol |
| 19 | Jørgensen CK et al. 2021 | Study protocol |
| 20 | Wolters M et al. 2021 | ROBIS High risk bias |
| 21 | Guzek D et al. 2023 | ROBIS High risk bias |
| 22 | Muttoni S et al. 2019 | ROBIS High risk bias |
| 23 | Abbasowa L et al. 2013 | ROBIS High risk bias |
| 24 | Gudayol-Ferré E et al. 2021 | ROBIS High risk bias |
| 25 | Wan LB et al. 2015 | ROBIS High risk bias |
| 26 | Yi L et al. 2024 | ROBIS High risk bias |
| 27 | Mosca D et al. 2017 | ROBIS High risk bias |
| 28 | Zhou X et al. 2015 | ROBIS High risk bias |
| 29 | Marcantoni WS et al. 2020 | ROBIS High risk bias |
| 30 | Lian J et al. 2024 | ROBIS High risk bias |
| 31 | Ahmad A et al. 2024 | ROBIS High risk bias |
| 32 | Berhan A et al. 2013 | AMSTAR 2 Critically low level of quality |
| 33 | Al-Karawi D et al. 2016 | AMSTAR 2 Critically low level of quality |
| 34 | Citrome L. 2014 | AMSTAR 2 Critically low level of quality |
| 35 | Florea I et al. 2017 | AMSTAR 2 Critically low level of quality |
| 36 | Majeed A et al. 2021 | AMSTAR 2 Critically low level of quality |
| 37 | Maruf AA et al. 2022 | AMSTAR 2 Critically low level of quality |
| 38 | Zheng W et al. 2016 | AMSTAR 2 Critically low level of quality |
| 39 | Ng QX et al. 2017 | AMSTAR 2 Critically low level of quality |

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