Clinical Practice Guidelines for Mental Health Disorders in the Philippines: A 2025 Update of the Pharmacologic Treatment of Bipolar Disorder, Anxiety Disorder, Schizophrenia, and Depressive Disorders

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Disclaimer and Contact Information

In 2017, the Philippine Psychiatric Association released a **Consensus Treatment Guideline (CTG)** on the management of Bipolar Mood Disorder, Anxiety Disorder, Schizophrenia, and Depressive Disorder. This document served as a key reference for clinicians at the time.

Since then, both the national framework for guideline development and the legal landscape have evolved, particularly with the enactment of the **Mental Health Law** and the adoption of the Department of Health's **Clinical Practice Guideline (CPG) process**. In this context, the present document represents an **update of the 2017 CTG**, now developed as a **Clinical Practice Guideline (CPG)** using more rigorous and standardized methods.

For clarity, readers may encounter both terms—**CTG** and **CPG**—in reference to previous and current versions of this guideline. In this document, **CPG** is the official and updated terminology, and it supersedes the 2017 CTG.

This clinical practice guideline specifically addresses the **pharmacologic treatment** of four common psychiatric conditions: **Bipolar Disorder, Anxiety Disorder, Schizophrenia, and Depressive Disorders.** It is intended to assist physicians and other healthcare professionals by providing evidence-based recommendations for medication management.

While the Department of Health (DOH) encourages adherence to this guideline, it is not meant to replace clinical judgment or individualized patient care. Clinicians should integrate these recommendations with their professional expertise, individual patient needs, and institutional protocols, ensuring that treatment decisions align with patient values, needs, and preferences.

Healthcare providers and relevant stakeholders should exercise sound clinical decision-making, recognizing that patient histories, current health status, and responses to treatment may vary. While payors, policymakers, hospital administrators, and employers may reference this guideline, nonconformance with its recommendations should not be the sole basis for approving or denying financial assistance, insurance claims, or other administrative decisions. Furthermore, these recommendations should not be regarded as a rigid basis for legal or regulatory actions.

The developers acknowledge the limitations of this guideline. The evidence summaries presented are based on the best available scientific data at the time of its development. It is subject to periodic updates as new evidence emerges, and users are encouraged to refer to the most current version when making clinical decisions.

For further inquiries, please contact the National Center for Mental Health and Philippine Psychiatric Association.

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This clinical practice guideline (CPG) was funded by the **National Center for Mental Health (NCMH)**. The funding bodies had no role in the formulation of the clinical questions, selection and appraisal of the evidence, development of recommendations, or drafting of the guideline. They did not have any decision-making authority, influence, or exclusive rights over the content, conclusions, or dissemination of this guideline.

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We also acknowledge the Consensus Panel members, whose diverse expertise and perspectives ensured that the recommendations were contextualized, clinically relevant, and responsive to the needs of Filipino patients.

We sincerely thank the External Reviewers for their valuable comments that enhanced the clarity, feasibility, and applicability of the guideline.

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Participating Societies, Organizations, Agencies, and/or Institutions

Philippine Psychiatric Association

National Center for Mental Health

Philippine Academy of Family Physicians

#MentalHealthPH

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1. Executive Summary

Mental health disorders are a leading cause of disability in the Philippines, affecting millions of Filipinos and contributing significantly to the national burden of disease. According to the World Health Organization, as of 2017, an estimated 3.3 million Filipinos live with depressive disorders and 3 million with anxiety disorders—figures that have likely increased in the wake of the COVID-19 pandemic. Schizophrenia and bipolar disorder, while less prevalent, cause profound functional impairment and long-term disability.

In response to this growing public health concern, the Philippine Psychiatric Association (PPA), in collaboration with the National Center for Mental Health (NCMH), updated its 2017 Consensus Treatment Guidelines. This 2025 Clinical Treatment Guideline (CTG) provides evidence-based, context-specific recommendations on the pharmacologic management of adults with anxiety disorders, depressive disorders, bipolar disorder, and schizophrenia.

This guideline addresses 12 priority questions covering four major psychiatric conditions, with a focus solely on pharmacologic interventions. It provides therapeutic recommendations for acute treatment, relapse prevention, and maintenance phases. The recommendations are based on a structured review of clinical evidence, contextual factors, patient values, and resource availability in the Philippine setting.

The guideline was developed by a multidisciplinary team composed of psychiatrists, clinical epidemiologists, methodologists, patient advocates, and primary care representatives. A de novo process was used following the 2018 DOH Manual for Clinical Practice Guideline Development and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Current best available evidence for each topic was synthesized through a systematic literature review and evaluated for certainty. Recommendations were formulated over 4 online consensus meetings held from March 20-22, 2025. The strength of each recommendation was classified as strong or weak/conditional, based on a transparent assessment of benefits, harms, certainty of evidence, feasibility, cost, and values/preferences.

As a result of this deliberative process, 13 recommendations were made (Table 1). This CTG is primarily intended for psychiatrists and psychiatric residents-in-training, but may also be used by primary care physicians, mental health professionals, and health institutions involved in treating individuals with the prioritized mental health disorders. Patients and the public are indirect beneficiaries of this CTG, as its implementation is expected to promote equitable, affordable, and effective care across the country.

Table 1. Summary of recommendations: 2025 Consensus Treatment Guidelines for Mental Health Disorders in the Philippines.

No.	Recommendation	Strength	Certainty
Anxiety Disorder			
1-A	We suggest against the use of **vortioxetine** as first-line treatment among patients with generalized anxiety disorder.	Weak	Very Low
1-B	We recommend the use of **agomelatine** as a first-line treatment among patients with generalized anxiety disorder.	Strong	Moderate
2	We suggest against the use of **atypical antipsychotics and SSRI/SNRI combination** as first line treatment for patients with treatment-resistant generalized anxiety disorder.	Weak	Very Low
3	We suggest against the use of **mirtazapine** as first-line treatment in patients with panic disorder.	Weak	Very low
Bipolar Disorder			
4	We suggest against the use of **brexpiprazole monotherapy** as treatment in patients with bipolar 1 disorder presenting with acute mania.	Weak	Very low
5	We suggest against the use of **SSRI or SNRI** as an adjunct in the treatment of patients with bipolar 1 disorder with acute depression. Remarks: Available evidence only supports the use of fluoxetine and olanzapine as separate medications, not as the combination drug (Symbyax)	Weak	Very low
6	We suggest the use of **valproic acid*** among patients with bipolar 1 disorder in the maintenance phase of treatment. *Remarks: Includes all other derivatives of valproic acid.	Weak	Very low
Depressive Disorder			
7	We recommend **antidepressant plus antipsychotic combination** rather than antidepressant monotherapy among patients with major depressive disorder with psychotic features.	Strong	Very low
8	We suggest against the use of **antidepressant plus benzodiazepine combination** at the outset among patients with major depressive disorder with anxious distress.	Weak	Very low
9	We suggest the use of **intranasal esketamine** as add-on therapy to antidepressants among patients with treatment-resistant depression.	Weak	Very low
Schizophrenia			
10	We suggest the use of **dopamine partial agonists** as a non-inferior alternative to serotonin-dopamine antagonists in the treatment of patients with schizophrenia in the acute phase.	Weak	Very Low
11	We suggest the use of **long-acting injectable antipsychotics** as an alternative to oral antipsychotic monotherapy in the treatment of adults with schizophrenia in the acute* phase.	Weak	Low

	**Remarks: The acute phase of schizophrenia is defined as the period of an acute psychotic episode. This phase begins with a new onset or acute exacerbation of symptoms and lasts until symptoms are reduced to a level considered to be the patient's expected "baseline." (APA, 2010)*		
12	We recommend the use of **long-acting injectable antipsychotics** instead of oral antipsychotic monotherapy in the treatment of patients with schizophrenia in the chronic or residual phase.	Strong	Very Low

2. Background

Introduction

Mental health disorders are a global health concern. In fact, according to the World Health Organization, there will be approximately 970 million people worldwide in 2019 who are suffering from a mental disorder; with depression and anxiety being the most prevalent.[1] This increase in numbers can also be seen in other psychiatric disorders such as schizophrenia affecting 1 in 300 people worldwide and bipolar disorder with 40 million people affected worldwide. In the Philippines, there are 3.3 million cases of depressive disorders and 3 million cases of anxiety disorders in 2017. With the COVID 19 pandemic, the number of people living with anxiety and depressive disorders increased significantly with initial estimates to be that of 26% for anxiety and 28% for major depressive disorders.[2]

To address this growing mental health need and to provide standardized patient care, the Philippine Psychiatric Association released a consensus treatment guideline last 2017 on Bipolar Mood disorder, Anxiety Disorder, Schizophrenia and Depressive Disorder. The guideline is used as a reference to the treatment of mental illness in the Philippines. However, as mental health illness and its treatment is continuously evolving, there is a need for an updated clinical practice guideline to ensure that the recommendations include the current developments in treatment. Furthermore, The National Center for Mental Health in accordance to the Department of health Department Order no 2021-0001 and Section 30 of the Implementing Rules and Regulation of Republic Act 11036 (Mental Health Law) has collaborated with the Philippine Psychiatric Association as the organization with expertise to update the consensus treatment guidelines for mental health disorders in the Philippines.

Rationale for this CTG

Mental health disorders are among the top contributors to disability and healthcare burden in the Philippines. While psychotropic medications are widely available, treatment gaps persist, especially in primary care and community settings. Variability in prescribing practices, underutilization of evidence-based therapies, and limited contextual guidance on drug selection and duration are common challenges.

[1] World Health Organization(2024) Mental Disorders WHO. https://www.who.int/news-room/fact-sheets/detail/mental-disorders

[2] World Health Organization. (2021). Prevention and management of mental health conditions in the Philippines: The case for investment. World Health Organization Regional Office for the Western Pacific

Although international practice guidelines exist, many are developed in high-income countries and may not fully consider the realities of access, availability, and affordability in the Philippine context. Thus, this CTG was developed de novo by the Philippine Psychiatric Association (PPA), following the Department of Health (DOH) 2018 Manual for CPG Development and using the GRADE approach. It aims to improve quality of care by guiding clinicians in delivering rational, person-centered pharmacologic therapy adapted to the Filipino setting.

Scope

This update is composed of 12 key questions (Table 2) covering 4 priority conditions–**Anxiety Disorder**, **Bipolar Disorder**, **Depressive Disorder**, and **Schizophrenia**–with corresponding graded recommendations directed towards the treatment of adult patients.

Table 2. Guideline questions and topics.

Anxiety Disorder	
1	Should vortioxetine or agomelatine be used as an alternative treatment of patients with Generalized Anxiety Disorder?
2	Should atypical antipsychotics (Risperidone, Olanzapine, Aripiprazole, quetiapine) be used as add-on therapy to SSRI/ SNRI (escitalopram, sertraline, fluoxetine, duloxetine, escitalopram, paroxetine, venlafaxine) for patients with treatment resistant GAD?
3	Should mirtazapine be used in the treatment for panic disorder?
Bipolar Disorder	
4	Should we use brexpiprazole in patients with Bipolar I Disorder presenting with acute mania?
5	Should antidepressants (SSRIs, as a class) be used as an adjunct treatment in patients with Bipolar I Disorder presenting with acute depression?
6	Should valproic acid be used in patients with Bipolar I Disorder in the maintenance phase of treatment?
Depressive Disorder	
7	Should antidepressants combined with benzodiazepines (clonazepam, alprazolam, bromazepam) be used at the outset in patients with Major Depressive Disorder with Anxious Distress?
8	Should antidepressants combined with atypical antipsychotics (SGAs) be used at the outset in patients with Major Depressive Disorder with Psychotic Features?
9	Should novel medications such as esketamine be used as add-on therapy in patients with MDD who are non-responders or partial responders to conventional antidepressants (SSRIs, SNRIs, NaSSa) alone?
Schizophrenia	
10	Should dopamine partial agonists be used as an alternative to serotonin-dopamine antagonists be used in patients with schizophrenia in the acute phase?
11	Should long-acting injectable antipsychotics be used as an alternative to oral antipsychotic monotherapy among patients with schizophrenia in the acute phase?
12	Should long-acting injectable antipsychotics be used versus oral antipsychotic monotherapy in patients with schizophrenia in the chronic or residual phase?

Objectives of the Guideline

General Objective

To identify best practices in the pharmacologic management of adults with common mental health disorders—specifically Anxiety Disorders, Depressive Disorders, Bipolar Disorder, and Schizophrenia—through a comprehensive and systematic assessment of the benefits, harms, and costs of selected drug treatments.

Specific Objectives

- To provide evidence-based guidance on current pharmacologic options for the management of the four major mental health disorders, with consideration of prompt, effective, and feasible treatment strategies.
- To determine the effectiveness and safety of pharmacologic interventions used to improve clinical outcomes and quality of life among adults with mental health disorders.
- To determine the certainty of the evidence supporting each of the selected pharmacologic interventions using the GRADE approach.
- To incorporate insights from patient values, clinician experience, and system-level feasibility in making treatment recommendations.
- To develop evidence-based pharmacologic treatment recommendations through a structured, consensus-driven process, as outlined in the 2018 DOH Manual for Clinical Practice Guideline Development.

Target Population, Intended User/Audience, and Settings

Target Population

This Clinical Treatment Guideline (CTG) is intended for adults diagnosed with common mental health disorders, specifically Anxiety Disorders, Depressive Disorders, Bipolar Disorder, and Schizophrenia, who are being considered for or are already receiving pharmacologic treatment. The recommendations are applicable across the continuum of care, from acute symptom management to maintenance and relapse prevention.

Although this CPG focuses on the adult population, some recommendations may still be relevant for older adolescents transitioning into adult mental health services, as well as older adults, provided that clinical judgment is used to individualize care.

Intended Users

The guideline is primarily intended for psychiatrists and psychiatric residents-in-training involved in the management of mental health conditions. We hope that this guideline would provide support for Filipino psychiatrists in making decisions regarding pharmacological treatment that are grounded in the best available evidence. However, recognizing the critical role of other providers in mental health service delivery, it may also serve as a valuable resource for:

- **Primary care physicians** (e.g., general practitioners, family and community medicine doctors, internists) who often provide first-line mental health care, especially in remote or underserved areas with limited access to psychiatric specialists

- **Other mental health professionals**, such as psychiatric nurses and clinical psychologists, involved in the collaborative care of patients

- **Health program managers and policy-makers** involved in planning, implementing, and evaluating mental health services in both public and private sectors

- **Training institutions, professional societies, and accreditation bodies** engaged in mental health education and quality improvement

Moreover, this guideline aims to support patients and the general public by serving as a resource to advocate for the expansion of an accessible, affordable, and effective mental health care package under Universal Health Care (UHC).

Clinical Settings

This CPG is applicable in a wide range of outpatient and inpatient mental health care settings, including but not limited to:

- **Mental health specialty clinics** (hospital-based or stand-alone)

- **Primary care facilities** integrating mental health services

- **Inpatient psychiatric units** and **general hospital wards**

- **Community-based mental health centers** and **halfway homes**

Recommendations are contextualized for use within the Philippine healthcare system, taking into account medication availability, cost, patient access, and feasibility of implementation in both urban and rural settings.

3. Guideline Development Methodology

Overview of guideline development methodology

This Philippine Psychiatric Association (PPA) CTG was created in accordance with the Department of Health's 2018 Manual for Clinical Practice Guideline Development and is informed by the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. The methodology ensures that recommendations are evidence-based, patient-centered, and transparent. The guideline development process involved four main phases: (1) Preparatory Phase, (2) Evidence Synthesis, (3) Evidence to Decision, and (4) Knowledge Translation. Each step is detailed below.

Guideline Preparation

Organization of the Guideline Development Group

The Philippine Psychiatric Association (PPA) organized a multidisciplinary task force composed of several working groups: the Steering Committee (SC), Conflict of Interest (COI) Oversight Committee (OC), Evidence Review Experts (ERE)/Technical Working Group (TWG), and the Consensus Panel (CP). An independent External Review Group was also formed. Members of each group were identified and convened through appropriate coordination with relevant stakeholders and/or specialty societies.

Formulation of the Guideline and Review Questions

The formulation of review questions for this CTG followed a structured, evidence-informed approach as outlined in the 2018 DOH Manual for Clinical Practice Guideline Development. This step was essential in ensuring that the evidence gathered would directly inform actionable and patient-centered recommendations.

The process began with the identification and prioritization of key clinical issues relevant to Philippine psychiatric practice. These key issues were derived from initial scoping reviews, expert consultations, and stakeholder discussions conducted by the Steering Committee. Priority was given to areas with high disease burden, variable practice patterns, substantial cost implications, and emerging or conflicting evidence in mental health care delivery.

Once the key issues were finalized, the Steering Committee and Technical Working Group (TWG), in consultation with the Consensus Panel, collaboratively developed a set of guideline questions. These were phrased as foreground questions—not background knowledge—and were designed to yield recommendations that were clear, actionable, and specific. For example, they were structured using the following formats such as:

- Should Intervention A be used in patients with Condition X?
- Should Intervention A or B be used in patients with Condition X?

Following the formulation of guideline questions, the TWG refined these into specific evidence review questions using the PICO format (Population, Intervention, Comparator, Outcome). This enabled a targeted and systematic review of the literature for each question. Depending on the objective of the question (e.g., effectiveness, diagnostic accuracy, safety, cost-effectiveness),

appropriate study designs were identified—such as randomized controlled trials for interventions or observational studies for harms, values, or feasibility.

Each PICO question included:

- Population (P): Defined based on clinical characteristics (e.g., diagnosis, age group, care setting) aligned with the scope of the guideline.
- Intervention (I): A specific drug, procedure, diagnostic strategy, or non-pharmacologic therapy under evaluation.
- Comparator (C): The most relevant alternative, such as standard care or another treatment strategy.
- Outcomes (O): Patient-important outcomes, both beneficial and harmful. These were rated by the Consensus Panel using the GRADE scale to determine their importance for decision-making (1–3: limited importance; 4–6: important; 7–9: critical).

Only outcomes rated as critical or important were included in the evidence synthesis. The overall certainty of the body of evidence was then anchored to the outcome with the lowest certainty among the top seven rated outcomes, in accordance with the GRADE approach. This structured question development process ensured that all subsequent evidence synthesis and recommendation formulation activities were transparent, methodologically sound, and aligned with stakeholder priorities.

Selection and Rating of Critical Outcomes

Following GRADE guidance, the TWG coordinated with the SC and CP to identify and rate outcomes critical for decision-making. The SC initially provided a list of anticipated outcomes, which the TWG supplemented based on an initial scoping search. This comprehensive list of anticipated and encountered outcomes was then subjected to formal rating by members of the Consensus Panel (CP) using a structured Google Form.

Each CP member rated the outcomes using the GRADE 9-point scale, which reflects increasing importance for decision-making: outcomes rated 7–9 were considered critical, 4–6 as important but not critical, and 1–3 as of limited importance. This subjective scoring process was guided by both clinical expertise and the values and preferences of patients, recognizing that guideline recommendations are intended to support shared decision-making between clinicians and patients. The GRADE approach emphasizes identifying outcomes that represent both benefits and harms, and considers the patient’s perspective in determining which outcomes are most relevant and impactful.

The individual ratings were averaged, and the seven outcomes with the highest mean scores were selected as **critical** outcomes and prioritized for evidence synthesis, in accordance with GRADE methodology. Outcomes of limited importance were excluded from the evidence profile, as they were unlikely to influence the direction or strength of the recommendations. This structured process helped focus the guideline on the most meaningful outcomes, resolved potential disagreements, and ensured transparency in outcome prioritization.

Editorial Independence and Management of Conflicts of Interest

The Philippine Psychiatric Association (PPA) funded the development of this CTG but exerted no influence on the formulation of its final recommendations. The recommendations presented in this document were independently developed through consensus during the guideline panel's

en banc meetings, based on the best available evidence and the transparent application of the GRADE approach.

To ensure the integrity and independence of the guideline development process, all members involved in the development of this CPG—including the Steering Committee, Oversight Committee, Technical Working Group, and Consensus Panel—were required to complete a **Conflict of Interest (COI) Declaration Form**. This form required disclosure of any potential financial or intellectual conflicts that existed within four years prior to their engagement in the CPG development process.

An independent **COI Oversight Committee** was tasked with reviewing all submitted declarations, classifying each member's COI status, and advising the Steering Committee on appropriate levels of participation based on these classifications. The COI classifications used were:

1. **Allowed / Acceptable** – The member has no relevant intellectual or financial conflicts of interest.

2. **Manageable B (Broadcast)** – The member has intellectual COIs only. These members were allowed to vote on recommendations but were required to verbally declare their COIs (e.g., institutional affiliations, leadership roles, or authorship in related literature or guidelines) during the en banc meetings.

3. **Manageable C** – The member has both financial and intellectual COIs but was not disqualified. These members were not allowed to vote on recommendations but could contribute to discussions. This category included individuals from government agencies directly involved in policy implementation or those from organizations funding the CPG. Specific management terms were determined by the Oversight Committee and applied to particular clinical questions.

4. **Disqualified** – The member had significant financial and intellectual COIs that could compromise objectivity. These individuals were not allowed to participate in the development of recommendations.

The COI Oversight Committee ensured that all conflicts were managed transparently and consistently to uphold the credibility, trustworthiness, and scientific integrity of the guideline.

Evidence synthesis

This CPG was developed de novo by the Philippine Psychiatric Association (PPA) and its appointed Guideline Development Group, following the standard methodology described in the Department of Health (DOH) Manual for Practice Guideline Development. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was employed to appraise and synthesize the body of evidence and to rate the certainty of evidence for each outcome and recommendation. The entire process was overseen by a multidisciplinary Technical Working Group composed of psychiatrists, clinical epidemiologists, internists, pharmacists, and lived experience representatives.

Search Methods and Strategies

The Evidence Review Experts conducted a systematic literature search to identify relevant local and international studies addressing the key questions formulated by the PPA Guideline Development Group. Searches were performed between January to March 2025 using at least two major databases—MEDLINE and CENTRAL—and supplemented by handsearching the reference lists of included studies.

Each clinical question was translated into a structured PICO format, and tailored search strategies were applied per topic area (Anxiety, Depression, Bipolar Disorder, Schizophrenia). Search terms included both MeSH terms and free-text keywords relevant to the population, interventions, comparators, and outcomes of interest. No language or geographic restrictions were applied. Additional grey literature, such as reports from psychiatric associations and clinical trial registries (e.g., ClinicalTrials.gov), were also reviewed. Detailed search strategies and inclusion criteria for each guideline question are provided in the Annex.

When high-quality, recent systematic reviews were available, they were used as the primary source of evidence. Otherwise, individual randomized controlled trials (RCTs) were retrieved and synthesized. For safety outcomes, observational studies were included as needed. Economic evaluations were reviewed for cost-related considerations; in their absence, costing data were obtained from local pharmaceutical websites and healthcare facilities.

Inclusion and Exclusion Criteria

Each guideline question was framed using a PICO format, which guided the scope of study inclusion. Studies were included if they enrolled the relevant population and compared interventions consistent with the clinical question. Preference was given to RCTs for effectiveness outcomes and observational studies for adverse events and costs. Studies were excluded if they were not primary research, used ineligible populations, or lacked relevant outcomes. Detailed inclusion and exclusion criteria per clinical question are outlined in the Annex.

Study Quality (Risk of Bias) Assessment

The methodological quality of included studies was assessed using validated tools. The Cochrane Risk of Bias Tool (RoB 1) was used for RCTs. Two independent reviewers appraised the risk of bias for each study; disagreements were resolved through discussion or third-party arbitration.

Data Synthesis

Where appropriate, effect estimates for critical and important outcomes were synthesized through meta-analysis using Review Manager (RevMan 5.0). Effect measures included risk ratios (RR), mean differences (MD), and 95% confidence intervals (CI). If meta-analysis was not feasible due to heterogeneity, a narrative synthesis was conducted. Results were summarized in GRADE Summary of Findings tables, and each outcome was rated for certainty (very low, low, moderate, high) using the GRADE framework.

Each guideline question's evidence summary includes pooled data, interpretation of results, and key limitations. The overall certainty of evidence was determined by the lowest certainty rating

among critical outcomes. These summaries served as the basis for deliberations during the consensus panel meetings.

Evidence to Decision

A series of virtual en banc meetings were conducted from March 20 to 22, 2025 to formulate the recommendations for this CTG. Each session was facilitated by a trained guideline methodologist to ensure consistency, neutrality, and adherence to a structured consensus process. Quorum was achieved in all sessions, defined as the presence of at least 75% of the total panelists.

Prior to the meetings, evidence summaries and statements of evidence were prepared by the Technical Working Group (TWG) for each research question. These were distributed to all members of the Consensus Panel ahead of time to allow thorough review. Unlike other CPG processes where draft recommendations are pre-written, the PPA guideline followed a bottom-up approach, starting with statements of evidence. Panelists evaluated the evidence during live sessions and jointly formulated the recommendations.

How Recommendations Were Developed

The Consensus Panel used a modified nominal group technique to deliberate and formulate recommendations. For each review question, the lead evidence reviewer presented the GRADE summary and key findings. The panelists then discussed each item, referencing the GRADE EtD (Evidence to Decision) framework to assess:

1. Balance of desirable and undesirable effects
2. Certainty of the evidence
3. Resource use and cost implications
4. Patient and clinician values and preferences
5. Equity, feasibility, and acceptability
6. Local availability and contextual issues

Following discussion, panelists proceeded to a structured voting process. Each panelist voted on the direction (for or against the intervention) and the strength (strong or conditional/weak) of the recommendation using a visual cue system. A consensus threshold of 75% agreement was required for finalizing the recommendation.

If consensus was not reached in the first round, panelists were given the opportunity to raise further clarifications. Up to three rounds of voting were allowed per recommendation. When consensus was not achieved after three rounds (although this did not occur in this guideline), alternative decision-making strategies (e.g., Delphi process) were planned.

Certainty of Evidence and Rating of Outcomes

The certainty of evidence for each outcome was assessed using the GRADE methodology in GRADEpro. Each outcome was evaluated for risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall certainty rating per question was determined by the lowest certainty among the top seven outcomes considered critical or important.
Prior to the en banc meetings, an online survey was administered to all Consensus Panel members to rate outcomes by importance for decision-making. Using a 9-point Likert scale:

- 7–9 = Critical for decision-making
- 4–6 = Important but not critical
- 1–3 = Limited importance

The top seven outcomes were retained for each PICO question and used as the basis for formulating and grading recommendations.

Determining the Direction and Strength of Recommendations

Panelists voted on the direction (i.e., “for” or “against” the use of an intervention) and the strength (i.e., “strong” or “weak/conditional”) based on a judgment of trade-offs between benefits and harms, level of certainty, patient preferences, and contextual factors.

Recommendations were classified using standard GRADE language:

- **Strong** (e.g., “We recommend…”) – when the panel had high confidence that the benefits of the intervention clearly outweighed the harms (or vice versa).

- **Weak** (e.g., “We suggest…”) – when the balance of benefits and harms was less certain, or when evidence was of low certainty, had imprecision, or raised concerns about applicability in certain settings or populations.

Incorporation of Preferences and Values

Information on patient and public values and preferences was obtained through:

- Literature reviews of qualitative studies and surveys
- Consideration of real-world practice patterns and barriers from local and international sources
- Insights from clinicians and patient advocates serving on the panel, who contributed their experiences in care delivery and lived experience

These insights were integrated into the EtD framework and weighed during consensus deliberations. Where direct evidence was lacking, judgments were based on panelists’ expertise and experiences from diverse clinical settings in the Philippines.

External Review

The draft PPA CTG underwent a structured external review prior to its submission to the Department of Health (DOH) National Practice Guidelines Program. The purpose of the external review was to enhance the overall quality of the guideline, gather expert feedback on the clarity and validity of the draft recommendations, assess their clinical applicability and feasibility in psychiatric settings, and ensure that the evidence was appropriately contextualized to Philippine mental health care. The process also supported early dissemination of the guideline draft to key stakeholders in psychiatric practice.

Methods of External Review

The review was conducted using a structured evaluation tool developed specifically for this CPG. The form included both rating scales and open-ended questions. Reviewers were asked to assess:

- The completeness of the evidence search, synthesis, and interpretation for each clinical question
- The clarity, acceptability, and relevance of each recommendation
- The rationale for each recommendation, including trade-offs between benefits and harms, cost implications, feasibility, and patient values
- The implementability of each recommendation in routine psychiatric practice

Reviewers were invited to suggest alternative recommendations when appropriate and provide justifications for their feedback.

Profile of External Reviewers

All external reviewers were **psychiatrists** with expertise in the care of individuals with mental health conditions, including comorbid chronic illnesses such as diabetes and substance use disorders. A total of **13** reviewers participated, representing both **academic institutions and clinical practice settings** across the Philippines. These reviewers were independent of the guideline development group and were selected to ensure broad content expertise and familiarity with the local context.

Use of Feedback in Guideline Finalization

All feedback from the external reviewers was consolidated by the Technical Leads and reviewed by the Steering Committee. Suggestions that improved clarity, contextual relevance, or feasibility were integrated into the final draft. In cases of conflicting feedback, the Steering Committee deliberated and made consensus-based decisions, balancing evidence certainty, clinical judgment, and local practice realities.

The final version of the CPG thus reflects both a rigorous evidence review process and the informed perspectives of external content experts in psychiatry, ensuring that the guideline is both evidence-based and highly applicable to mental health practitioners across the country.

4. Evidence and Recommendations: Anxiety Disorder

Guideline Question 1: Should vortioxetine or agomelatine be used as an alternative treatment of patients with Generalized Anxiety Disorder?

Recommendation 1-A.	
We suggest against the use of vortioxetine as first-line treatment among patients with generalized anxiety disorder.	
Strength of Recommendation:	Weak
Certainty of Evidence:	Very Low

Recommendation 1-B.	
We recommend the use of agomelatine as a first-line treatment among patients with generalized anxiety disorder.	
Strength of Recommendation:	Strong
Certainty of Evidence:	Moderate

Justification

The panel unanimously issued a weak recommendation against using vortioxetine for generalized anxiety disorder (GAD) due to several concerns. Vortioxetine is primarily an antidepressant and not specifically indicated for GAD, and the available evidence does not demonstrate significant efficacy for this condition. Studies show little to no benefit over placebo, with potential adverse effects and uncertainty about safety. Local practitioners report mixed experiences, and patients cite high costs as a barrier to completing the standard eight-week treatment. Additionally, studies used lower doses (5 mg) than the usual 10 mg, raising concerns about effectiveness for anxiety alone. Given the availability of established alternatives like SSRIs and SNRIs, vortioxetine is not recommended as a first-line treatment for GAD but may be considered for patients with both anxiety and depression.

A strong recommendation supports agomelatine for generalized anxiety disorder (GAD) based on moderate-certainty evidence showing likely improvements in treatment response, acceptability, and symptom reduction compared to placebo. Local practitioners report positive experiences with its efficacy for both anxiety and depressive symptoms. While generally considered a viable first-line option, concerns remain regarding cost, availability, and potential side effects like drowsiness. Patients often prefer agomelatine over SSRIs and SNRIs due to its perceived better safety profile, though side effects vary. Safety considerations for elderly patients should also be considered.

Background

The Philippine Psychiatric Association (PPA) 2017 Anxiety Consensus Treatment Guidelines (CTG) have recommended SSRIs (e.g. escitalopram, sertraline, and paroxetine) and SNRIs (e.g. venlafaxine or duloxetine) as first-line management among patients with GAD. Since then, newer novel antidepressants have emerged. This review focuses on two newer antidepressants, vortioxetine and agomelatine as an update to the PPA CTG.

Vortioxetine is a novel antidepressant approved for the management of major depressive disorder (MDD). It is considered a serotonin modulator and stimulator and affects several serotonin receptors. It has both antidepressant and anxiolytic effects by facilitating the conduction of several chemical signals in the brain, such as serotonin and dopamine.[1] Studies have suggested that it may decrease anxiety symptoms in patients with GAD.[2,3]

Conversely, agomelatine is a unique antidepressant that acts as an antagonist in specific serotonin receptors and as an agonist on the melatonin receptor, an important chemical in the sleep cycle.[4] Just like vortioxetine, studies have suggested that agomelatine may exert anxiolytic effects by targeting the sleep cycle and blocking brain signals that may cause anxiety.[4]

Evidence

Five RCTs assessed the effectiveness of either vortioxetine and agomelatine in managing generalized anxiety disorder (GAD) compared to placebo included. [2,6-9] Two RCTs[2,6] assessed the effectiveness of vortioxetine while the remaining 3 studies[7-9] evaluated agomelatine. The study by Mahableshwarkar (n=781) was a 5-arm trial that assessed the effect of three different doses (2.5mg/day, 5mg/day, 10mg/day) of vortioxetine in managing symptoms of patients with GAD compared to either duloxetine or placebo.[6] On the other hand, RCT conducted by Bidzan et al was a multicenter randomized clinical trial done in Europe using 5mg/day vortioxetine.[2]

The remaining RCTs on agomelatine evaluated its effects at a dose of 25 to 50 mg/day for 12 weeks. The dosage was adjusted depending on the improvement assessed from 2 weeks onward. One of the studies was a three-arm trial where the other arm used escitalopram as comparator. Results were presented per drug.

As of March 15, 2025, no other ongoing studies were found in the clinicaltrial.gov registry.

Benefits and risks

Vortioxetine

Vortioxetine is associated with little to no benefit in treatment response, remission rates, or symptom reduction compared to placebo. It is also associated with a potential increase in adverse events, though the evidence for specific harms such as sleepiness or dropout rates remains uncertain. The overall certainty of the evidence is very low.

Agomelatine

Agomelatine likely increases treatment response and remission rates compared to placebo in patients with GAD. However, it appears to have little to no difference compared to placebo in terms of reducing symptoms as measured by the HAM-A. It also appears to be better tolerated, with lower dropout rates due to lack of efficacy or adverse events. The risk of adverse events is

likely similar to placebo though the evidence on sleepiness or drowsiness remains uncertain. The overall certainty of the evidence is moderate

Table Q1.1. Summary of findings for vortioxetine.

Outcomes	No. of participants (studies)	Pooled effect (95% CI)	Interpretation	Certainty of the evidence
Rate of treatment response (% of patients achieving 50% reduction in HAM-A score)	907 (2 RCTs)	RR 1.27 (0.86 to 1.87)	No significant difference	Low ⊕⊕◯◯
Acceptability (% of patients who dropped out for any reason)	625 (1 RCT)	RR 1.12 (0.81 to 1.55)	No significant difference	Moderate ⊕⊕⊕◯
Remission rate (% of patients with HAM-A score of ≤7)	(2 RCTs)	RR 1.46 (0.89 to 2.38)	No significant difference	Low ⊕⊕◯◯
Change in symptom level (change in HAM-A score)	497 (1 RCT)	MD - 2.21 (-5.46 to 1.03)	No significant difference	Low ⊕⊕◯◯
Adverse events	622 (1 RCT)	RR 1.21 (1.06 to 1.38)	Favors placebo	Moderate ⊕⊕⊕◯
Sleepiness / drowsiness	622 (1 RCT)	RR 1.55 (0.65 to 3.67)	Inconclusive	Very Low ⊕◯◯◯
Drop outs due to lack of efficacy	625 (1 RCT)	RR 0.59 (0.17 to 1.98)	Inconclusive	Very Low ⊕◯◯◯
Drop outs due to adverse events	625 (1 RCT)	RR 2.52 (0.9 to 7.03)	Inconclusive	Low ⊕⊕◯◯

Table Q1.2. Summary of findings for agomelatine.

Outcomes	No. of participants (studies)	Pooled effect (95% CI)	Interpretation	Certainty of the evidence
Rate of treatment response (% of patients achieving 50% reduction in HAM-A score)	733 (3 RCTs)	RR 1.93 (1.38 to 2.7)	Favors agomelatine	Moderate ⊕⊕⊕◯
Acceptability (% of patients who dropped out for any reason)	803 (3 RCT)	RR 0.60 (0.44 to 0.83)	Favors agomelatine	High ⊕⊕⊕⊕
Remission rate (% of patients with HAM-A score of ≤7)	289 (3 RCTs)	RR 2.06 (1.57 to 2.69)	Favors agomelatine	High ⊕⊕⊕⊕
Change in symptom level (change in HAM-A score)	799 (3 RCTs)	MD – 5.98 (-9.37 to 2.59)	No significant difference	Moderate ⊕⊕⊕◯
Adverse events	801 (3 RCTs)	RR 1.13 (0.94 to 1.37)	No significant difference	Moderate ⊕⊕⊕◯
Sleepiness / drowsiness	680 (3 RCTs)	RR 1.94 (0.65 to 6.27)	Inconclusive	Very Low ⊕◯◯◯
Drop outs due to lack of efficacy	803 (3 RCTs)	RR 0.45 (0.21 to 0.96)	Inconclusive	Moderate ⊕⊕⊕◯
Drop outs due to adverse events	803 (3 RCTs)	RR 1.14 (0.36 to 3.56)	Inconclusive	Moderate ⊕⊕⊕◯

Certainty of the evidence

For vortioxetine, the overall certainty of evidence was rated low to moderate due to several concerns. The primary reason for downgrading was serious imprecision, as confidence intervals crossed thresholds for clinical significance, making the true effect uncertain for several outcomes, including treatment response, remission, and symptom reduction. Inconsistency was also observed in some outcomes, such as treatment response and adverse events, which showed moderate heterogeneity. Additionally, for sleepiness/drowsiness and dropout rates due to efficacy or adverse events, the evidence was considered very low to low due to extremely wide confidence intervals that could indicate either benefit or harm.

For agomelatine, the overall certainty of evidence was moderate to high across outcomes. The main issue leading to downgrading was inconsistency, particularly in treatment response and symptom reduction, where substantial heterogeneity was detected (I^2 = 69% and I^2 = 83%, respectively). Although results were generally favorable for agomelatine, the inconsistency in effect sizes across studies reduced confidence in these findings. For adverse events and dropout rates due to adverse effects, serious imprecision was noted due to wide confidence intervals. However, evidence for acceptability and remission rate was high, as the results were consistent and precise, without major concerns regarding bias or indirectness.

Recommendations from other groups

Table Q1.3. Recommendations from other groups.

Group or Agency	Recommendation
UK NICE 2020	Consider offering combinations of psychological and drug treatments, combinations of antidepressants or augmentation of antidepressants with other drugs, but exercise caution and be aware that: ● evidence for the effectiveness of combination treatments is lacking and ● side effects and interactions are more likely when combining and augmenting antidepressants.
Royal Australian and New Zealand College of Psychiatrists 2018	If there is continued inadequate response to the combination of CBT and SSRI/SNRI treatment after an adequate treatment trial (good adherence to a sufficient dose for a sufficient duration), the following options can be considered: ***Changing*** *to pregabalin* ***or agomelatine (if no response to SSRI/SNRIs)***

Other considerations

There are no available economic evaluations conducted in the Philippines for vortioxetine or agomelatine in the treatment of GAD. The estimated costs of the drugs are presented below.

Table Q1.4. Estimated costs of vortioxetine and agomelatine.

Parameter	Vortioxetine (Brintellix)	Agomelatine (Valdoxan)
Price per tablet*	PhP 47.75 / 5 mg tablet PhP 88.00/10 mg tablet	PhP 71.00/ 25 mg tablet
Typical dosage	5mg tablet once a day	25 mg tablet once a day that can be titrated to 50 mg twice a day
Monthly expense	PhP 1,425.00 per month	PhP 2,130 per month up to Php 4,260 per month

**price from Watson / Southstar website*

References

1. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. *Pharmacol Ther*. Jan 2015;145:43-57. doi:10.1016/j.pharmthera.2014.07.001

2. Bidzan L, Mahableshwarkar AR, Jacobsen P, Yan M, Sheehan DV. Vortioxetine (Lu AA21004) in generalized anxiety disorder: Results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. *European Neuropsychopharmacology*. 2012/12/01/ 2012;22(12):847-857. doi:https://doi.org/10.1016/j.euroneuro.2012.07.012

3. Christensen MC, Loft H, Florea I, McIntyre RS. Efficacy of vortioxetine in working patients with generalized anxiety disorder. *CNS Spectrums*. 2019;24(2):249-257. doi:10.1017/S1092852917000761

4. Millan MJ. Agomelatine for the treatment of generalized anxiety disorder: focus on its distinctive mechanism of action. *Ther Adv Psychopharmacol*. 2022;12:20451253221105128. doi:10.1177/20451253221105128

5. Kopcalic K, Arcaro J, Pinto A, et al. Antidepressants versus placebo for generalised anxiety disorder (GAD). *Cochrane Database Syst Rev*. Jan 30 2025;1(1):Cd012942. doi:10.1002/14651858.CD012942.pub2

6. Mahableshwarkar AR, Jacobsen PL, Chen Y, Simon JS. A randomised, double-blind, placebo-controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine in the acute treatment of adults with generalised anxiety disorder. *Int J Clin Pract*. Jan 2014;68(1):49-59. doi:10.1111/ijcp.12328

7. Stein DJ, Ahokas AA, de Bodinat C. Efficacy of agomelatine in generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. Oct 2008;28(5):561-6. doi:10.1097/JCP.0b013e318184ff5b

8. Stein DJ, Ahokas A, Márquez MS, et al. Agomelatine in generalized anxiety disorder: an active comparator and placebo-controlled study. *J Clin Psychiatry*. Apr 2014;75(4):362-8. doi:10.4088/JCP.13m08433

9. Stein DJ, Ahokas A, Jarema M, et al. Efficacy and safety of agomelatine (10 or 25 mg/day) in non-depressed out-patients with generalized anxiety disorder: A 12-week, double-blind, placebo-controlled study. *Eur Neuropsychopharmacol*. May 2017;27(5):526-537. doi:10.1016/j.euroneuro.2017.02.007

Guideline Question 2: Should atypical antipsychotics (Risperidone, Olanzapine, Aripiprazole, quetiapine) be used as add-on therapy to SSRI/ SNRI (escitalopram, sertraline, fluoxetine, duloxetine, escitalopram, paroxetine, venlafaxine) for patients with treatment resistant GAD?

Recommendation 2.	
We suggest against the use of atypical antipsychotics and SSRI/SNRI combination as first line treatment for patients with treatment-resistant generalized anxiety disorder.	
Strength of Recommendation:	Weak
Certainty of Evidence:	Very Low

Justification

Current best available evidence does not appear to show significant symptom relief or quality-of-life benefits from adding atypical antipsychotics to SSRIs/SNRIs. Moreover, these medications are linked to higher discontinuation rates due to adverse effects such as sedation, weight gain, and gastrointestinal distress. Concerns about patient safety arise with polypharmacy, and personal experiences with olanzapine and aripiprazole by healthcare providers indicate excessive side effects leading to dose reductions. The certainty of evidence is very low, and psychiatric associations offer conflicting recommendations. While some patients may consider this option due to limited alternatives, shared decision-making is essential.

Background

Atypical antipsychotics, also known as second-generation antipsychotics, include risperidone, olanzapine, aripiprazole, and quetiapine.[1] These medications are used to treat various mental health disorders, such as schizophrenia, affective disorders (including depression and mania), and agitation in older adults.[1,2] Unlike typical antipsychotics, which primarily target the dopamine system, atypical antipsychotics also modulate serotonin (5-HT), norepinephrine, and histamine neurotransmission.[3] This mechanism of action has the potential to treat anxiety disorder and mood disorders.[3]

Atypical antipsychotics have been reported to reduce the risk of extrapyramidal symptoms compared to typical antipsychotics.[1,2] Atypical antipsychotics have been associated with metabolic side effects, including increased fasting plasma glucose, diabetes, dyslipidemia, elevated fasting lipid levels, and weight gain. Other adverse effects (AEs) that were associated with atypical antipsychotics are: dizziness, sedation, extrapyramidal symptoms, akathisia, weight gain, increased appetite, and somnolence, orthostatic hypotension, agitation and headache.[1]

Evidence

We found seven (7) placebo-controlled RCTs (n=895) published between 2005 and 2014evaluating the efficacy of atypical antipsychotics as an add-on treatment in patients with treatment-resistant generalized anxiety disorder. One study examined the efficacy of olanzapine with fluoxetine, two assessed quetiapine with SSRI/SNRI, and one study determined the

efficacy of quetiapine XR with SSRI/SNRI, either alone or with a benzodiazepine. Two studies evaluated risperidone and one study assessed ziprasidone with SSRI/SNRI or other antidepressants/anxiolytics, alone or with a benzodiazepine. Due to limited studies, we included two pre-post studies on aripiprazole with other antidepressants or anxiolytics, alone or with a benzodiazepine. One of these studies also included patients with treatment-resistant panic disorder with persistent anxiety. The dose of atypical antipsychotics used in the included studies were flexible according to the patient's tolerability and clinical response. The duration of treatment in these studies ranges from 5 to 8 weeks.

Outcomes measured in these studies include response rate, as defined by the study (a ≥50% reduction in the Hamilton Anxiety Rating Scale [HAM-A] score in four RCTs and improvement on the Clinical Global Impression-Improvement [CGI-I] scale in two RCTs), remission rate (patients who achieved a HAM-A score of ≤7), changes in HAM-A total scores, changes in CGI-I or Clinical Global Impression-Severity (CGI-S) scores, quality of life (assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q]), discontinuation due to adverse effects (AEs), serious AEs and overall adverse events.

Benefits and risks

Atypical antipsychotics as add-on therapy to SSRI/SNRI did not significantly improve symptoms or quality of life in patients with treatment-resistant generalized anxiety disorder (GAD). However, subgroup analyses showed that quetiapine XR improved symptoms based on the CGI-S total score, while pre-post studies suggested that aripiprazole reduced anxiety symptoms measured by the HAM-A total score. Despite these findings, atypical antipsychotics were associated with a higher rate of discontinuation due to adverse effects.

Pooled results indicated no significant difference between atypical antipsychotic augmentation and placebo in improving anxiety symptoms, depressive symptoms, disease severity, or quality of life. Discontinuation due to adverse events was significantly higher in the atypical antipsychotic group. The most commonly reported adverse effects included sedation, somnolence, weight gain, gastrointestinal distress, increased appetite, dry mouth, dizziness, headache, and sexual dysfunction.

Certainty of the evidence

The overall certainty of evidence ranges from low to very low. Out of the seven (7) RCTs included, 5 had an overall high risk of bias and 2 had a moderate overall risk of bias due to unclear allocation concealment (n=4), high dropout rates (n=6), open-label design (n=1), blocked randomization (n=1), possible selective reporting (n=2), and differences in baseline characteristics (n=3). Additionally, the two included pre-post studies were also rated as high risk of bias due to inherent methodological limitations, such as no blinding, no control group, difference in pre-existing treatments, and potential performance bias.

Downgrading was also done due to indirectness, as the primary treatment or comparator was not limited to SSRI/SNRI monotherapy but also included antidepressants, anxiolytics, and benzodiazepines, either alone or in combination. One study also included patients diagnosed with panic disorder with persistent anxiety symptoms. Additionally, some results lacked precision, and several studies showed heterogeneity ($I^2 \geq 50\%$).

Table Q2.1. Effects of atypical antipsychotics on anxiety symptoms.

Outcomes	No. of participants (studies)	Effect Size (95% CI)	Interpretation	Certainty of the evidence
Response rate (as defined by the study)	897 (5 RCTs)[1,2,3,4,5,6]	RR 0.91 (0.81 to 1.02)	Inconclusive	Very low[a,b,c,d,e] ⨁◯◯◯
Response - Olanzapine	24 (1 RCT)[1]	RR 0.64 (0.38 to 1.06)	Inconclusive	Low[f,g] ⨁⨁◯◯
Response - Quetiapine	444 (3 RCTs)[2,3,4]	RR 0.91 (0.78 to 1.06)	Inconclusive	Very low[a,b,c,d,e] ⨁◯◯◯
Response - Risperidone	429 (1 RCT)[5,6]	RR 0.89 (0.62 to 1.28)	Inconclusive	Low[c,e,f,g] ⨁⨁◯◯
Remission rate (HAM-A score of ≥7)	858 (5 RCTs)[1,2,3,4,5]	RR 0.94 (0.88 to 1.01)	Inconclusive	Very low[a,b,c,d,e] ⨁◯◯◯
Remission - Olanzapine	24 (1 RCT)[1]	RR 0.73 (0.47 to 1.12)	Inconclusive	Low[f,g] ⨁⨁◯◯
Remission - Quetiapine	444 (3 RCTs)[2,3,4]	RR 0.91 (0.83 to 1.01)	Inconclusive	Very low[a,b,c,d,e] ⨁◯◯◯
Remission - Risperidone	390 (1 RCT)[5]	RR 0.98 (0.89 to 1.08)	Inconclusive	Low[e,g] ⨁⨁◯◯
HAM-A Total Score	485 (6 RCTs)[1,2,4,5,6,7]	MD 1.17 higher (0.2 lower to 2.53 higher)	Inconclusive	Very low[a,b,c,e] ⨁◯◯◯
HAM-A Total Score - Olanzapine	18 (1 RCT)[1]	MD 3.1 lower (4.73 lower to 10.93 higher)	Inconclusive	Very low[f,h] ⨁◯◯◯
HAM-A Total Score - Quetiapine	42 (2 RCTs)[2,4]	MD 3.46 higher (1.32 lower to 8.23 higher)	Inconclusive	Very low[a,b,h] ⨁◯◯◯
HAM-A Total Score - Risperidone	408 (2 RCTs)[5,6]	MD 1.56 lower (1.77 higher to 4.9 lower)	Inconclusive	Very low[c,e,f,g,h,i] ⨁◯◯◯
HAM-A Total Score - Ziprasidone	17 (1 RCT)[7]	MD 2.8 lower (10.71 lower to 5.11 higher)	Inconclusive	Very low[e,f,g,h] ⨁◯◯◯
HAM-A Total Score Aripiprazole (pre-post-study)	46 (1 non-RCT)[8]	MD 5.2 higher (9.13 higher to 1.27 higher)	Benefit	Very low[e,h,j,k] ⨁◯◯◯
HAM-A Total Score - Quetiapine XR	400 (1 RCT)[3]	MD 1.13 higher (0.13 lower to 2.39 higher)	Inconclusive	Low[d,e,g] ⨁⨁◯◯

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).CI: confidence interval; MD: mean difference; RR: risk ratio

Response Rate Definition
HAM-A score reduction by 50%: Pollack et al, 2006; Altamura et al, 2011; Khan et al, 2014; Pandina et al, 2007
CGI-I score of 1 [“very much improved”] or 2 [“much improved”]): Simon et al, 2008; Brawman-Mintzer et al, 2005
Remission Rate Definition
HAM-A score of ≥7: Pollack et al, 2006; Altamura et al, 2011; Khan et al, 2014; Simon et al, 2008; Pandina et al, 2007

Explanations
a. open-label trial; no data on allocation concealment; attrition bias; b. blocked randomization (possible to predict future assignments); c. possible selective reporting; d. possible difference in baseline characteristics; e. as an add-on to other antidepressant/anxiolytic (other than SSRI/SNRI), benzodiazepines either alone or in combination; f. No data on allocation concealment, difference in baseline characteristics; g. attrition bias; h. Wide Confidence interval; i. Heterogeneity; I^2≥50%%); j. Open label trial, no control group; attrition bias; k. Patients with panic disorder were included

References
1. Pollack 2006; 2. Simon 2008; 3. Khan 2014; 4. Altamura 2011; 5. Pandina 2007; 6. Brawman-Mintzer 2005; 7. Lohoff 2010; 8. Hoge 2008

Table Q2.2. Effects of atypical antipsychotics on disease severity (CGI Scores).

Outcomes	No. of participants (studies)	Effect Size (95% CI)	Interpretation	Certainty of the evidence
Change in CGI-S	428 (4 RCTs)[1,2,3,4]	MD 0.36 lower (0.25 lower to 0.97 higher)	Inconclusive	Very low[a,b,c,d,e,f] ⨁◯◯◯
Quetiapine	42 (2 RCTs)[3,4]	MD 0.77 lower (0.44 lower to 1.97 higher)	Inconclusive	Very low[a,b,c,e,g] ⨁◯◯◯
Risperidone	369 (1 RCT)[2]	MD 0 (0.19 lower to 0.19 higher)	Inconclusive	Low[c,f] ⨁⨁◯◯
Ziprasidone	17 (1 RCT)[1]	MD 0.56 higher (0.81 lower to 1.93 higher)	Inconclusive	Very low[b,c,d,f] ⨁◯◯◯
Aripiprazole	46 (1 non-RCT)[5]	MD 1 lower (1.53 lower to 0.47 lower)	Benefit Augmentation with Aripiprazole lowers the severity of the disease	Very low[c,e,f,h,i] ⨁◯◯◯
Quetiapine XR	402 (1 RCT)[6]	MD 0.23 higher (0.42 higher to 0.03 higher)	Benefit Augmentation with Quetiapine XR lowers the severity of the disease	Low[c,d,f] ⨁⨁◯◯
Change CGI-I Ziprasidone	17 (1 RCT)[1]	MD 0.57 higher (0.41 lower to 1.55 higher)	Inconclusive	Very low[b,c,d,f] ⨁◯◯◯

Explanations
a. blocked randomization (possible to predict future assignments); b. no data on allocation concealment; c. attrition bias d. possible difference in baseline characteristics e. open label study; f. as add on to SSRI/SNRI treatment or other antidepressant/anxiolytics, (alone or in combination with a benzodiazepine); g. Heterogeneity (I2≥50%); h. no control group; i. the study also included patients with panic disorder;

References
1. Lohoff 2010; 2. Pandina 2007; 3. Altamura 2011; 4. Simon 2008; 5. Hoge 2008; 6. Khan 2014

Table Q2.3. Quality of Life

Outcomes	No. of participants (studies)	Effect Size (95% CI)	Interpretation	Certainty of the evidence
Change in Q-LES-Q total score	391 (2 RCTs)[1,2]	MD 0.66 higher (2.89 lower to 4.21 higher)	Inconclusive	Very low[a,b,c,d] ⨁◯◯◯
Quetiapine	22 (1 RCT)[2]	MD 0.34 higher (9.96 lower to 10.64 higher)	Inconclusive	Very low[a,b,d] ⨁◯◯◯
Risperidone	369 (1 RCT)[1]	MD 0.7 lower (3.08 lower to 4.48 higher)	Inconclusive	Very low[c,d,e] ⨁◯◯◯
Quetiapine XR	402 (1 RCT)	MD 0.9 higher (1.79 lower to 3.59 higher)	Inconclusive	Very low[c,e,f] ⨁◯◯◯

Explanations
a. blocked randomization (possible to predict future assignments); no data on allocation concealment; attrition bias; b. possible selective reporting; c. as add on to SSRI/SNRI treatment or other antidepressant/anxiolytics, (alone or in combination with a benzodiazepine); d. Wide confidence interval; e. attrition bias; f. possible difference baseline score

References
1. Pandina 2007; 2. Simon 2008

Table Q2.3. Discontinuation due to adverse effects

Outcomes	No. of participants (studies)	Effect Size (95% CI)	Interpretation	Certainty of the evidence
Discontinuation due to AE	875 (5 RCTs)[1,2,3,4,5]	RR = 3.08 (1.79 to 5.29)	Harm More discontinuation due to AE	Very low[a,b,c,d,e,f,g] ⊕◯◯◯
Olanzapine	24 (1 RCT)[5]	RR = 4.00 (0.52 to 30.76)	Inconclusive	Very low[a,b,c,g] ⊕◯◯◯
Quetiapine	422 (2 RCTs)[3,4]	RR = 5.86 (2.20 to 15.59)	Harm More discontinuation due to AE	Very low[a,c,d,e,g,h] ⊕◯◯◯
Risperidone	429 (2 RCTs)[1,2]	RR = 2.17 (1.09 to 4.32)	Harm More discontinuation due to AE	Very low[a,b,c,e,g,h] ⊕◯◯◯

Explanations
a. no data on allocation concealment; b. possible difference baseline characteristics; c. attrition bias; d. blocked randomization (possible to predict future assignments); e. possible selective reporting; f. as add on to SSRI/SNRI treatment or other antidepressant/anxiolytics, (alone or in combination with a benzodiazepine); g. Wide Confidence Interval; h. as add on to SSRI/SNRI treatment or other antidepressant/anxiolytics, (alone or in combination with a benzodiazepine)

References
1.Brawman-Mintzer et al., 2005; 2.Pandina et al., 2007; 3.Khan et al., 2013;; 4.Simon et al., 2008; 5.Pollack et al., . .2006.

Recommendations from other groups

Table Q2.4: Recommendations from Other Groups

Group/Agency	Recommendation	Strength of Recommendation & Certainty of Evidence
Canadian Clinical Practice Guidelines for the Management of Anxiety, Posttraumatic Stress, and Obsessive-Compulsive Disorders[19]	Recommend aripiprazole, olanzapine, quetiapine, quetiapine XR, risperidone as third-line adjunctive therapy in patients with an inadequate response to SSRI therapy. **May be considered for treatment-resistant GAD.**	Risperidone: Two RCTs suggest possible benefits, but superiority over placebo was observed only in patients with moderate to severe residual symptoms. *(Level 1, conflicting)* Quetiapine: Mixed results—one negative RCT, one unblinded RCT showing limited benefits. *(Level 1, conflicting)* Quetiapine XR: Some benefits observed. *(Level 3)* Olanzapine: Small RCT showed efficacy in patients still symptomatic after six weeks of SSRI therapy. *(Level 2)* Aripiprazole: Some benefits observed. *(Level 3)*
NICE Clinical Guideline [CG113]: Generalised Anxiety Disorder and Panic Disorder in Adults (Published: 2011, Updated: 2020) [20,21]	**Do not offer antipsychotics for GAD treatment in primary care.** Limited data on antipsychotics (olanzapine, risperidone, ziprasidone) showed no conclusive evidence of effectiveness as augmentation treatment. Increased discontinuation due to adverse events was noted. **Antipsychotic augmentation should not be routine and should only occur in specialist settings.**	Certainty of Evidence: - Olanzapine Augmentation (n=1): No significant improvement in anxiety symptoms, remission, or response. Increased discontinuation due to adverse events. *(Quality: Low)* - Risperidone Augmentation (n=2): No significant improvement in anxiety symptoms or response. Mixed evidence for remission. Increased discontinuation due to adverse events. *(Quality: Moderate to High)*
Brazilian Psychiatric Association (2024)[22]	Due to limited and small-effect studies, no specific level of evidence is provided. **Psychiatrists should determine individualized treatment for treatment-resistant GAD.**	N/A

Group/Agency	Recommendation	Strength of Recommendation & Certainty of Evidence
Royal Australian and New Zealand College of Psychiatrists (2018) [23]	The atypical antipsychotics may lead to some symptomatic relief, but the risk/benefit ratio is such that they are less likely to lead to gains than the options listed above. Their use is not supported by evidence from RCTs. **If used, the starting dose should be very low and the patient should be monitored carefully** for extrapyramidal side effects, particularly akathisia. It is important to monitor for metabolic side effects and to monitor QTc length by regular ECGs.	Not mentioned

Other considerations

Resource implications

No cost effectiveness study was found. Below is the list of atypical antipsychotics and their price in the community pharmacy.

Table Q2.5: List of Cost of Atypical Antipsychotics

Medication	Dosage	Price Range (₱)
Risperidone	1 mg	49.15 – 105.50
	2 mg	53.57 – 210.25
	4 mg	110.00
	1 mg	49.15 – 105.50
Olanzapine	5 mg	42.50 – 73.25
	10 mg	52.75 – 131.25
Aripiprazole	5 mg	62.10 – 181.50
	10 mg	97.77 – 264.25
	15 mg	264.25
Quetiapine	25 mg	29.50 – 41.25
	50 mg	28.00
	100 mg	47.25
Quetiapine Fumarate	25 mg	29.46 – 85.25
	100 mg	45.00 - 179.75
	200 mg	247.50
	300 mg	311.75
Quetiapine Fumarate XR	50 mg	109.75
	300 mg	65.00 - 297.50

Stakeholder values, preferences and acceptability

No study on the acceptability of atypical antipsychotics as add on for treatment-resistant GAD.

Equity and feasibility

No study on equity and feasibility of atypical antipsychotics as add on for treatment-resistant GAD.

References

1. Chokhawala K, Stevens L. Antipsychotic medications [Internet]. National Library of Medicine. StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519503/

2. Willner K, Vasan S, Abdijadid S. Atypical Antipsychotic Agents [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448156/

3. Grinchii D, Dremencov E. Mechanism of Action of Atypical Antipsychotic Drugs in Mood Disorders. International Journal of Molecular Sciences. 2020;21(24):9532.

4. Lalonde CD, Van Lieshout RJ. Treating Generalized Anxiety Disorder With Second Generation Antipsychotics. Journal of Clinical Psychopharmacology. 2011 Jun;31(3):326–33.

5. Depping AM, Komossa K, Kissling W, Leucht S. Second-generation antipsychotics for anxiety disorders. Cochrane Database of Systematic Reviews. 2010 Dec 8;

6. Samuel M, Zimovetz EA, Gabriel Z, Beard SM. Efficacy and safety of treatments for refractory generalized anxiety disorder. International Clinical Psychopharmacology. 2011 Mar;26(2):63–8.

7. Zhornitsky S, Potvin S, Hoda Moteshafi, Dubreucq S, Pierre-Paul Rompré, Stip E. Dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders. International Clinical Psychopharmacology. 2011 Jul 1;26(4):183–92.

8. Abejuela HR, Osser DN. The Psychopharmacology Algorithm Project at the Harvard South Shore Program. Harvard Review of Psychiatry. 2016;24(4):243–56.

9. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry [Internet]. 2014;14(Suppl 1):S1. Available from: https://bmcpsychiatry.biomedcentral.com/articles/10.1186/1471-244X-14-S1-S1

10. Pollack MH, Simon NM, Zalta AK, Worthington JJ, Hoge EA, Mick E, et al. Olanzapine Augmentation of Fluoxetine for Refractory Generalized Anxiety Disorder: A Placebo Controlled Study. Biological Psychiatry. 2006 Feb;59(3):211–5.

11. Simon NM, Connor KM, LeBeau RT, Hoge EA, Worthington JJ, Zhang W, et al. Quetiapine augmentation of paroxetine CR for the treatment of refractory generalized anxiety disorder: preliminary findings. Psychopharmacology. 2008 Feb 2;197(4):675–81.

12. Khan A, Atkinson S, Mezhebovsky I, She F, Leathers T, Pathak S. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in patients with generalized anxiety disorder and a history of inadequate treatment response: a randomized, double-blind study. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists [Internet]. 2014 Feb;26(1):3–18. Available from: https://pubmed.ncbi.nlm.nih.gov/24660224/

13. Altamura AC, Serati M, Buoli M, Dell'Osso B. Augmentative quetiapine in partial/nonresponders with generalized anxiety disorder. International Clinical Psychopharmacology. 2011 Jul;26(4):201–5.

14. Pandina GJ, Canuso CM, Turkoz I, Kujawa M, Mahmoud RA. Adjunctive risperidone in the treatment of generalized anxiety disorder: a double-blind, prospective, placebo-controlled, randomized trial. Psychopharmacology bulletin [Internet]. 2007;40(3):41–57. Available from: https://pubmed.ncbi.nlm.nih.gov/18007568/

15. Menza MA, Dobkin RD, Marin H. An Open-Label Trial of Aripiprazole Augmentation for Treatment-Resistant Generalized Anxiety Disorder. Journal of Clinical Psychopharmacology. 2007 Apr;27(2):207–10

16. Brawman-Mintzer O, Knapp RG, Nietert PJ. Adjunctive Risperidone in Generalized Anxiety Disorder. The Journal of Clinical Psychiatry. 2005 Oct 15;66(10):1321–5

17. Lohoff FW, Etemad B, Mandos LA, Gallop R, Rickels K. Ziprasidone Treatment of Refractory Generalized Anxiety Disorder. Journal of Clinical Psychopharmacology. 2010 Apr;30(2):185–9

18. Hoge EA, Worthington JJ, Kaufman RE, Delong HR, Pollack MH, Simon NM. Aripiprazole as Augmentation Treatment of Refractory Generalized Anxiety Disorder and Panic Disorder. CNS Spectrums. 2008 Jun;13(6):522–5.

19. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry [Internet]. 2014;14(Suppl 1):S1. Available from: https://bmcpsychiatry.biomedcentral.com/articles/10.1186/1471-244X-14-S1-S1

20. National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder in adults: management Clinical guideline [Internet]. 2020 Jun. Available from: https://www.nice.org.uk/guidance/cg113/resources/generalised-anxiety-disorder-and-panic-disorder-in-adults-management-pdf-35109387756997

21. National Institute for Health & Clinical Excellence. Generalised Anxiety Disorder in Adults. The NICE Guideline on Management in Primary, Secondary and Community Care [Internet]. 2011. Available from: https://www.nice.org.uk/guidance/cg113/evidence/anxiety-full-guidance-pdf-136340461

22. Baldaçara L, Paschoal A, Pinto A, Loureiro F, Antonio L, Gaiotto V, et al. BJP Pre-proof Brazilian Psychiatric Association guidelines for the treatment of generalized anxiety disorder (GAD). Pharmacological and Psychotherapy approach. Perspectives. Revista Brasileira De Psiquiatria (Sao Paulo, Brazil : 1999) [Internet]. 2024;46. Available from: https://cdn.publisher.gn1.link/bjp.org.br/pdf/bjp-2023-sa-3235%20preproof.pdf

23. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Australian & New Zealand Journal of Psychiatry [Internet]. 2018 Nov 30;52(12):1109–72. Available from: https://journals.sagepub.com/doi/full/10.1177/0004867418799453

Guideline Question 3: Should mirtazapine be used in the treatment for panic disorder?

Recommendation 3.	
We suggest against the use of mirtazapine as first-line treatment in patients with panic disorder.	
Strength of Recommendation:	Weak
Certainty of Evidence:	Very low

Review question: In patients with panic disorder, how effective and safe is mirtazapine compared with SSRI/ SNRI in symptom control?

Justification

A weak recommendation was made against the use of mirtazapine as a first-line treatment for panic disorder due to very low-certainty evidence. While small studies suggest mirtazapine may be as effective as SSRIs like fluoxetine and paroxetine in reducing panic attacks and anxiety symptoms, it is associated with greater weight gain and drowsiness, though it may cause less nausea. Further research is needed to determine optimal dosing, long-term effects, and cost-effectiveness.

Nevertheless, mirtazapine may be beneficial for specific populations, such as patients with poor sleep, poor appetite, or cancer-related panic disorder. However, given the availability of well-established first-line treatments like SSRIs and SNRIs, and the potential for weight gain and sedation, its use should be considered on a case-by-case basis. Before prescribing mirtazapine, clinicians should assess whether patients prioritize avoiding weight gain or sedation over other potential benefits. While not recommended as a first-line option, it remains a viable alternative for patients who have not responded to standard therapies.

Background

Panic disorder is a common and disabling condition affecting about 5% of the population at some point in life and is associated with increased healthcare costs[1] and reduced productivity.[2] Panic disorder is mainly characterized by recurrent unexpected panic attacks, which are defined as abrupt surges of intense fear or discomfort that occurs from a calm or anxious state peaking within minutes and resolving within an hour.[3] In addition, at least one of the panic attacks must be followed by ≥ 1 month of either worry about future attacks or their consequences, or a significant maladaptive change in behavior (e.g., avoidance of situations).

SSRIs or SNRIs have been shown to be effective in treating panic disorder.[4,5] However, their delayed onset of action, potential for an initial increase in anxiety, troublesome side effects, and risk of relapse pose significant challenges in their use.[6] This highlights the need for alternative and potentially more effective treatments, such as mirtazapine. Mirtazapine has a different mode of action than SSRIs, enhancing both noradrenergic transmission via blockade of α2-adrenoceptors and serotonergic neurotransmission without reuptake inhibition.[7] It may lower anxiety and other SSRI-related adverse effects through its ability to block 5-HT2 and 5-HT3

postsynaptic serotonin neuron receptors. Some observational studies on mirtazapine have reported good response rates and symptomatic improvements for patients with panic disorder, suggesting its viability as a potential alternative to SSRIs/SNRIs.[8-11]

Evidence

Mirtazapine vs. fluoxetine

A 2001 double-blind RCT by Ribeiro et al in Brazil compared the effect of mirtazapine and fluoxetine in adult patients with panic disorder. Patients (N=27) were adults diagnosed by a qualified psychiatrist with panic disorder based on the DSM-IV criteria, without major depressive disorder. At least 60% were women, ≥67% presented with agoraphobia, and had an average duration of illness of 3 years and average age of 36 years. Patients were randomly assigned to receive either daily mirtazapine 15 mg (n=14) or fluoxetine 10 mg (n=13). Doses were maintained for the first 2 weeks and were increased to 30 mg and 20 mg for mirtazapine and fluoxetine, respectively, according to the investigators' judgment of the clinical response or adverse events. Outcomes included: number of panic attacks, adverse events, phobic anxiety, phobic avoidance, and panic disorder severity—assessed weekly until 8 weeks.

Mirtazapine vs. paroxetine

A non-randomized trial done in Spain by Montañes-Rada et al. 2005 compared the effects of mirtazapine with paroxetine in panic disorder. The median age was 43 years old and at least 60% had agoraphobia, generalized anxiety disorder, or obsessive personality disorder traits. Some baseline differences were noted between groups—patients in the mirtazapine group were mostly females (70.6% vs. 46.2%), had more comorbid major depression (33.3% vs. 23.1%), dysthymia (16.6% vs. 0%). Efficacy outcomes were assessed after 3 and 8 weeks, including the following: (1) number of panic attacks, (2) severity of panic disorder, (3) severity of depression, (4) severity of anxiety, (5) number of responders, (6) number of patients experiencing recurrence. Safety outcomes were also reported.

No ongoing trials were found regarding mirtazapine for treating panic disorder. Several research gaps remain, including the lack of placebo-controlled studies for mirtazapine, trials comparing mirtazapine with other SSRIs/SNRIs, optimal dosage determination, long-term efficacy and relapse prevention outcomes, and the impact of concomitant medications and comorbidities.

Benefits and risks

Both mirtazapine and SSRIs significantly reduced panic attacks over 8 weeks. Paroxetine showed a slightly greater reduction than mirtazapine, but the difference was uncertain. Mirtazapine and fluoxetine had comparable effects. Panic disorder severity, anxiety, and depression improved similarly with both treatments, though mirtazapine led to faster anxiety relief at three weeks and greater depression reduction at eight weeks. Treatment response and recurrence rates were also comparable, with 77% of patients improving and over 94% maintaining symptom control.

Regarding safety, dropout rates due to adverse events were similar between mirtazapine and SSRIs. Mirtazapine was associated with a higher incidence of weight gain and drowsiness, whereas fluoxetine caused more nausea and paresthesia.

Table Q3.1. Summary of findings for mirtazapine versus paroxetine for panic disorder: efficacy outcomes.

Outcome	No. of participants (studies)	Relative effect (95% CI)	Absolute effects (95% CI)			Interpretation	Certainty of the evidence
			SSRIs	mirtazapine	Difference		
Number of panic attacks per month	62 (1 non-RCT)	-	-12.3 attacks	-8.8 attacks	3.5 (-1.42 to 10.02)	Mirtazapine may result in a smaller or similar degree of reduction as paroxetine on number of panic attacks per month but the evidence is very uncertain.	Very low[a,b] ⨁◯◯◯
Severity of panic disorder	62 (1 non-RCT)	-	-2.7 points	-2.72 points	-0.02 (-0.46 to 0.42)	Mirtazapine may result in a similar degree of improvement as paroxetine on severity of panic disorder but the evidence is very uncertain.	Very low[a,b] ⨁◯◯◯
Severity of anxiety disorder	62 (1 non-RCT)	-	-15.1 points	-18.65 points	-3.55 (-8.69 to 1.59)	Mirtazapine may result in a larger or similar effect as paroxetine on severity of anxiety disorder but the evidence is very uncertain.	Very low[a,b] ⨁◯◯◯
Number of responders	62 (1 non-RCT)	RR 1.06 (0.80 to 1.42)	731 per 1,000	775 per 1,000 (585 to 1,000)	44 more per 1,000 (from 146 fewer to 307 more)	Mirtazapine may be similar with paroxetine in terms of the number of responders but the evidence is very uncertain.	Very low[a,b] ⨁◯◯◯
Number of recurrence	62 (1 non-RCT)	RR 0.98 (0.88 to 1.10)	962 per 1,000	942 per 1,000 (846 to 1,000)	19 fewer per 1,000 (from 115 fewer to 96 more)	Mirtazapine may be similar with paroxetine in terms of its effect on number of recurrence but the evidence is very uncertain.	Very low[a] ⨁◯◯◯
Severity of depression*	62 (1 non-RCT)	-	-6.8 points	-11.40 points	-4.6 (-8.79 to -0.41)	Mirtazapine may reduce severity of depression more than paroxetine but the evidence is very uncertain.	Very low[a] ⨁◯◯◯

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanation

a. Serious risk of bias due to randomization (non-randomized treatment assignment, more patients with depression and dysthymia in mirtazapine arm, longer onset of disease in paroxetine), deviations from intended interventions (unblinded, with 20% receiving co-intervention [lorazepam])

b. Serious imprecision from wide confidence intervals crossing 1.00

*Important but not critical outcome

Table Q3.2. Summary of findings for mirtazapine versus fluoxetine for panic disorder: efficacy outcomes.

Outcome	No. of participants (studies)	Absolute effects (95% CI)			Interpretation	Certainty of the evidence
		SSRIs	mirtazapine	Difference		
Number of panic attacks per week	27 (1 RCT)	-4 attacks	-2.83 attacks	1.17 attacks (-0.14 to 2.48)	Mirtazapine may result in a smaller or similar degree of reduction as fluoxetine on number of panic attacks per month but the evidence is very uncertain.	Low[b,c] ⨁⨁◯◯
Patient global evaluation of phobic anxiety)	27 (1 RCT)	-2.7 levels	-3.4 levels	-0.7 levels (-2.62 to 1.22)	Mirtazapine may result in a slightly higher or similar degree of improvement as fluoxetine on severity of panic disorder but the evidence is very uncertain.	Low[b,c] ⨁⨁◯◯
Phobic anxiety	27 (1 RCT)	-51 points	-60.5 points	-9.5 pts (-39.7 to 20.7)	Mirtazapine may result in little to no difference with fluoxetine in terms of reducing phobic anxiety.	Low[b,c] ⨁⨁◯◯
Phobic avoidance	27 (1 RCT)	-18.5 points	-17 points	1.5 pts (-7.77 to 10.77)	Mirtazapine may result in little to no difference with fluoxetine in terms of reducing phobic avoidance.	Low[b,c] ⨁⨁◯◯
Severity of anxiety	27 (1 RCT)	-17 points	-15 points	2 pts (-4.77 to 8.77)	Mirtazapine may result in little to no difference with fluoxetine in terms of reducing anxiety severity.	Low[b,c] ⨁⨁◯◯

Explanation
b. Serious risk of bias due to some concerns related to uncertainty around blinding, missing outcome data (i.e., dropout rates of 23% fluoxetine, 14% mirtazapine), outcome measurement (i.e., psychometric properties of some measures not sufficiently described), reporting of result (i.e., unclear influence of pharmaceutical company that provided mirtazapine)
c. Serious imprecision from wide confidence intervals crossing 1.00

Table Q3.3. Summary of findings for mirtazapine versus fluoxetine/paroxetine for panic disorder: safety outcomes.

Outcome	No. of participants (studies)	Effect estimate (95% CI)	Interpretation	Certainty of the evidence
Weight gain	89 (2 RCTs)	RR 2.73 (1.11 to 6.72)	Mirtazapine likely results in a larger increase in weight gain compared to SSRI.	Moderate[a,c] ⨁⨁⨁◯
Drowsiness	89 (2 RCTs)	RR 1.63 (0.80 to 3.31)	Mirtazapine may result in little to no difference with SSRI in terms of drowsiness.	Low[a,b,c] ⨁⨁◯◯
Headache, sexual dysfunction, gastrointestinal side effects (combined)	62 (1 RCT)	RR 0.24 (0.03 to 2.19)	Mirtazapine may result in little to no difference with SSRI in terms of headache, sexual dysfunction, gastrointestinal side effects (combined).	Low[a,b,c] ⨁⨁◯◯
Nausea	27 (1 RCT)	RR 0.21 (0.05 to 0.78)	Mirtazapine likely results in fewer nausea events compared to fluoxetine.	Moderate[c] ⨁⨁⨁◯
Paresthesia	27 (1 RCT)	RR 0.10 (0.01 to 1.76)	Mirtazapine may result in a fewer or similar number of paresthesia events as fluoxetine.	Low[b,c] ⨁⨁◯◯
Number of dropouts due to adverse events*	89 (2 RCTs)	RR 0.81 (0.21 to 3.09)	Mirtazapine may result in little to no difference with SSRI in terms of dropouts due to adverse events.	Low[a,b,c] ⨁⨁◯◯

Explanation:
b. Serious risk of bias due to some concerns related to uncertainty around blinding, missing outcome data (i.e., dropout rates of 23% fluoxetine, 14% mirtazapine), outcome measurement (i.e., psychometric properties of some measures not sufficiently described), reporting of result (i.e., unclear influence of pharmaceutical company that provided mirtazapine)
c. Serious imprecision from wide confidence intervals crossing 1.00
*Important but not critical outcome

Certainty of the evidence

Overall, the certainty of evidence was classified as “very low” for efficacy outcomes and “low” for safety outcomes. The evidence was downgraded due to serious risk of bias in the two included studies and serious imprecision resulting from wide confidence intervals. For the Ribeiro et al. 2001 trial, high risk of bias due to some concerns related to uncertainty around blinding, missing outcome data (i.e., dropout rates of 23% fluoxetine, 14% mirtazapine), outcome measurement (i.e., psychometric properties of some measures not sufficiently described), and reporting of result (i.e., unclear influence of pharmaceutical company that provided mirtazapine). For the Montañes et al. 2005 trial, serious risk of bias was due to non-randomization, baseline imbalances (i.e., more patients with depression and dysthymia in mirtazapine arm, longer onset of disease in paroxetine), deviations from intended interventions (i.e., unblinded carers and patients, 20% patients receiving co-intervention [lorazepam]).

Recommendations from other groups

The most recent recommendations from the Australian and New Zealand College of Psychiatrists considers mirtazapine as an alternative treatment option if there is inadequate response to other standard treatments (e.g., CBT, SSRI, SNRI, TCA).[17] Similarly, the 2009 guidelines from the American Psychiatric Association also does not recommend mirtazapine as a first-line treatment for panic disorder, citing tolerability issues (e.g., somnolence, weight gain) and limited evidence of efficacy from large, controlled studies.[18] Mirtazapine is also considered only as a second-line treatment in the 2014 Canadian Anxiety Guidelines.[19] The UK NICE does not have a specific recommendation regarding mirtazapine for panic disorder.[20]

Table Q3.4. Recommendations from other groups.

Group or Agency	Recommendation/s	Strength of Recommendation / Certainty / Quality of Evidence
Royal Australian and New Zealand College of Psychiatrists (RANZCP, 2018)[17]	If treatment is indicated, use any of the following options: - CBT: either 8–12 sessions of face-to-face CBT, provided by an experienced clinician or a programme of guided dCBT for panic disorder; - SSRI (or SNRI) antidepressant (together with advice about graded exposure to anxiety triggers); - The combination of CBT and medication.	Consensus-based recommendation
	If there is inadequate response to CBT, SSRI, SNRI and TCA then MAOI or mirtazapine can be considered.	Consensus-based recommendation (cited Ribeiro 2001 RCT (16))
American Psychiatric Association (APA, 2009)[18]	Other medications with less empirical support (e.g., mirtazapine, anticonvulsants such as gabapentin) may be considered as monotherapies or adjunctive treatments for panic disorder when patients have failed to respond to several standard treatments or based on other individual circumstances.	III (May be recommended on the basis of individual circumstances; cited Ribeiro 2001 RCT (15), Montañes-Rada 2005 RCT (15) and 4 open-label studies (8–11))
UK National Institute for Health and Care Excellence (NICE, 2020)[20]	No statement on the use of mirtazapine. Antidepressants should be the only pharmacological intervention used in the longer-term management of panic disorder. The classes of antidepressants that have an evidence base for effectiveness are the SSRIs, SNRIs, and TCAs. At the time of this amendment (June 2020) escitalopram, sertraline, citalopram, paroxetine and venlafaxine are licensed for the treatment of panic disorder.	Not applicable
Canadian Anxiety Guidelines Initiative Group (2014)[19]	Pharmacotherapeutic approaches should begin with a first-line agent (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine XR, escitalopram, paroxetine). If response to optimal dosing is inadequate or the agent is not tolerated, treatment should be switched to another first-line agent before considering second-line medications. Second-line choices include the TCAs (clomipramine and imipramine), mirtazapine, reboxetine, or benzodiazepines (alprazolam, clonazepam, lorazepam, and diazepam).	Level of evidence 2‡ (based on Ribeiro 2001 RCT and 2 open-label studies (8,10,16))

Group or Agency	Recommendation/s	Strength of Recommendation / Certainty / Quality of Evidence
Acronyms: CBT, cognitive behavioral therapy; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitor, MAOI, monoamine oxidase inhibitors; TCA, tricyclic antidepressants ‡ At least 1 RCT with placebo or active comparison condition		

Other considerations

Based on publicly available price estimates, mirtazapine is more expensive compared to SSRIs. No health economic studies were identified evaluating the cost-effectiveness and resource implications of using mirtazapine specifically for patients with panic disorder.

Table Q3.5. Estimated costs of mirtazapine and SSRIs.

Drug	Price (in PHP)	Reference
Mirtazapine 30 mg tablet (Menelat®)	75.75	(21)
Paroxetine Hcl 20 mg tablet (Seroxat®)	66.75	(22)
Fluoxetine 20 mg capsule (generic)	11.62 – 20.00	(23)
Fluoxetine 20 mg capsule (Motivest®)	50.50	(24)
Fluoxetine 20 Hcl mg capsule (Prodin®)	44.00	(25)
Sertraline 50 mg tablet (generic)	6.50 – 7.90	(23)
Sertraline Hcl 50 mg tablet (Zoloft®)	138.75	(26)
Sertraline Hcl 50 mg tablet (Exulten®)	56.00	(27)
Escitalopram 10 mg tablet (generic)	1.90 – 198.00	(23)

No research evidence was identified showing which outcomes are valued the most by Filipino patients with panic disorder and their health care providers. It is also uncertain whether patients would find the side effects of mirtazapine (e.g., weight gain, drowsiness) to be more acceptable compared to those from other anti-depressants (e.g., nausea, headache, etc.), as well as the associated costs and potential efficacy. Mirtazapine is currently registered in the Philippine Food and Drug Administration as an anti-depressant and is available in 15mg, 30mg, and 45mg doses.

References

1. Batelaan N, Smit F, Graaf RD, Balkom AV, Vollebergh W, Beekman A. Economic costs of full-blown and subthreshold panic disorder. Journal of Affective Disorders. 2007 Dec;104(1–3):127–36.

2. Roy-Byrne PP, Craske MG, Stein MB. Panic disorder. The Lancet. 2006 Sep;368(9540):1023–32.

3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders [Internet]. 5th edition. 2013. Available from: https://doi.org/10.1176/appi.books.9780890425596

4. Mitte K. A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. Journal of Affective Disorders. 2005 Sep;88(1):27–45.

5. Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: a meta-analysis. International Clinical Psychopharmacology. 2013 Jan;28(1):33–45.

6. Zulfarina MS, Syarifah-Noratiqah SB, Nazrun SA, Sharif R, Naina-Mohamed I. Pharmacological Therapy in Panic Disorder: Current Guidelines and Novel Drugs Discovery for Treatment-resistant Patient. Clin Psychopharmacol Neurosci. 2019 May 31;17(2):145–54.

7. Anttila SAK, Leinonen EVJ. A Review of the Pharmacological and Clinical Profile of Mirtazapine. CNS Drug Reviews. 2001 Sep;7(3):249–64.

8. Sarchiapone M, Amore M, De Risio S, Carli V, Faia V, Poterzio F, et al. Mirtazapine in the treatment of panic disorder: an open-label trial: International Clinical Psychopharmacology. 2003 Jan;18(1):35–8.

9. Carli V, Sarchiapone M, Camardese G, Romano L, DeRisio S. Mirtazapine in the Treatment of Panic Disorder. Arch Gen Psychiatry [Internet]. 2002 Jul 1 [cited 2025 Mar 12];59(7). Available from: http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archpsyc.59.7.661

10. Boshuisen ML, Slaap BR, Vester-Blokland ED, Den Boer JA. The effect of mirtazapine in panic disorder: an open label pilot study with a single-blind placebo run-in period: International Clinical Psychopharmacology. 2001 Nov;16(6):363–8.

11. Carpenter L, Leon Z, Yasmin S, Price L. Clinical Experience with Mirtazapine in the Treatment of Panic Disorder. Ann of Clinical Psychiatry. 1999 Jun 1;11(2):81–6.

12. Higgins JP, Li T, Deeks JJ. Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. 1st ed. Wiley; 2019 [cited 2025 Mar 13]. p. 143–76. Available from: https://onlinelibrary.wiley.com/doi/10.1002/9781119536604.ch6

13. Chawla N, Anothaisintawee T, Charoenrungrueangchai K, Thaipisuttikul P, McKay GJ, Attia J, et al. Drug treatment for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2022 Jan 19;e066084.

14. Guaiana G, Meader N, Barbui C, Davies SJ, Furukawa TA, Imai H, et al. Pharmacological treatments in panic disorder in adults: a network meta-analysis. Cochrane Common Mental Disorders Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2023 Nov 28 [cited 2025 Mar 15];2023(11). Available from: http://doi.wiley.com/10.1002/14651858.CD012729.pub3

15. Montañés-Rada F, De Lucas-Taracena MT, Sánchez-Romero S. Mirtazapine versus paroxetine in panic disorder: an open study. International Journal of Psychiatry in Clinical Practice. 2005 Jan;9(2):87–93.

16. Ribeiro L, Busnello JV, Kauer-Sant'Anna M, Madruga M, Quevedo J, Busnello EAD, et al. Mirtazapine versus fluoxetine in the treatment of panic disorder. Braz J Med Biol Res. 2001 Oct;34(10):1303–7.

17. Andrews G, Bell C, Boyce P, Gale C, Lampe L, Marwat O, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. Aust N Z J Psychiatry. 2018 Dec;52(12):1109–72.

18. Practice Guideline for the Treatment of Patients With Panic Disorder. In: APA Practice Guidelines for the Treatment of Psychiatric Disorders: Comprehensive Guidelines and Guideline Watches [Internet]. 1st ed. Arlington, VA: American Psychiatric Association; 2006 [cited 2025 Mar 12]. Available from: http://www.psychiatryonline.com/content.aspx?aID=51396

19. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14(Suppl 1):S1.

20. Nationale Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder in adults: management [Clinical Guideline CG113]. https://www.nice.org.uk/guidance/cg113/chapter/Recommendations#stepped-care-for-people-with-panic-disorder. 2020 Jun 15;

21. https://www.watsons.com.ph/mirtazapine-30mg-1-film-coated-tablet-prescription-required/p/BP_10093074.

22. https://www.watsons.com.ph/paroxetine-hcl-20mg-1-tablet-prescription-required/p/BP_10059102.

23. Department of Health. Drug Price Reference Index [Internet]. [cited 2025 Mar 13]. Available from: https://dpri.doh.gov.ph/

24. https://www.watsons.com.ph/fluoxetine-20mg-1-capsule-prescription-required/p/BP_10093285.

25. https://www.watsons.com.ph/fluoxetine-hcl-20mg-1-capsule-prescription-required/p/BP_10092763.

26. https://www.watsons.com.ph/sertraline-hydrochloride-50mg-1-tablet-prescription-required/p/BP_10059639.

27. https://www.watsons.com.ph/sertraline-hydrochloride-50mg-1-tablet-prescription-required/p/BP_10093528.

5. Evidence and Recommendations: Bipolar Disorder

Guideline Question 4: Should we use brexpiprazole in patients with Bipolar I Disorder presenting with acute mania?

Recommendation 4.	
We suggest against the use of brexpiprazole monotherapy as treatment in patients with bipolar 1 disorder presenting with acute mania.	
Strength of Recommendation:	Weak
Certainty of Evidence:	Very low

Justification

The available evidence showed that brexpiprazole monotherapy does not significantly improve symptom control in patients with acute mania associated with bipolar I disorder. Additionally, although it was not linked to a significant increase in serious or non-serious adverse events overall, it was associated with a higher risk of akathisia. Given the lack of demonstrated efficacy and the potential for adverse effects, the panel unanimously voted against recommending brexpiprazole monotherapy for this population. Until more robust evidence becomes available, the panel does not support its use as a standalone treatment for acute mania.

Introduction

Brexpiprazole is an antipsychotic drug that is a partial agonist of dopamine D_2/D_3 receptors and belongs to a group of dopamine receptor partial agonists or DRPAs approved for clinical use.[1] When it binds to dopamine receptors, it does not completely block them leaving a level of arousal[2] that may have a role in lowering the risk of akathisia. In addition, the higher affinity of brexpiprazole for histamine receptors may likely lead to a stronger sedative effect and a lower risk of akathisia, agitation and insomnia.[2]

Brexpiprazole is used in various countries for the treatment of schizophrenia and is also prescribed as an adjunct to antidepressants for the treatment of major depressive disorders.[7] Other RCTs and open-label studies have shown that this is a safe and well-tolerated drug, and AEs range from mild to moderate.[3] However, its use particularly as monotherapy for bipolar I disorder has not been explored extensively.[3]

Evidence

Two (2) RCTs that used brexpiprazole monotherapy for people with bipolar I disorder presenting with acute mania were found in clinicaltrials.gov (NCT03257865 or Trial 081, NCT03259555 or Trial 080).[5,6] Unfortunately, these were placebo-controlled studies as the highly sensitive search did not reveal any study that randomized people with bipolar I disorder to brexpiprazole versus a mood stabilizer or another antipsychotic. These 2 RCTs were the subject of a review that also stipulated that these were the first controlled trials of this drug in acute mania.[7]

The RCTs included a total of 655 patients diagnosed with bipolar I disorder, with or without mixed features, presenting with mania. The definition was based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[8] Patients were given brexpiprazole orally with flexible dosing from 2 to 4 mg per day and titrated to a maximum of 4 mg/day or a matching placebo administered in the same way to maintain blinding.

Benefits and risks

In the 3 weeks duration of the study, brexpiprazole did not show any significant effect in Young Mania Rating Scale (YMRS) and the Clinical Global Impressions-Bipolar Severity of Illness (CGI-BP) scale when compared with placebo. Total serious adverse events (SAE) and mania were shown to be inconclusive. No significant difference was also seen in any reported adverse events (AE) and other adverse events such as constipation, nausea and headache. However, there was a noted increase in the adverse event of akathisia for those on brexpiprazole. A systematic review and network meta-analysis[9], as well as one review that included these 2 RCTs[7], reported that brexpiprazole did not show a better response to treatment than placebo for patients with bipolar I disorder presenting with acute mania. This evidence summary is consistent with those reports.

Table Q4.1. Brexpiprazole monotherapy versus placebo for bipolar I disorder presenting with acute mania for outcomes reported in 2 RCTs.

Outcomes	No. of participants (studies)	Effect estimate (95%CI)	Interpretation	Certainty of Evidence
Change from Baseline in YMRS Score at Week 3	519 (2 RCTs)	Reported as least squares mean difference for the 2 studies **[Trial 081]** -1.62 (-3.56 to 0.32) **[Trial 080]** 0.14 (-1.74 to 2.03)	Inconclusive	Very low[a,b,d] ⨁◯◯◯
Change from Baseline in CGI-BP Severity Score in Mania at Week 3	519 (2 RCTs)	MD -0.08 (-0.41 to 0.26)	Inconclusive	Very low[a,b,d] ⨁◯◯◯
All-cause mortality	653 (2 RCTs)	Not estimable		
Total SAE	652 (2 RCTs)	RR 0.92 (0.04 to 23.97)	Inconclusive	Very low[b,c,d] ⨁◯◯◯
SAE: Mania	653 (2 RCTs)	RR 0.50 (0.06 to 3.85)	Inconclusive	Very low[b,c] ⨁◯◯◯
SAE: Epilepsy	332 (1 RCT)	RR 0.35 (0.01 to 8.52)	Inconclusive	Very low[b,c] ⨁◯◯◯
SAE: Thrombocytopenia, varicella, akathisia and dystonia	321 (1 RCT)	RR 3.09 (0.13 to 75.39)	Inconclusive	Very low[b,c] ⨁◯◯◯
Total Other (Not Serious) AE	653 (2 RCTs)	RR 1.05 (0.74 to 1.49)	Inconclusive	Low[b,c] ⨁⨁◯◯
Other AE: Akathisia	653 (2 RCTs)	RR 3.64 (1.49 to 8.89)	Favors Placebo	Moderate[b] ⨁⨁⨁◯
Explanation a. risk of bias; b. indirectness; c. imprecision; d. inconsistency				

Certainty of the evidence

Certainty of evidence was affected by indirectness and was the reason for the immediate downgrading by one level across all outcomes. The original question was on the efficacy and safety of brexpiprazole compared with mood stabilizers or antipsychotics and not with placebo. The two studies also had an unclear risk of bias due to the incomplete outcome data of around 18-21% in the brexpiprazole and placebo groups on the measurement of the YMRS score and the CGI-BP severity score. The exclusion of these participants in the analysis of these outcomes actually downgraded the certainty of evidence by one level for this primary and secondary outcome. On the other hand, the bias was not serious in the safety outcomes because almost all patients were accounted for in the serious adverse events and other adverse events. Since some of the outcomes also showed results that were inconsistent and imprecise, overall certainty was deemed to be very low as the primary and secondary outcomes, considered critical outcomes, had very low certainty of evidence.

Recommendations from Other Groups

Other CPGs for the management of bipolar disorder, specifically bipolar I disorder with acute mania from relevant groups were reviewed (Table Q4.2).

Table Q4.2. Recommendations from other groups.

Group or Agency	Recommendation	Certainty of Evidence & Strength of Recommendation
Bipolar Disorders: Evaluation and Treatment (American Association of Family Physicians) 2021[10]	Silent on the use of brexpiprazole (not listed as a choice of treatment)	
VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder 2023[11]	We suggest against brexpiprazole, topiramate, or lamotrigine as a monotherapy for acute mania.	Weak against
The CANMAT and ISBD Guidelines for the Treatment of Bipolar Disorder: Summary and a 2023 Update of Evidence[12]	Silent on the use of brexpiprazole (not listed as a choice of treatment)	
NICE (National Institute of Health and Care Excellence) Bipolar Disorder Assessment and Management Clinical Guideline 2014; 2023[13]	Silent on the use of brexpiprazole (not listed as a choice of treatment)	
Practice Guidelines for Bipolar Disorder by the Japanese Society of Mood Disorder 2024[14]	Silent on the use of brexpiprazole (not listed as a choice of treatment)	

Other considerations

Resource implications

Cost-effectiveness studies will also be needed if brexpiprazole is proven to be beneficial for patients with bipolar I disorder. Systematic reviews on economic comparisons utilizing multi-country or global evidence on second-generation antipsychotics were mainly for the treatment of schizophrenia.[15,16] There were also retrospective studies comparing the impact on

psychiatric cost or health care cost of treatment with brexpiprazole compared to other atypical antipsychotic therapy, but these were also on patients with schizophrenia and major depressive disorders.[17,18] In the study by Adhikari (2024), lurasidone and ziprasidone were associated with the lowest total lifetime costs when given as maintenance.[16] In both studies by Yan (2020), brexpiprazole was shown to have lower psychiatric costs than lurasidone and quetiapine.[17,18] The conflicting results may be due to differences in methodology or models used. In the VA/DoD Clinical Practice Guideline for the Management of Bipolar Disorder (2023), it was mentioned that brexpiprazole is more expensive than topiramate and lamotrigine when considering monotherapy for acute mania.[11]

Stakeholder values, preferences, and acceptability

There are currently no studies on values, preferences, and acceptability of brexpiprazole monotherapy in the treatment of mania in patients with bipolar I disorder. Considering that effectiveness data on this question is still lacking, it is understandable that studies on values and preferences are nil.

Equity and feasibility

As of this time, there is not enough evidence on the effectiveness of brexpiprazole monotherapy for the management of mania in patients with bipolar I disorder to plan for equity and feasibility studies.

References

1. Mohr P, Masopust J and Kopeček M. Dopamine Receptor Partial Agonists: Do They Differ in Their Clinical Efficacy? Front. *Psychiatry*, 2022: 12:781946. Doi: 10.3389/fpsyt.2021.781946

2. Bieńkowski P, Wichniak A. Efficacy and tolerability of brexpiprazole – a new antipsychotic drug from the group of dopamine D2 receptor partial agonists. *Psychiatr Pol* 2024; 58(2): 237–248. DOI: https://doi.org/10.12740/PP/OnlineFirst/169646

3. Siwek M, Wojtasik-Bakalarz K, Krupa AJ, Chrobak AA. Brexpiprazole-Pharmacologic Properties and Use in Schizophrenia and Mood Disorders. *Brain Sci.* 2023 Feb 25;13(3):397. doi: 10.3390/brainsci13030397. PMID: 36979208; PMCID: PMC10046771.

4. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.5 (updated August 2024). *Cochrane*, 2024. Available from www.training.cochrane.org/handbook.

5. A Trial to Assess Brexpiprazole Versus Placebo for the Treatment of Acute Manic Episodes, Associated With Bipolar I Disorder. ClinicalTrials.gov Identifier: NCT03257865 (Other Study ID Number: 331-201-00081). Updated February 11, 2020. Accessed February 2025

6. A Trial to Assess Brexpiprazole Versus Placebo for the Treatment of Acute Manic Episodes Associated With Bipolar I Disorder. ClinicalTrials.gov Identifier: NCT03259555 (Other Study ID Number: 331-201-00080). Updated February 10, 2020. Accessed February 2025

7. Vieta E, Sachs G, Chang D, Hellsten J, Brewer C, Peters-Strickland T, Hefting N. Two randomized, double-blind, placebo-controlled trials and one open-label, long-term trial of brexpiprazole for the acute treatment of bipolar mania. *J Psychopharmacol.* 2021 Aug;35(8):971-982. doi: 10.1177/0269881120985102. Epub 2021 Mar 10. PMID: 33691517; PMCID: PMC8366183.

8. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (5th Edition)—DSM-5 2013. Arlington, VA: American Psychiatric Association.

9. Kishi T, Ikuta T, Matsuda Y, Sakuma K, Okuya M, Nomura I, Hatano M, and Iwata N. Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials. *Molecular Psychiatry* 2022; 27:1136–1144; https://doi.org/10.1038/s41380-021-01334-4

10. Marzani G, Neff AM. Bipolar Disorder: Evaluation and Treatment. *Am Fam Physician* 2021;103(4): 227-239

11. Management of Bipolar Disorder Work Group. Department of Veteran Affairs (VA) / Department of Defense (DoD) Clinical Practice Guideline for Management of Bipolar Disorder. VA/DoD Clinical Practice Guideline 2023. Washington, DC: U.S. Government Printing Office.

12. Keramatian K, Chithra NK, Yatham LN.The CANMAT and ISBD Guidelines for the Treatment of Bipolar Disorder: Summary and a 2023 Update of Evidence. *Focus* 2023; 21:344–353; doi: 10.1176/appi.focus.20230009

13. Bipolar disorder: assessment and management. London: National Institute for Health and Care Excellence (NICE); 2023 Dec 21. (NICE Guideline, No.185) Available from: https://www.ncbi.nlm.nih.gov/books/NBK547001/

14. Kato T, Ogasawara K, Motomura K for the JSMD Bipolar Disorder Guidelines Revision Working Group, JSMD Bipolar Disorder Committee, JSMD Guidelines Committee. Practice Guidelines for Bipolar Disorder by the JSMD (Japanese Society of Mood Disorders). *Psychiatry and Clinical Neurosciences* 2024; 78(11): 633-645.

15. Kearns B, Cooper K, Cantrell A, Thomas C. Schizophrenia Treatment with Second-Generation Antipsychotics: A Multi-Country Comparison of the Costs of Cardiovascular and Metabolic Adverse Events and Weight Gain. *Neuropsychiatr Dis Treat.* 2021 Jan 20;17:125-137. doi: 10.2147/NDT.S282856. PMID: 33505160; PMCID: PMC7829121.

16. Adhikari K, Kamal KM, Jeun KJ, Nolfi DA, Ashraf MN, Zacker C. Real-World Effectiveness, Economic, and Humanistic Outcomes of Selected Oral Antipsychotics in Patients with Schizophrenia: A Systematic Review Evaluating Global Evidence. *Clinicoecon Outcomes Res.* 2024 Sep 6;16:621-645. doi: 10.2147/CEOR.S469024. PMID: 39257455; PMCID: PMC11385900.

17. Yan T, Greene M, Chang E, Houle CR, Tarbox MH, Broder MS. Impact of Atypical Antipsychotics as Adjunctive Therapy on Psychiatric Cost and Utilization in Patients with Major Depressive Disorder. *Clinicoecon Outcomes Res.* 2020 Feb 7;12:81-89. doi: 10.2147/CEOR.S231824. PMID: 32104020; PMCID: PMC7012250.

18. Yan T, Greene M, Chang E, Houle CR, Waters HC, Tarbox MH, Broder MS. Health Care Cost in Patients With Schizophrenia Treated With Brexpiprazole Versus Other Oral Atypical Antipsychotic Therapy. *Clin Ther.* 2020 Jan;42(1):77-93. doi: 10.1016/j.clinthera.2019.11.009. Epub 2020 Jan 10. PMID: 31928831.

Guideline Question 5: Should antidepressants (SSRIs, as a class) be used as an adjunct treatment in patients with Bipolar I Disorder presenting with acute depression?

Recommendation 5.

We suggest against the use of SSRI or SNRI as an adjunct in the treatment of patients with bipolar 1 disorder with acute depression.

Strength of Recommendation: Weak
Certainty of Evidence: Very low

Remarks: Available evidence only supports the use of fluoxetine and olanzapine as separate medications, not as the combination drug (Symbyax)

Justification

While the overall evidence was inconclusive, one trial demonstrated improved response rates and a decreased risk of treatment discontinuation with the combination of fluoxetine and olanzapine compared to olanzapine alone. However, evidence for other SSRIs and SNRI was insufficient, leading the panel to unanimously vote against recommending the entire drug class as adjunctive treatment.

The panel also considered safety concerns, including an increased risk of treatment-emergent mania and greater use of anticholinergic medications in patients receiving SSRIs. Additionally, the certainty of evidence was low due to serious indirectness and imprecision. The panel determined that their recommendation should remain weak given these limitations. A footnote has been added to clarify that the recommendation specifically refers to fluoxetine and olanzapine taken as separate pills, not as the combination drug Symbyax. Further research is needed to evaluate the safety and effectiveness of other SSRI/SNRI combinations in this patient population.

Background

Mental health disorders are increasingly prevalent in the Philippines, with 520,614 individuals diagnosed with bipolar disorder in 2020, according to the World Health Organization.[1,2] Bipolar depression, the depressive phase of bipolar disorder, is particularly disabling and challenging to treat. The American Psychiatric Association recommends lithium or lamotrigine as first-line therapy, though lithium alone is ineffective for managing bipolar depression.[3,4] Studies on antidepressant use in this population are conflicting, with concerns about inducing mania, rapid mood cycling, and emotional destabilization.[6]

A systematic review of 19 studies found that adjunctive antidepressants did not significantly improve depressive symptoms or response rates compared to mood stabilizers or antipsychotics alone.[7] However, they were not associated with a higher risk of mood switching and had lower dropout rates due to ineffectiveness when used alongside standard therapy. Some reports suggest that SSRIs, either as monotherapy or combined with a mood stabilizer, may be effective in treating acute bipolar I depression with a low risk of manic switch. This

review examines the evidence for SSRIs and SNRIs as adjuncts to standard treatment in managing bipolar I disorder with acute depression.

Evidence

Three randomized trials involving a total of 984 patients diagnosed to have bipolar disorder with acute depression were included in this review.[3-5] The diagnosis of bipolar disorder was based on the Diagnostic and Statistical Manual of Mental Disorders handbook III-R or IV, while assessment of depressed state was facilitated using the Hamilton depression scale or the Montgomery-Asberg Depression Rating Scale. None of the three trials compared the use of SNRIs as adjunct to standard of care versus standard of care alone. SSRIs used in the trials include Paroxetine and Fluoxetine. Length of follow-up varies from 8 to 10 weeks.[3-5] More studies are needed to provide data on the utility of antidepressants, specifically SSRIs or SNRIs among patients with Bipolar I Disorder and Acute Depression.

Benefits and risks

Adjunctive treatment with SSRIs, specifically paroxetine and fluoxetine, was associated with better treatment response among patients with Bipolar I Disorder with acute depression compared to standard of care alone. Likewise, remission rates were also better among those given combination of fluoxetine and olanzapine compared to olanzapine alone.

Use of SSRIs as adjunctive treatment to standard of care was associated with increased risk for use of anticholinergic drugs. On the other hand, SSRIs as adjunctive therapy did not significantly affect the rates of adverse reactions such as treatment emergent mania, QTc interval prolongation, weight gain, and discontinuation of treatment due to relapse to depression, or due to adverse events. Specific reasons for discontinuation, like adverse events or relapse, showed no significant difference. Side effects such as somnolence, tremors, and insomnia were reported more frequently with adjunctive paroxetine.

Certainty of the evidence

The certainty of evidence for the use of SSRIs as adjunctive therapy in patients with bipolar disorder and acute depression is low to very low. This is due to concerns about indirectness (heterogeneity in diagnostic criteria, patient populations, and outcome definitions), imprecision (wide confidence intervals, few events), and inconsistency across trials.

Table Q5.1. Summary of findings for SSRIs as adjunctive therapy in patients with bipolar disorder.

Outcomes	№ of participants (studies)	Effect estimate (95% CI)	Interpretation	Certainty of evidence
Treatment response • **Bipolar Disorder** • **Bipolar I**	484 (2 RCTs)	RR 1.32 (1.00 to 1.74)	Inconclusive	Low[a,b]
	51 (1 RCT)	RR 1.04 (0.63 to 1.71)	Inconclusive	Low[a,b]
	433 (1 RCT)	RR 1.44 (1.14 to 1.81)	Favors treatment	High

Outcomes	№ of participants (studies)	Effect estimate (95% CI)	Interpretation	Certainty of evidence
Remission	433 (1 RCT)	RR 1.48 (1.14 to 1.95)	Favors treatment	High ⊕⊕⊕⊕
Treatment emergent mania	413 (3 RCTs)	RR 1.25 (0.53 to 2.97)	Inconclusive	Very low[a,b] ⊕◯◯◯
Use of anticholinergic medications	446 (1 RCT)	RR 2.93 (1.15 to 7.48)	Risk of using anticholinergic medications during treatment is increased by 3-fold	Moderate[a] ⊕⊕⊕◯
QTc interval prolongation	456 (1 RCT)	RR 1.42 (0.06 to 34.600	Inconclusive	Low[b] ⊕⊕◯◯
Treatment discontinuation • **Overall** • **Due to adverse events** • **Due to relapse to depression**	456 (1 RCT)	RR 0.70 (0.52 to 0.94)	Decrease in risk for treatment discontinuation	High ⊕⊕⊕⊕
	456 (1 RCT)	RR 0.25 (0.06 to 1.03)	Inconclusive	Low[b] ⊕⊕◯◯
	1 RCT (n=456)	RR 0.86 (0.10 to 7.27)	Inconclusive	Low[b] ⊕⊕◯◯
Explanation a. serious indirectness; b. serious imprecision				

Recommendations from other groups

Table Q5.2. Recommendations from other groups.

Group or Agency	Recommendation
Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders 2018	Lurasidone (Level 1) and Lamotrigine (Level 2) are recommended as first-line adjunctive treatment. Adjunctive use of antidepressant therapy (selective serotonin reuptake inhibitors or bupropion) with lithium/divalproate or an atypical antipsychotic may also be considered as a second-line add-on treatment. Antidepressants should not be used as monotherapy in patients with BDI depression, as available trials do not support monotherapy their efficacy and there are concerns about their safety in terms of mood switching (Level 2 negative)
British Association for Psychopharmacology 2016	For patients who suffer a depressive episode while taking long-term treatment, ensure that the current choice of long-term treatments is likely to protect the patient form manic relapse (e.g. lithium, valproate, dopamine receptor antagonist/partial agonist drugs), by checking adequate doses of medicines and/or serum concentrations of lithium within the usual target range (Standard of Care) Antidepressants (Moderate)

Other considerations

Resource implications

There are no published cost-effectiveness studies on the use of adjunctive SNRIs or SSRIs for the treatment of Bipolar I Disorder in Acute Depression. The table below shows the average cost of each of the medications included in this review.

Table Q5.3. Average cost in the Philippines.

Drug	Dose	Estimated Cost (in Php)
Fluoxetine	20mg	26.79 – 50.50
Paroxetine	20mg	66.00 – 66.75
Olanzapine	5mg 10mg	44.42 52.75
Lithium carbonate	450mg	4.76

Stakeholder values, preferences, acceptability, and equity

Studies on patient values, preferences, and acceptability of antidepressants, specifically SSRIs or SNRIs, are also lacking.

References

1. Alibudbud R. Comment Towards transforming the mental health services of the. Lancet Reg Heal - West Pacific [Internet]. 2023;39(October):100935. Available from: https://doi.org/10.1016/j.lanwpc.2023.100935

2. Uno-Rayco C, Sorian J, Dela Cruz L, Noscal M, Sanchez D, Santos A, et al. DSM5-BASED DIAGNOSIS AND DEMOGRAPHICS OF THE PHILIPPINE MENTAL HEALTH ASSOCIATION INC .' S PSYCHIATRIC. ASEAN J Psychiatry. 2022;23(November-December):1–7.

3. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of Olanzapine and Olanzapine-Fluoxetine Combination in the Treatment of Bipolar I Depression. 2003;60.

4. Nemeroff C, Evans D, Gyulai L, Sachs G, Bowden C, Gergel I, et al. Double-Blind, Placebo-Controlled Comparison of Imipramine and Paroxetine int he Treatment of Bipolar Depression. Am J Psychiatry [Internet]. 2001;158(June):906–12. Available from: https://doi.org/10.1176/appi.ajp.158.6.906

5. Amsterdam JD, Shults J. Comparison of fluoxetine , olanzapine , and combined fluoxetine plus olanzapine initial therapy of bipolar type I and type II major depression — lack of manic induction. 2005;87:121–30.

6. Vasquez G, Tondo L, Undurraga J, Baldessarini RJ. Overview of antidepressant treatment of bipolar depression. Int J Neuropsychopharmacol. 2013;16:1673–85.

7. Hu Y, Zhang H, Wang H, Wang C, Kung S, Li C. Adjunctive antidepressants for the acute treatment of bipolar depression : A systematic review and meta-analysis. Psychiatry Res [Internet]. 2025;311(February 2022):114468. Available from: https://doi.org/10.1016/j.psychres.2022.114468

Guideline Question 6: Should valproic acid be used in patients with Bipolar I Disorder in the maintenance phase of treatment?

Recommendation 6.

We suggest the use of valproic acid* among patients with bipolar 1 disorder in the maintenance phase of treatment

Strength of Recommendation: Weak
Certainty of Evidence: Very low

***Remarks:** Includes all other derivatives of valproic acid.

Justification

The panel concluded that the overall safety profile appeared comparable to standard of care, with no significant difference in the total number of patients experiencing adverse events. However, the evidence was insufficient to draw clear conclusions regarding its impact on hospital admission, symptom severity, and quality of life. Safety concerns, particularly reproductive safety, were also highlighted, with emerging evidence from observational studies suggesting potential risks that were not captured in randomized controlled trials. Despite these concerns, the panel found no significant difference in efficacy between valproic acid and other treatments, such as lithium, which led to a weak recommendation for its use in the maintenance phase of treatment.

The panel also considered resource implications, including the availability and cost of the alternative treatments (i.e, lithium), and acknowledged that local considerations—such as the accessibility of other medications and cost concerns—warranted maintaining valproic acid use despite changes in other international guidelines. The lack of significant evidence for valproic acid's superiority, combined with its reproductive safety concerns, contributed to the weak recommendation. Future updates to the guideline should incorporate emerging evidence on valproic acid's reproductive effects as well as the effects of different valproic acid derivatives and combinations available for maintenance treatment. Additionally, the resource implications of using lithium as an alternative should be addressed, as well as the local context regarding valproic acid use.

Background

Valproic acid and its derivatives, including divalproex sodium, sodium valproate, and valproate semisodium, are anticonvulsant (anti-epileptic) medications widely used in the treatment of various neurological and psychiatric disorders, including bipolar disorder (BD).[1] While its exact mechanism of action in BD remains unclear, valproic acid is believed to reduce or prevent manic episodes by increasing the amount of gamma-aminobutyric acid (GABA) in the brain. This neurotransmitter inhibits nerve transmissions in the brain, producing a calming effect.[2]

Limited studies have been conducted on the maintenance treatment of BD with valproates. A recent systematic review and meta-analysis found that valproates were more effective than placebo in preventing new BD episodes of mania or depression, but showed no significant advantage over antipsychotics or other mood stabilizers in the long-term treatment of BD.[3]

Several guidelines recommend valproate as a first-line treatment in the prevention of mania or any mood episode in BD.[4] However, the National Institute for Health and Care Excellence (NICE) updated its guidance on valproic acid use in bipolar I disorder following a regulatory change by the MHRA in December 2022. Previously, lithium was the first-line treatment, with the addition of valproate as a second-line option. However, due to safety concerns and side effects, valproate is now a third-line option, with an alternative antipsychotic recommended as the second-line option.[4] This review aims to evaluate valproate's efficacy and safety on the long-term use of valproates compared to standard of care. Valproic acid and its derivatives are collectively referred to as valproates in the succeeding sections.

Evidence

We identified 7 RCTs comprising a total of 1,258 patients with bipolar disorder. Three (3) RCTs conducted in the UK, France, the US, and Italy included patients diagnosed with bipolar I disorder according to DSM-IV criteria.[6,7,8] Another RCT from the US[9] and its post-hoc analysis[10] recruited patients with bipolar I disorder using DSM-III criteria. Additionally, 2 RCTs from the US and Germany included patients with either bipolar I or II disorder based on DSM-IV criteria[11,12]; among these, 1 study also included patients with rapid-cycling bipolar disorder.[12]

Comparators of valproate included olanzapine[6], quetiapine[12], lithium[7,9-11], or lithium in combination with valproate.[8] The dose of valproate was flexible in most studies until it reached a targeted therapeutic range of 50-125 µg/ml. Outcome measures during the follow-up period of 12 to 24 months included hospital admission[8], changes from baseline on the Young Mania Rating Scale (YMRS)[6,9,12], Clinical Global Impression scale (CGI)[6], and Montgomery-Asberg Depression Scale (MADRS)[13], episodes of deliberate self-harm[8], proportion of patients with early discontinuation due to depression[10], quality of life[7,8], and adverse events.[6,9,11,12]

Benefits and risks

Among patients with bipolar I disorder in the maintenance phase of treatment, valproic acid did not demonstrate a significant difference compared to standard of care (SoC) in terms of symptom control, including hospital admissions, symptom severity (YMRS, CGI, MADRS), deliberate self-harm, and quality of life scores. Similarly, the overall safety profile of valproic acid was comparable to standard of care, with no significant difference in the total number of patients experiencing adverse events (very low certainty of evidence). However, reported adverse events varied across studies, with nausea, sedation, tremor, diarrhea, and weight gain being frequently observed in both treatment groups.

Certainty of the evidence

Overall certainty of evidence has been downgraded to very low because of these serious risks of bias across the different critical outcomes, indirectness, and imprecision. Most RCTs had some concerns regarding the randomization process, missing outcome data, and selection of the reported results. Several studies, such as those by Langosch (2008) and Revicki (2005), were open-label, increasing the risk of bias. High risk of bias was commonly noted in missing outcome data due to high attrition rates.[7,12] Geddes (2010) had the lowest overall risk, with low risk in all domains, while other studies exhibited high risk due to issues like outcome measure revisions.[8] Two studies recruited participants with either bipolar I or II disorders[11,12] reducing overall directness of the studies. Sponsorship bias remains a possibility in 3 studies due to funding from pharmaceutical companies.[6,7,9]

Table Q6.1. Valproate vs. standard of care for maintenance treatment of bipolar disorder.

Outcomes	№ of participants (studies)	Effect estimate (95% CI)	Interpretation	Certainty of evidence
Efficacy outcomes				
Hospital admission (ffup 2 years)	220 (1 RCT)	RR 1.56	Inconclusive	Low ⊕⊕◯◯
Mean change in YMRS from baseline (ffup 1 year)	288 (2 RCTs)	MD 0.84 (-3.88 to 5.55)	Inconclusive	Very low[a,b,c,d] ⊕◯◯◯
Mean change in YMRS from baseline (ffup 1 year) – Olanzapine	251 (1 RCT)	MD 2.88 (0.19 to 5.57)	Favors SoC (Greater improvement in YMRS score)	Very low ⊕◯◯◯
Mean change in YMRS from baseline (ffup 1 year) - Quetiapine	37 (1 RCT)	MD -2.00 (-6.70 to 2.70)	Inconclusive	Very low ⊕◯◯◯
Mean change in YMRS from baseline (ffup 2 years)	277 (1 RCT)	MD 0.10 (-2.55 to 2.75)	Inconclusive	Low[e,g] ⊕⊕◯◯
Mean change in CGI severity of illness from baseline (ffup 47 weeks)	250 (1 RCT)	MD 0.28 (-0.09 to 0.65)	Inconclusive	Very low[b,d,e] ⊕◯◯◯
Mean change in MADRS from baseline (ffup 1 year)	134 (1 RCT)	MD 2.10 (-5.64 to 9.84)	Inconclusive	Very low[a,d,e] ⊕◯◯◯
Episodes of deliberate self-harm (ffup 2 years)	220 (1 RCT)	RR 1.25 (0.34 to 4.53)	Inconclusive	Very low[e] ⊕◯◯◯
Quality of life (SF-36 Physical Component Summary; ffup 1 year)	134 (1 RCT)	MD 0.20 (-4.61 to 5.01)	Inconclusive	Very low[e,f] ⊕◯◯◯
Quality of life (SF-36 Mental Component Summary; ffup 1 year)	134 (1 RCT)	MD 0.10 (-6.26 to 6.46)	Inconclusive	Very low[e,f] ⊕◯◯◯
Safety outcomes				
Adverse events	29 (1 RCT)	RR 0.72 (0.48 to 1.10)	Inconclusive	Very low[i,j,k] ⊕◯◯◯

Explanation

a. Issues on randomization process (allocation was not concealed; there are differences in treatment groups (longer duration of illness in the quetiapine vs VPA group), outcome measurement (not blinded), attrition, and reporting bias (Langosch 2008), risk of bias

b. No information on randomization method, but participants allocated to each treatment group were comparable; High attrition rate; Possibility for selection bias (some outcomes were emphasized over others) (Tohen 2003), risk of bias

c. Significant heterogeneity (I2>50%); issue on inconsistency

d. Mixture of bipolar I and II patients (Langosch 2008); issue on indirectness

e. Wide confidence interval; imprecision 95% CI included null value

f. Open-label trial; Issues on allocation concealment, attrition bias (Revicki 2005)

g. Issues on allocation concealment, attrition bias. Outcome measures were also revised at suggestion of reviewers. (Bowden 2000)

h. Issues on allocation concealment, attrition bias, selective reporting (Gyulai 2008)

i. Issues on randomization process (allocation was not concealed; there are differences in treatment groups (longer duration of illness in the quetiapine vs VPA group), outcome measurement (not blinded), attrition, and reporting bias (Langosch 2008)

j. Mixture of bipolar I and II patients (Langosch 2008)

k. 95% CI included null value

Recommendations from other groups

Table Q6.2. Recommendations from other groups.

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
NICE[5]	Offer lithium as a first-line, long-term pharmacological treatment for bipolar disorder. [2014] If lithium is ineffective, poorly tolerated, or is not suitable (for example, because the person does not agree to routine blood monitoring), consider an antipsychotic (for example asenapine, aripiprazole, olanzapine, quetiapine or risperidone). [2014, amended 2023] If the first antipsychotic is poorly tolerated at any dose (including rapid weight gain) or ineffective at the maximum licensed dose, consider an alternative antipsychotic from the drugs listed in recommendation 1.7.8). [2014, amended 2023] If an alternative antipsychotic is ineffective, consider a combination of valproate with either: an antipsychotic or lithium. [2014]	"No quality assessment of the included studies was undertaken as recency was prioritised over quality" – NICE, 2024
WHO (last updated 2023)[14]	Maintenance therapy with mood stabilizers or antipsychotic medicines should be considered for at least six months for adults with bipolar disorder in remission, carefully balancing effectiveness, side-effects and individual preference.	Strength of recommendation: CONDITIONAL Certainty of evidence: LOW
British Association for Psychopharmacology (BAP) – 3rd ed (2016)	Considered valproate as a first-line effective treatment in the prevention of mania or any mood episode	Overall quality assessment based on the AGREE-II domains: 92% Quality score for Domain 3 (Rigor of development): 82%
Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) (2018)	Considered valproate as a first-line effective treatment in the prevention of mania or any mood episode	Overall quality assessment based on the AGREE-II domains: 67% Quality score for Domain 3 (Rigor of development): 60%
Royal Australian and New Zealand College of Psychiatrists (RANZCP) (2015)	Considered valproate as a first-line effective treatment in the prevention of mania or any mood episode	Overall quality assessment based on the AGREE-II domains: 67% Quality score for Domain 3 (Rigor of development): 64%
The International College Psychopharmacology (CINP) (2017)	CINP-BD-201723 considered valproate as a second-line treatment. Even though it is often considered to be quite effective as lithium, the evidence for long-term prophylactic efficacy of valproate is rather poor and data is much more limited than that for lithium.	Overall quality assessment based on the AGREE-II domains: 58% Quality score for Domain 3 (Rigor of development): 66%
World Federation of Societies of Biological Psychiatry (WFSBP) (2012)	Considered valproate as a first-line treatment but in the prevention of depression and scored it as a second-line in the prevention of any mood episode whilst no rating was provided for the prevention of mania.	Overall quality assessment based on the AGREE-II domains: 83% Quality score for Domain 3 (Rigor of development): 78%

Other considerations

Resource implications

No studies that assessed the cost effectiveness of valproates compared to standard of care (olanzapine, quetiapine, and lithium) in the Philippines were found. Online pharmacy websites based in the Philippines (watsons.com.ph) and a list of drugs & medicines for consignment from the National Center for Mental Health (as of December 2024) state that these drugs are available at the following prices:

Table Q6.3. Price list of valproic acid, olanzapine, quetiapine, and lithium carbonate in the Philippines.

Drug	Dose	Estimated price (in Philippine peso)
Valproic acid[a]	250 mg tablet	19.00 php
	500 mg tablet	25.00 php
	250 mg/5 mL syrup (120 mL)	921.75 php
Olanzapine[a]	5 mg tablet	44.42 php
	10 mg tablet	52.75 php
Quetiapine[a]	25 mg tablet	28.00 php
	100 mg tablet	179.75 php
	200 mg tablet	247.50 php
	300 mg tablet	311.75 php
Lithium carbonate[b]	450 mg tablet	4.76 php

a. Watsons online. Watsons.com.ph. Accessed March 14, 2025.
b. National center for mental health (NCMH). List of requirements for medicine consignment CY 2025. Price Quotations. https://ncmh.gov.ph/images/pdf/bids/itc-12172027-meds.pdf. Published December 17, 2024. Accessed March 14, 2025.

Additionally, a U.S. study found that the mean total medical costs for patients who discontinued therapy with any mood stabilizer (valproate or lithium) were three times higher than those who remained on treatment (p = 0.023). This difference was largely driven by higher hospitalization costs in the discontinuation group ($29,770 vs. $6,300, p = 0.022), with a slight increase in outpatient treatment costs ($3,410 vs. $2,366, p = 0.273).[7]

Stakeholder values, preferences and acceptability

No studies on the acceptability of valproates were found.

Equity and feasibility

No studies describing the barriers and facilitators for the use, compliance to, and the delivery of the intervention were found for valproates.

References

1. Rahman M, Awosika AO, Nguyen H. Valproic Acid. [Updated 2024 Mar 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559112/

2. NHS. Valproic acid [Internet]. London: National Health Service (NHS); [cited 2025 Mar 14]. Available from: https://www.nhs.uk/medicines/valproic-acid/#:~:text=Valproic%20acid%20is%20an%20anticonvulsant,(GABA)%20in%20the%20brain

3. Yee CS, Vázquez GH, Hawken ER, Biorac A, Tondo L, Baldessarini RJ. Long-Term Treatment of Bipolar Disorder with Valproate: Updated Systematic Review and Meta-analyses. *Harv Rev Psychiatry.* 2021;29(3):188-195. doi:10.1097/HRP.0000000000000292

4. Verdolini N, Hidalgo-Mazzei D, Del Matto L, Muscas M, Pacchiarotti I, Murru A, Samalin L, Aedo A, Tohen M, Grunze H, Young AH, Carvalho AF, Vieta E. Long-term treatment of bipolar disorder type I: A systematic and critical review of clinical guidelines with derived practice algorithms. *Bipolar Disord.* 2021 Jun;23(4):324-340. doi: 10.1111/bdi.13040. Epub 2021 Jan 7. PMID: 33354842.

5. National Institute for Health and Care Excellence (NICE). Bipolar disorder: assessment and management [Internet]. London: NICE; [cited 2025 Mar 14]. Available from: https://www.nice.org.uk/guidance/cg185/chapter/Recommendations#managing-bipolar-disorder-in-adults-in-the-longer-term-in-secondary-care

6. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry.* 2003;160(7):1263-1271. doi:10.1176/appi.ajp.160.7.1263

7. Revicki DA, Hirschfeld RM, Ahearn EP, Weisler RH, Palmer C, Keck PE Jr. Effectiveness and medical costs of divalproex versus lithium in the treatment of bipolar disorder: results of a naturalistic clinical trial. *J Affect Disord.* 2005;86(2-3):183-193. doi:10.1016/j.jad.2005.01.002

8. Geddes JR, Goodwin GM, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet.* 2010;375(9712):385-395. doi:10.1016/S0140-6736(09)61828-6

9. Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry.* 2000;57(5):481-489. doi:10.1001/archpsyc.57.5.481

10. Gyulai L, Bowden CL, McElroy SL, et al. Maintenance efficacy of divalproex in the prevention of bipolar depression. *Neuropsychopharmacology.* 2003;28(7):1374-1382. doi:10.1038/sj.npp.1300190

11. Calabrese JR, Shelton MD, Rapport DJ, et al. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry.* 2005;162(11):2152-2161. doi:10.1176/appi.ajp.162.11.2152

12. Langosch JM, Drieling T, Biedermann NC, et al. Efficacy of quetiapine monotherapy in rapid-cycling bipolar disorder in comparison with sodium valproate. *J Clin Psychopharmacol.* 2008;28(5):555-560. doi:10.1097/JCP.0b013e318185e75f

13. World Health Organization (WHO). Duration of maintenance treatment with antipsychotics or mood stabilizers in individuals with bipolar disorder [Internet]. Geneva: WHO; [cited 2025 Mar 14]. Available from: https://www.who.int/teams/mental-health-and-substance-use/treatment-care/mental-health-gap-action-programme/evidence-centre/psychosis-and-bipolar-disorders/duration-of-maintenance-treatment-with-antipsychotics-or-mood-stabilizers-in-individuals-with-bipolar-disorder

6. Evidence and Recommendations: Depressive Disorder

Guideline Question 7: Should antidepressants combined with benzodiazepines (clonazepam, alprazolam, bromazepam) be used at the outset in patients with Major Depressive Disorder with Anxious Distress?

Recommendation 7.	
We suggest against the use of antidepressant + benzodiazepine combination at the outset among patients with major depressive disorder with anxious distress.	
Strength of Recommendation:	Weak
Certainty of Evidence:	Very low

Justification

Current evidence shows some short-term benefits of combining antidepressants with benzodiazepines, but the evidence is of very low certainty. Most studies were older and did not specifically address MDD with anxious distress. The panel discussed the potential risks of benzodiazepine use, including dependence and addiction, and expressed concerns about these risks despite the favorable short-term evidence. Benzodiazepines are generally recommended for short-term use due to their addictive potential, and the panel believes that antidepressant monotherapy or antidepressants combined with psychotherapy are more appropriate first-line treatment options.

The panel also noted resource implications, stakeholder preferences, and equity considerations related to prescribing benzodiazepines. Given these factors and the limited evidence of benefit, the panel unanimously suggests against combining antidepressants with benzodiazepines as initial treatment for MDD with anxious distress. Specific guidance on the duration of benzodiazepine use when combined with antidepressants should be included in the final guidelines.

Background

Major Depressive Disorder (MDD) is a prevalent and disabling mental health condition that often presents with anxious distress, a specifier characterized by excessive worry, restlessness, and difficulty concentrating. The presence of anxious distress in MDD is associated with greater severity of symptoms, poorer treatment response, and increased risk of suicide.[1] In a survey of outpatient consultation in a psychiatric clinic, the most common mental health condition was depressive disorders as 21%.[2]

Benzodiazepines, such as clonazepam, alprazolam, and bromazepam, are gamma-aminobutyric acid (GABA)-ergic anxiolytics commonly prescribed for short-term relief of anxiety symptoms. They are often used off-label as adjuncts to antidepressants to target the distressing anxious features of MDD). While benzodiazepines provide rapid symptom relief,

concerns exist regarding their potential for dependence, withdrawal, cognitive impairment, and lack of sustained efficacy.[3]

Given the uncertainty regarding the benefits and risks of benzodiazepine augmentation in MDD with anxious distress, this review evaluates the available evidence to determine whether combining benzodiazepines with antidepressants at treatment initiation improves clinical outcomes compared to antidepressant monotherapy. The findings aim to inform clinical practice recommendations and guide appropriate prescribing practices in this population.

Evidence

The evidence review included 10 RCTs conducted across various countries, with six studies from the United States and one each from the Netherlands, Spain, Norway, and Japan. Participants were diagnosed with MDD using established criteria, including the Feighner criteria, DSM-III, DSM-III-R, or DSM-IV, with mean ages ranging from 34.8 to 48.8 years. The studies evaluated antidepressants such as fluoxetine, imipramine, amitriptyline, desipramine, and mianserin in combination with benzodiazepines, including clonazepam, triazolam, lormetazepam, bentazepam, alprazolam, diazepam, flunitrazepam, mexazolam, and chlordiazepoxide.

Critical outcomes assessed included depression severity (measured using Hamilton Rating cale for Depression [HRSD]), response in depression (evaluated via HRSD or BDI), and anxiety severity (measured using HAM-A, BAI, and State-Trait Anxiety Inventory Scale [STAI-T]). Adverse effects were also analyzed, with dropout rates due to adverse events serving as an indicator of tolerability. Depression severity and treatment response were assessed at different time points: early phase (1–4 weeks), acute phase (5–12 weeks), and continuous phase (>12 weeks), while anxiety severity was evaluated in the early and acute phases.

There are no ongoing studies looking at benzodiazepine use in MDD. There is a need to conduct newer trials of high methodologic rigor to determine the benefits as well as risks of use of benzodiazepines in this setting. A systematic review on depression care in the Philippines highlight the gaps on the knowledge on the role of benzodiazepines in the patient journey touchpoints among people living with depression.

Benefits and risks

The use of benzodiazepine as an adjunct to antidepressants resulted in small improvements in depression severity and response rates in the early phase (1–4 weeks) but showed no sustained benefit beyond this period. Pooled analysis on anxiety severity was inconclusive. Dropouts due to adverse effects were lower in the combination group, suggesting better early tolerability. However, the included studies did not assess long-term risks such as dependence, withdrawal, or cognitive impairment.

Table Q7.1. Benzodiazepines as adjunct to antidepressants compared to antidepressants alone for major depressive disorder with anxious distress

Outcomes	№ of participants (studies)	Effect estimate (95% CI)	Interpretation	Certainty of evidence
Depression severity				
Early phase (2 weeks) follow-up: range 1-4 wks	598 (10 RCTs)	SMD -0.25 (-0.46 to -0.03)	Favors combination therapy	Very low[a,b,c] ⊕◯◯◯
Acute phase (8 weeks) follow-up: range 5-12 wks	347 (7 RCTs)	SMD -0.18 (-0.40 to 0.03)	inconclusive	Very low[a,b,c] ⊕◯◯◯
Continuous phase (>12 weeks)	50 (1 RCT)	SMD -0.21 (-0.76 to 0.35)	inconclusive	Very low[a,b,c] ⊕◯◯◯
Response in depression				
Early phase (2 weeks) follow-up: range 1-4 wks	731 (10 RCTs)	RR 1.34 (1.13 to 1.58)	Favors combination therapy	Very low[a,b] ⊕◯◯◯
Acute phase (8 wks)	383 (7 RCTs)	RR 1.12 (0.93 to 1.35)	inconclusive	Very low[a,b,c] ⊕◯◯◯
Continuous phase (>12 weeks)	52 (1 RCT)	RR 0.97 (0.73 to 1.29)	Inconclusive	Very low[a,b,c] ⊕◯◯◯
Anxiety severity				
Early phase (2 weeks) follow-up: range 1-4 wks	129 (3 RCTs)	SMD -0.76 (-1.67 to 0.14)	inconclusive	Very low[a,b,c] ⊕◯◯◯
Acute phase (8 weeks) follow-up: range 5-12 wks	129 (3 RCTs)	SMD -0.48 (-1.06 to 0.10)	inconclusive	Very low[a,b,c,d] ⊕◯◯◯
Dropouts due to adverse effects	731 (10 RCTs)	RR 0.54 (0.32 to 0.90)	Favors combination therapy	Very low[a,b] ⊕◯◯◯

Explanation
a. very serious risk of bias; b. serious indirectness; c. serious imprecision; d. serious inconsistency

Certainty of the evidence

The certainty of evidence was very low across all critical outcomes due to high risk of bias, indirectness, and imprecision, with a lack of long-term data limiting conclusions on the safety and sustained efficacy of benzodiazepines in this population. Risk of bias assessment showed that most studies had unclear risks related to randomization, allocation concealment, and blinding. Notably, 9 out of 10 RCTs exhibited high attrition bias due to significant dropout rates, which affected the reliability of results. Imprecision was another concern, with small sample sizes and wide confidence intervals further weakening the strength of evidence. Indirectness was evident as the specifier of anxious distress was inconsistently defined, given that most studies were published before its inclusion in DSM-5. Additionally, high statistical heterogeneity ($I^2 = 81\%$) was observed in anxiety severity outcomes.

Recommendations from other groups

Table Q7.2. Recommendations from other groups

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the Management of Adults with Major Depressive Disorder 2016	Recommends the use of benzodiazepines in MDD with catatonic features	Level 3
	Recommends the use of an antidepressant with efficacy in generalized anxiety disorder	Level 4
Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for Mood Disorders: Major Depression 2020	Recommends the use of escitalopram and venlafaxine in patients with MDD with anxiety as a key symptom	N/A

Other considerations

Resource implications

The cost implications of using benzodiazepines as an adjunct to antidepressants in MDD with anxious distress should be evaluated based on direct medication costs, healthcare utilization, and long-term economic impact. However, no economic evaluation studies currently assess their use in this setting.

Benzodiazepines are generally affordable, with widely available generic formulations making them a cost-effective short-term option compared to newer anxiolytics or atypical antipsychotic augmentation. However, cost considerations related to benzodiazepine use in MDD with anxious distress involve balancing short-term affordability with long-term economic consequences. While benzodiazepines remain a low-cost pharmacologic option, their potential for dependence, increased healthcare utilization, and indirect costs highlight the need for careful prescribing practices in the acute phase as well as patient monitoring.

Table Q7.3. Estimated costs of benzodiazepines.

Drug		Unit cost	2-week course
Alprazolam	Generic 0.25mg	19.50	Php 273
	Generic 0.5mg	29.4	Php 412
	Branded 0.25mg	28.25	Php 395
	Branded 0.5mg	39	Php 546
Clonazepam	Generic 0.5mg	8.85	Php 124
	Generic 2mg	11.8	Php 165
	Branded 2mg	14.75	Php 265
Bromazepam	Branded	8	Php 112

Stakeholder values, preferences and acceptability

Patients may value benzodiazepines for rapid symptom relief but may also have concerns about dependence, withdrawal, and cognitive effects. Clinicians acknowledge their short-term efficacy but remain cautious due to risks of prolonged use. About 94% of patients with anxiety or depressive disorders were long-term benzodiazepine users, often unaware of alternative

treatments.[5] Patients with greater awareness of alternative treatments were less likely to use benzodiazepines long-term. In contrast, older adults (≥65 years) and those with difficulty falling asleep had a higher likelihood of prolonged use. Higher daily benzodiazepine doses were associated with greater depressive symptoms, second-generation antipsychotic use, sleep disturbances, limited knowledge of alternatives, comorbid chronic illnesses, and smoking.[5] While benzodiazepines may be acceptable as a short-term adjunct in select cases, safety concerns and the potential for dependence limit their routine use

Equity and feasibility

The majority of mental health services are concentrated in urban areas in the Philippines, with 71% of psychiatric beds located in or near the largest city, limiting access for rural populations.[6] This urban-centric distribution poses challenges for individuals in remote areas to access both pharmacological and non-pharmacological treatments.

Implementing guidelines for benzodiazepine use as an adjunct in MDD treatment in the Philippines requires consideration of the existing healthcare system's capacity. The country faces a shortage of mental health professionals, with fewer than 600 psychiatrists serving over 100 million people, leading to limited access to specialized care, especially in rural areas.[2] This scarcity may result in primary care physicians prescribing benzodiazepines without adequate training in mental health, increasing the risk of inappropriate use.

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. *American Psychiatric Association.* 2022.

2. Soriano Jr U-R, Dela Cruz L, Noscal M, Sanchez D, Santos A, Urbano M. DSM5-BASED Diagnosis And Demographics Of The Philippine Mental Health Association Inc.'S Psychiatric Outpatients. *ASEAN J Psychiatry* [Internet]. 2022;23(December):1–7. Available from: https://www.aseanjournalofpsychiatry.org/abstract/dsm5based-diagnosis-and-demographics-of-the-philippine-mental-health-association-incs-psychiatric-outpatients-94776.html

3. Parish AL, Gillis B, Anthamatten A. Pharmacotherapy for Depression and Anxiety in the Primary Care Setting. *J Nurse Pract* [Internet]. 2023 Apr;19(4):104556. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1555415523000417

4. Ogawa Y, Takeshima N, Hayasaka Y, Tajika A, Watanabe N, Streiner D, et al. Antidepressants plus benzodiazepines for adults with major depression. *Cochrane Database Syst Rev*. 2019;2019(5):1–65.

5. Chen YT, Liu CY, Chang CM, Lai YM, Wang BH, Yang TY, et al. Perceptions, clinical characteristics, and other factors associated with prolonged and high daily dose of benzodiazepine use among patients with anxiety or depressive disorders. *J Affect Disord* [Internet]. 2020;271(April):215–23. Available from: https://doi.org/10.1016/j.jad.2020.03.077

6. WHO-AIMS Report on Mental Health System in The Philippines, WHO and Department of Health, Manila, The Philippines, 2006

Guideline Question 8: Should antidepressants combined with atypical antipsychotics (SGAs) be used at the outset in patients with Major Depressive Disorder with Psychotic Features?

Recommendation 8.	
We recommend antidepressant plus antipsychotic combination rather than antidepressant monotherapy among patients with major depressive disorder with psychotic features.	
Strength of Recommendation:	Strong
Certainty of Evidence:	Very low

Justification

This strong recommendation is made despite very low certainty of evidence regarding the efficacy and safety of antidepressant plus antipsychotic combination in this subgroup of MDD patients with psychotic features. Combination treatment is recommended because it targets both depressive and psychotic symptoms more effectively than antidepressant monotherapy alone. The panel also cited more recent guidelines, such as the APA 2022, which strongly recommend combination therapy, and clinical experience showing faster and more effective treatment with this approach. The severity of psychotic features in MDD further supports the need for adjunct antipsychotic treatment.

The panel also notes that newer drugs are likely more effective and safer than those studied in older trials, and combination therapy has already become accepted practice among local providers. Access issues were acknowledged, as some of the medications reviewed (e.g., perphenazine, imipramine) are no longer available locally. Aligning with the recommendations of other groups and local clinical experience, the panel believes the benefits of combination therapy outweigh the risks, justifying the strong recommendation.

Background

Major Depressive Disorder with psychotic features is a subtype of MDD with presence of delusions and/or hallucinations. It is associated with longer duration, greater morbidity and mortality, lower response to antidepressants and psychotherapy, higher rate of suicide risk, higher comorbidity of anxiety disorders, cognitive dysfunction, somatic disorders, and personality disorders.[1] The Philippines has 0.86% prevalence of MDD with psychotic experiences (age- and sex-adjusted).[2] International guidelines recommend treatment of antidepressant with an antipsychotic combination (APA 2010; NICE 2009).[3,4] However, evidence is lacking on whether combination therapy is better than monotherapy.

Evidence

A 2021 Cochrane review by Kruizinga et al.[6] analyzed 4 RCTs[7-10] comparing the efficacy of an antidepressant-plus-antipsychotic combination versus placebo-plus-antipsychotic in patients with major depressive disorder with psychotic features. The 4 RCTs studies included 245 patients diagnosed using HRSD-17 score thresholds (>18, >17, >14[9]) or DSM-IV criteria.[10]

The interventions involved combinations of nortriptyline, amitriptyline, or venlafaxine with atypical antipsychotics such as perphenazine or quetiapine. Comparators included placebo plus the same antidepressant or another antidepressant (amoxapine or imipramine). Interventions examined in the available studies predominantly belong to the TCA drug class – which are losing its prevalence of use in the clinical practice setting in the Philippines. Clinical response, defined by at least a 50% reduction[7,10] in HRSD-17 scores or raw score thresholds (<11[8] or <7)[9], was the primary efficacy outcome. Mortality was assessed but no events were recorded. For safety, overall dropout rates were analyzed, with the 2010 study by Wijkstra also reporting on serious adverse events (SAEs) and adverse events (insomnia, nervousness, restlessness).

Benefits and risks

The combination of atypical antipsychotics (SGAs) and antidepressants showed a significant effect on clinical response. Subgroup analysis comparing this combination to the same antidepressant as monotherapy also demonstrated a significant improvement in clinical response. However, safety outcomes were inconclusive, with no clear differences in overall dropouts, mortality, serious adverse events (SAEs), or other adverse events such as insomnia, nervousness, and restlessness.

Table Q8.1. Antidepressant + antipsychotic compared to placebo + antidepressant for psychotic depression

Outcomes	No. of participants (studies)	Effect estimate (95% CI)	Interpretation	Certainty of evidence
Clinical response	245 (4 RCTs)	RR 1.42 (1.11 to 1.80)	Benefit (Favors antidepressants combined with atypical antipsychotics)	Very Low [a,b,c] ⨁◯◯◯
Overall dropouts	245 (4 RCTs)	RR 0.91 (0.55 to 1.50)	Inconclusive	Very Low [a,b,c] ⨁◯◯◯
Mortality	245 (4 RCTs)	0 events	Not estimable	Very Low [a,b,c] ⨁◯◯◯
Overall SAE	122 (1 RCT)	RR 1.98 (0.52 to 7.55)	Inconclusive	Low [b,c] ⨁⨁◯◯
Insomnia	122 (1 RCT)	RR 0.50 (0.11 to 2.24)	Inconclusive	Low [b,c] ⨁⨁◯◯
Nervousness	122 (1 RCT)	RR 1.05 (0.49 to 2.28)	Inconclusive	Low [b,c] ⨁⨁◯◯
Restlessness	122 (1 RCT)	RR 0.58 (0.23 to 1.46)	Inconclusive	Low [b,c] ⨁⨁◯◯
Subgroup analysis: antidepressant + antipsychotic compared to placebo + same antidepressant				
Clinical Response of Depression	157 (3 RCTs)	RR 1.70 (1.19 to 2.43)	Benefit (Favors antidepressants combined with atypical antipsychotics)	Very Low [a,b,c] ⨁◯◯◯
Overall Dropouts	157 (3 RCTs)	RR 1.04 (0.52 to 2.07)	Inconclusive	Very Low [a,b,c] ⨁◯◯◯
Explanation a. serious risk of bias; b. serious imprecision; c. publication bias				

Certainty of the evidence

Overall certainty of evidence is very low due to high risk of bias (attrition), imprecision, and high risk of publication bias. There was a serious risk of bias due deviation in the treatment duration criteria of participants who will be analyzed.

Recommendations from other groups

Table Q8.2. Recommendations from other groups

Group	Recommendation
NICE 2022	Recommends the following for patients with **psychotic depression**: 1. **Consider combination antidepressant + antipsychotic** (e.g. olanzapine or quetiapine) 2. Add psychological therapy when acute symptoms improve 3. c) Offer referral to specialist mental health services and include risk assessment, multidisciplinary care coordination.[11]
APA 2010	APA considers Electroconvulsive therapy as highly effective in treating **psychotic depression** and can be considered as a first-line treatment option. Pharmacotherapy can also be used as a first-line treatment option **favoring combination of an antipsychotic and an antidepressant medication rather than treatment with either component alone** for treatment response although some research has shown comparable responses for antidepressive treatment or antipsychotic treatment alone. Lithium augmentation suggested to some patients who have not responded to combined treatment with antidepressant and antipsychotic medication.

Other considerations

Resource implications

No cost effectiveness studies were found in relation to interventions in the context of MDD with psychotic features. The following are price list of drugs used by the Pharmacy Section of National Center of Mental Health.[13]

Table Q8.3. Estimated costs of atypical antipsychotics and antidepressants.

Atypical antipsychotics	Price (Php/tablet)	Antidepressants	Price (Php/tablet)
Aripiprazole 10mg	58.00	Escitalopram 10mg	198.00
Clozapine 100mg	8.15	Fluoxetine 20mg	20.00
Risperidone 1mg/2mg/4mg	13.73/ 64.98/ 13.20	Sertraline 50mg	7.90
Quetiapine 25mg/100mg/200mg/300mg	17.00/ 138.00/ 32.00/ 43.00		
Olanzapine 5mg/10mg	49.90/ 29.29		

Stakeholder values, preferences and acceptability

No research evidence was found regarding the stakeholder values, preferences, and acceptability of this intervention.

Equity and feasibility

A 2023 time-series cross-sectional study (2014–2019) found that the baseline use of antidepressants and antipsychotics was lower in Low- to Middle-Income Countries (LMICs) compared to High-Income Countries (HICs) (0.35–0.38 vs. 2.15 per population for

antidepressants; 0.13–0.15 vs. 0.69 per population for antipsychotics). However, the rate of growth in LMICs outpaced that of HICs, with antidepressant use increasing by 42%–69% in LMICs versus 20% in HICs and antipsychotic use rising by 69%–79% in LMICs compared to 27% in HICs.[14]

References

1. Wang, Mq., Wang, Rr., Hao, Y. et al. Clinical characteristics and sociodemographic features of psychotic major depression. *Ann Gen Psychiatry* 20, 24 (2021). doi:10.1186/s12991-021-00341-7

2. Koyanagi, A., Oh, H., Stubbs, B., Haro, J. M., & DeVylder, J. E. (2016). Epidemiology of depression with psychotic experiences and its association with chronic physical conditions in 47 low- and middle-income countries. *Psychological Medicine*, 47(03), 531–542. doi:10.1017/s0033291716002750

3. Depression in adults: treatment and management (2010) NICE guideline

4. Swartz CM. Psychotic Depression or Schizophrenia. *Psychiatric Annals*. 2010;40(2):92-97. doi:10.3928/00485718-20100127-05

5. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017 Sep 21;358:j4008.

6. Kruizinga J, Liemburg E, Burger H, Cipriani A, Geddes J, Robertson L, Vogelaar B, Nolen WA. Pharmacological treatment for psychotic depression. *Cochrane Database Syst Rev*. 2021 Dec 7;12(12):CD004044. doi: 10.1002/14651858.CD004044.pub5. PMID: 34875106; PMCID: PMC8651069.

7. Anton RF Jr, Burch EA Jr. Amoxapine versus amitriptyline combined with perphenazine in the treatment of psychotic depression. *American Journal of Psychiatry* 1990;147(9):1203-8.

8. Mulsant BH, Sweet RA, Rosen J, Pollock BG, Zubenko GS,, Flynn T, et al. A double-blind randomized comparison of nortriptyline plus perphenazine versus nortriptyline plus placebo in the treatment of psychotic depression in late life. *Journal of Clinical Psychiatry* 2001;62(8):597-604.

9. Spiker DG, Weiss JC, Dealy RS, GriHin SJ, Hanin I, Neil JF, et al. The pharmacological treatment of delusional depression. *American Journal of Psychiatry* 1985;142(4):430-6.

10. Wijkstra J, Burger H, van den Broek WW, Birkenhäger TK, Janzing JG, Boks MP, et al. Treatment of unipolar psychotic depression: a randomized, double-blind study comparing imipramine, venlafaxine, and venlafaxine plus quetiapine. *Acta Psychiatrica Scandinavica* 2010;121(3):190-200.

11. Depression in adults: treatment and management (2022) NICE guideline [NG222]

12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

13. National Center of Mental Health List of Requirements of Medicine Consignment CY 2025. Retrieved: 12 March 2025 from [https://ncmh.gov.ph/images/pdf/bids/itc-12172027-meds.pdf]

14. Alabaku O, Yang A, Tharmarajah S, Suda K, Vigod S, Tadrous M (2023) Global trends in antidepressant, atypical antipsychotic, and benzodiazepine use: A cross-sectional analysis of 64 countries. *PLoS ONE* 18(4): e0284389. https://doi.org/10.1371/journal.pone.0284389

Guideline Question 9: Should novel medications such as esketamine be used as add-on therapy in patients with Major Depressive Disorder (MDD) who are non-responders or partial responders to conventional antidepressants (SSRIs, SNRIs, NaSSa) alone?

Recommendation 9.	
We suggest the use of intranasal esketamine as add-on therapy to antidepressants among patients with treatment-resistant depression.	
Strength of Recommendation:	Weak
Certainty of Evidence:	Very low

Justification

The panel suggests a weak recommendation supporting the use of intranasal esketamine as add-on therapy for treatment-resistant depression and MDD with active suicidal ideation, based on low to very low certainty evidence of its efficacy and safety. Esketamine has shown potential to improve symptom severity and response rates in patients with treatment-resistant depression with serious adverse events comparable to placebo. For MDD patients with suicidal ideation, esketamine demonstrates greater reduction in depressive symptoms within 24 hours and higher early response rates. However, long-term effects remain uncertain and require further research.

Cost-effectiveness studies indicate that esketamine is unlikely to be cost-effective at current prices, and access is limited by logistical challenges such as the need for medical supervision and frequent visits. The panel raised concerns about the drug's high cost, limited distribution, and the need for centers where patients can rest post-administration due to its potential side effects and the drug's status as a regulated medication. Despite these concerns, anecdotal experience from patients and healthcare providers perspectives are generally positive. More local data, such as from Makati Medical Center and private centers in Visayas, should be collected to inform future updates to this guideline recommendation.

Background

MDD is a prevalent psychiatric condition characterized by persistent feelings of sadness, loss of interest, and impaired daily functioning. In 2021, approximately 8.3% of U.S. adults experienced at least one major depressive episode, with a higher prevalence among females (10.3%) compared to males (6.2%).[1] A significant subset of individuals with MDD does not respond adequately to standard antidepressant therapies, leading to Treatment-Resistant Depression (TRD). Patients with TRD often endure prolonged depressive episodes, increased healthcare utilization, and heightened suicide risk. Traditional antidepressants typically require several weeks to achieve therapeutic effects, underscoring the need for rapid-acting treatments.[2]

Esketamine, the S-enantiomer of ketamine, has emerged as a novel intervention for TRD. Administered intranasally, esketamine offers a rapid onset of antidepressant effects by modulating glutamatergic neurotransmission through N-methyl-D-aspartate (NMDA) receptor antagonism. In 2019, the U.S. Food and Drug Administration (FDA) approved esketamine nasal spray for adults with TRD in conjunction with an oral antidepressant.[3] In January 2025, the FDA

expanded its approval, allowing esketamine to be used as a standalone treatment for adults with major depressive disorder who have not adequately responded to at least two oral antidepressants. This development underscores the evolving landscape of depression treatment and the critical need for effective therapies for individuals with TRD and MDD with active suicidal ideation.

Evidence

Treatment-Resistant Depression (TRD)

We included five randomized controlled trials (RCTs) that examined the efficacy and safety of intranasal esketamine in patients with treatment-resistant depression (TRD), enrolling a total of 1,626 patients.

The Fedgchin et al. (2019) (TRANSFORM-1) trial was a phase 3, double-blind, multicenter, active-controlled study that enrolled 346 patients with moderate-to-severe TRD who had failed at least two antidepressants. The study compared fixed-dose intranasal esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant versus placebo plus an oral antidepressant. The primary outcome was the change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at day 28, with additional outcomes assessing the incidence of adverse events, including nausea, dizziness, dissociation, vertigo, and headache.

The Daly et al. (2017) study was a phase 2, double-blind, placebo-controlled trial that enrolled 67 patients with TRD. It evaluated the dose-response relationship of intranasal esketamine (28 mg, 56 mg, 84 mg) as an adjunct to an oral antidepressant compared to placebo plus an oral antidepressant. The primary outcome was the change in MADRS total score at day 8, while secondary outcomes included the dose-response effect of esketamine on depressive symptoms. Reported adverse events included syncope, headache, dissociative syndrome, and ectopic pregnancy.

The Chen et al. (2023) study was a phase 3, multicenter, double-blind, active-controlled trial conducted in China and the USA, enrolling 252 patients with TRD. The study compared flexibly dosed intranasal esketamine plus an oral antidepressant to placebo plus an oral antidepressant. The primary outcome was the change in MADRS total score at day 28, with secondary outcomes assessing the change in MADRS score at 24 hours post-dose and the incidence of adverse events.

The Ochs-Ross et al. (2020) (TRANSFORM-3) trial was a phase 3, double-blind, active-controlled study focusing on elderly patients (≥65 years) with TRD and enrolled 138 patients. The study compared flexibly dosed esketamine plus an oral antidepressant versus placebo plus an oral antidepressant, with the primary outcome being the change in MADRS total score at day 28. Additional outcomes included the incidence of adverse events and treatment effects analyzed by age subgroup (65–74 vs. ≥75 years).

The Popova et al. (2019) (TRANSFORM-2) trial was a phase 3, double-blind, active-controlled study in adult TRD patients, enrolling 227 patients who had failed at least two antidepressants in the current episode. The study compared flexibly dosed esketamine (56 mg or 84 mg) plus a newly initiated oral antidepressant to placebo plus an oral antidepressant. The primary outcome was the change in MADRS total score at day 28, with additional outcomes assessing the incidence of adverse events, including dissociation, nausea, dizziness, and dysgeusia.

Major Depressive Disorder (MDD) with Active Suicidal Ideation

We included three randomized controlled trials (RCTs) that examined the efficacy and safety of intranasal esketamine in patients with major depressive disorder (MDD) and active suicidal ideation, enrolling a total of 524 patients.

The Canuso et al. (2018) study was a phase 2, double-blind, multicenter trial that enrolled 68 patients with MDD at imminent risk of suicide. The study compared intranasal esketamine (84 mg) plus standard-of-care treatment to placebo plus standard-of-care treatment. The primary outcome was the change in MADRS total score at 4 hours, 24 hours, and day 25, while secondary outcomes assessed the severity of suicidal ideation.

The ASPIRE I (Fu et al., 2020) and ASPIRE II (Ionescu et al., 2021) trials were phase 3, double-blind, multicenter RCTs conducted to confirm the antidepressant efficacy of esketamine nasal spray in patients with MDD and active suicidal ideation with intent. The ASPIRE I trial enrolled 226 patients, while the ASPIRE II trial enrolled 230 patients. Both trials compared intranasal esketamine (84 mg) plus comprehensive standard-of-care to placebo plus standard-of-care over four weeks. The primary outcome in both trials was the change in MADRS score at 24 hours post-first dose, while secondary outcomes included the severity of suicidal ideation and the incidence of adverse events, such as dizziness, dissociation, nausea, somnolence, and headache.

There were no identified ongoing studies as of the last search.

Benefits and risks

Among patients with treatment-resistant depression (TRD), intranasal esketamine as an add-on therapy to conventional antidepressants improved symptom severity (MADRS score reduction) and response rates, with a higher proportion of patients achieving remission compared to placebo (moderate to low certainty of evidence).

Among patients with major depressive disorder (MDD) and active suicidal ideation, esketamine led to a greater reduction in depressive symptoms within 24 hours post-dose and a higher response rate at early time points (high to moderate certainty of evidence). However, long-term effects at 90 days remain uncertain (very low certainty of evidence).

Esketamine did not result in a significant difference in serious adverse events compared to placebo (very low certainty of evidence). However, nausea, dizziness, dissociation, headache, and vertigo were commonly reported adverse events, occurring at higher rates than in the placebo group.

Table Q9.1. Esketamine vs. placebo or standard of care for treatment-resistant depression.

Outcomes	No. of participants (studies)	Effect estimate (95% CI)	Interpretation	Certainty of evidence
Mean Change in MADRS Total Score from Baseline to Day 28	1626 (5 RCTs)	SMD -3.25 (-4.75 to -1.76)	Favors use of esketamine	Moderate[a] ⊕⊕⊕◯
Proportion of patients who achieved response	770 (4 RCTs)	RR 1.99 (1.28 to 3.10)	Favors use of esketamine	Moderate[a] ⊕⊕⊕◯

Proportion of patients who achieved response ≥50% reduction in MADRS	770 (4 RCTs)	RR 2.99 (1.02 to 8.79)	Favors use of esketamine	Low[a,b] ⊕⊕◯◯
Remission rate (reduction to ≤12 points on the MADRS)	703 (3 RCTs)	RR 1.55 (1.23 to 1.99)	Favors use of esketamine	Low[a,b] ⊕⊕◯◯
Serious adverse events	703 (3 RCTs)	RR 1.55 (0.53 to 4.50)	Inconclusive	Very Low[a,c] ⊕◯◯◯
Explanation a. Serious risk of bias; b. serious inconsistency; c. extremely serious imprecision				

Table Q9.2. Esketamine vs. placebo or standard of care for treatment of MDD with active suicidal ideation.

Outcomes	No. of participants (studies)	Effect estimate (95% CI)	Interpretation	Certainty of evidence
Mean Reduction in MADRS one day after 1st dose	522 (3 RCTs)	SMD -3.18 (-4.78 to -1.58)	Favors use of esketamine	Moderate[a] ⊕⊕⊕◯
Mean Reduction in MADRS 25-days follow-up	522 (3 RCTs)	SMD -2.94 (-4.99 to -0.89)	Favors use of esketamine	Moderate[a] ⊕⊕⊕◯
Mean Reduction in MADRS 90-days follow-up	522 (3 RCTs)	SMD -1.75 (-1.28 to -2.22)	Favors use of esketamine	Very Low[a,b] ⊕◯◯◯
Remission Rate (≤12 points on the MADRS) 24-hours post 1st dose	296 (2 RCTs)	RR 1.82 (1.00 to 9.03)	Inconclusive	Very Low[a,e] ⊕◯◯◯
Remission Rate (≤12 points on the MADRS) pre-dose 25-day follow-up	296 (2 RCTs)	RR 1.07 (0.87 to 1.31)	Inconclusive	Low[a,d] ⊕⊕◯◯
Response ≥ 50% reduction in baseline MADRS follow-up one day post-dose	296 (2 RCTs)	RR 3.14 (1.72 to 5.74)	Favors use of esketamine	Moderate[a] ⊕⊕⊕◯
Response ≥ 50% reduction in baseline MADRS follow-up 25 day pre-dose	296 (2 RCTs)	RR 1.07 (0.87 to 1.31)	Inconclusive	Low[a,d] ⊕⊕◯◯
Serious adverse event within 25 days	522 (3 RCTs)	RR 1.62 (0.70 to 3.73)	Inconclusive (no difference in the number of serious adverse events	Very Low[a,f] ⊕◯◯◯
Explanation a. serious risk of bias; b. very serious inconsistency; c. serious inconsistency; d. serious imprecision; e. very serious imprecision; f. extremely serious imprecision				

Certainty of the evidence

Of the nine efficacy outcomes for treatment-resistant depression (TRD) and major depressive disorder (MDD) with active suicidal ideation, two had high certainty, four moderate, two low, and one very low due to methodological limitations.
For TRD, certainty was moderate for mean MADRS change, response rate, and ≥50% MADRS reduction, downgraded for risk of bias. Remission rate had low certainty due to bias and inconsistency, while serious adverse events had very low certainty due to imprecision and bias.

For MDD with active suicidal ideation, certainty was high for mean MADRS reduction and remission at 24 hours, moderate for 25-day outcomes (downgraded for bias), and very low for 90-day MADRS reduction due to bias and inconsistency. Safety outcomes had very low certainty due to bias and serious imprecision. Overall, efficacy certainty ranged from high to very low, while safety evidence remained very low.

Recommendations from other groups

Table Q9.3. Recommendations from other groups.

Group or Agency	Recommendation
VA/DoD Clinical Practice Guideline. (2022). The Management of Major Depressive Disorder. Washington, DC: U.S. Government Printing Office	(Treatment of MDD that is Severe or has a Partial or Limited Response to Initial Treatment) For patients with MDD who have not responded to several adequate pharmacologic trials, we suggest ketamine or esketamine as an option for augmentation.
American Psychiatric Association	No explicit recommendations states
NICE, 2020	NICE reviewed esketamine nasal spray for treatment-resistant depression but did not recommend its use within the National Health Service (NHS) due to uncertainties about its clinical and cost-effectiveness.
Canadian Network for Mood and Anxiety Treatments (CANMAT) – Esketamine for Treatment-Resistant Depression CANMAT, 2020	CANMAT recommends esketamine as a third-line treatment option for adults with major depressive disorder who have not responded to at least two adequate trials of standard antidepressant therapies.

Other considerations

Resource implications

While its efficacy has been demonstrated, economic evaluations are essential to determine its cost-effectiveness, especially in specific healthcare settings such as the Philippines. Several studies have assessed the cost-effectiveness of esketamine, primarily in the United States.

A study by Ross and Soeteman (2020) projected that over five years, esketamine increased time in remission from 25.3% to 31.1% of life-years, resulting in a gain of 0.07 quality-adjusted life-years (QALYs). However, it also increased healthcare costs by approximately $16,995, leading to an incremental cost-effectiveness ratio (ICER) of $242,496 per QALY. The study concluded that esketamine is unlikely to be cost-effective in the U.S. unless its price decreases by more than 40% from the current $240 per 28-mg dose. The Institute for Clinical and Economic Review (ICER) (2019) found that the fair value-based price benchmark for esketamine is between $17,700 and $25,200 per year, necessitating a 25-52% discount from its list price of $32,400. A study by Bahji et al. (2022) comparing esketamine nasal spray to intravenous ketamine for TRD patients in the U.S. concluded that esketamine is unlikely to be cost-effective unless its price is reduced by at least 40%.

Stakeholder values, preferences and acceptability

Esketamine has been introduced as a novel treatment for patients with treatment-resistant depression (TRD). Understanding the perspectives of key stakeholders—patients, healthcare providers, policymakers, and funders—is crucial for assessing its acceptability and integration into healthcare systems.

Studies suggest that patients generally perceive esketamine treatment positively due to its rapid onset of action and efficacy. In a qualitative study by Katz et al. (2020), 23 patients undergoing esketamine treatment were interviewed regarding their experiences. Findings revealed that 91.8% of patients perceived improvements in emotional health, daily functioning, and social interactions. Furthermore, all participants reported being either satisfied (52%) or very satisfied (48%) with the treatment.[14]

Another study by Mansfield et al. (2020) investigated patient tradeoff preferences regarding ketamine-based treatments, including esketamine.[16] The results showed that patients prioritized treatment effectiveness over concerns about side effects and logistical burdens, such as post-administration monitoring. This suggests that despite the challenges associated with esketamine administration, patients value its potential benefits in alleviating depressive symptoms.

Healthcare providers and policymakers recognize the potential of esketamine but express concerns regarding its long-term safety, cost-effectiveness, and appropriate use. According to an assessment by the Institute for Clinical and Economic Review (ICER) (2019), while esketamine provides a novel treatment option, its high cost and uncertain long-term risk-benefit profile have raised concerns among providers and funding agencies. The review emphasized the need for further studies to clarify the long-term safety profile of esketamine and establish cost-effective prescribing guidelines.[12]

Equity and feasibility

Esketamine is administered intranasally under direct medical supervision. The treatment protocol consists of a four-week induction phase (twice-weekly sessions) followed by a maintenance phase (weekly or biweekly sessions).[19] Each session requires patients to remain under observation for at least two hours due to potential adverse effects such as dissociation, increased blood pressure, and sedation.[4]

The need for direct medical supervision and prolonged monitoring presents logistical challenges. Healthcare facilities must allocate dedicated treatment rooms and personnel to observe patients, which can strain resources, particularly in settings with limited mental health infrastructure.[13] Additionally, the frequent visits required during the induction phase can be challenging for patients who reside in remote areas or have limited transportation options, potentially leading to treatment discontinuation.[17]

The structured administration of esketamine raises several equity concerns. Access to esketamine is limited to specialized centers. Patients in rural or underserved regions may have difficulty reaching clinics, creating disparities in treatment availability.[8] The cost of esketamine treatment is substantial, with estimates ranging from $7,000 to $11,000 for the first two months in the United States.[14] Without adequate health insurance coverage or financial support, many patients may be unable to afford this treatment. Finally, the frequent clinic visits and prolonged

observation periods may be impractical for individuals with rigid work schedules, caregiving responsibilities, or financial constraints.[13]

Implementation in the Philippines

In October 2023, Makati Medical Center launched the first Esketamine Care Center in the Philippines, providing supervised esketamine administration for TRD patients.[18] Patients self-administer intranasal esketamine in two doses spaced 5 minutes apart under medical supervision and must remain in the clinic until potential side effects have subsided. However, the cost of treatment in the Philippines has not been widely documented, making local affordability assessments necessary. Applicability of esketamine use in the Philippines requires careful consideration due to differences in healthcare systems, cost structures, and economic thresholds.

References

1. National Institute of Mental Health (NIMH). Major Depression [Internet]. 2021 [cited 2025 Mar 18]. Available from: https://www.nimh.nih.gov/health/statistics/major-depression

2. Johns Hopkins Medicine. Esketamine for Treatment-Resistant Depression [Internet]. 2023 [cited 2025 Mar 18]. Available from: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/esketamine-for-treatment-resistant-depression

3. U.S. Food and Drug Administration (FDA). FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic [Internet]. 2019 [cited 2025 Mar 18]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified

4. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Drevets WC, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A double-blind, randomized, placebo-controlled study. *JAMA Psychiatry*. 2018;75(2):139–48.

5. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidal ideation in patients at imminent risk for suicide: A double-blind, randomized, placebo-controlled study. *Am J Psychiatry*. 2018;175(7):620–30.

6. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: Results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *J Clin Psychiatry*. 2019;80(3):19m12949.

7. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: A randomized, double-blind, active-controlled study (TRANSFORM-2). *JAMA Psychiatry*. 2019;76(9):893–903.

8. Ochs-Ross R, Daly EJ, Zhang Y, Lane R, Lim P, Morrison RL, et al. Efficacy and safety of intranasal esketamine in elderly patients with treatment-resistant depression (TRANSFORM-3): A randomized, double-blind, active-controlled study. *Am J Geriatr Psychiatry*. 2020;28(2):121–41.

9. Fu DJ, Ionescu DF, Li X, Lane R, Lim P, Sanacora G, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients at imminent risk for suicide: ASPIRE I double-blind, randomized, placebo-controlled study. *J Clin Psychiatry*. 2020;81(3):19m13191.

10. Ionescu DF, Fu DJ, Qiu X, Lane R, Lim P, Kasper S, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients at imminent risk for suicide: ASPIRE II double-blind, randomized, placebo-controlled study. *J Clin Psychiatry*. 2021;82(1):20m13609.

11. Chen C, Wang H, Wang J, Yang Y, Huang J, Chen J, et al. Efficacy and safety of intranasal esketamine in treatment-resistant depression: A multicenter, double-blind, randomized controlled trial. *Neuropsychopharmacology*. 2023;48(3):563–73.

12. Institute for Clinical and Economic Review (ICER). Esketamine for the treatment of treatment-resistant depression: Effectiveness and value [Internet]. 2019 [cited 2025 Mar 19]. Available from: https://icer.org/news-insights/press-releases/trd_final_report/

13. Buchmayer F, Kasper S. Overcoming the myths of esketamine administration: different and not difficult. Front Psychiatry. 2023 Nov 23;14:1279657. doi: 10.3389/fpsyt.2023.1279657

14. Ross EL, Soeteman DI. Cost-effectiveness of esketamine nasal spray for patients with treatment-resistant depression in the United States. *Psychiatr Serv*. 2020;71(10):988–97. https://doi.org/10.1176/appi.ps.201900625

15. Katz EG, Hough DW, Doherty T, Lane R, Singh J, Levitan B. Patient-reported early health changes with esketamine nasal spray in treatment-resistant depression. *CNS Spectr*. 2020;26(5):442–50. https://doi.org/10.1017/S1092852920001662

16. Mansfield C, Lloyd A, Chen J, Pulikottil-Jacob R, Mühlbacher A, Cook S. Estimating patients' willingness to accept tradeoffs for treatment benefits: A case study of esketamine for treatment-resistant depression. *J Affect Disord*. 2020;276:697–705. https://doi.org/10.1016/j.jad.2020.07.021

17. Bahji A, Vazquez GH, Zarate CA, McIntyre RS. Cost-effectiveness of intranasal esketamine versus intravenous ketamine for treatment-resistant depression: A decision analytic model. *J Affect Disord*. 2022;306:160–7. https://doi.org/10.1016/j.jad.2022.07.026

18. Makati Medical Center. Makati Medical Center launches the first Esketamine Care Center in the Philippines [Internet]. 2023 [cited 2025 Mar 19]. Available from: https://www.makatimed.net.ph/news/makati-medical-center-launches-the-first-esketamine-care-center-in-the-philippines/

19. Janssen Pharmaceuticals, Inc. SPRAVATO (esketamine) nasal spray, CIII: Full Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2025.

7. Evidence and Recommendations: Schizophrenia

Guideline Question 10: Should dopamine partial agonists be used as an alternative to serotonin-dopamine antagonists be used in patients with schizophrenia in the acute phase?

Recommendation 10.
We suggest the use of dopamine partial agonists as a non-inferior alternative to serotonin-dopamine antagonists in the treatment of patients with schizophrenia in the acute phase.
Strength of Recommendation: Weak Certainty of Evidence: Very low

Justification

Current evidence from randomized controlled trials suggests that both drug classes have comparable efficacy and side effect profiles, supporting the use of dopamine partial agonists as a non-inferior alternative to serotonin-dopamine antagonists, although the certainty of evidence is low to very low. High-quality studies comparing newer dopamine partial agonists to existing antipsychotics are lacking.

Cost is an important consideration, as dopamine partial agonists are generally more expensive, though generic options may help reduce this difference. Long-term affordability is crucial, given the lifelong nature of schizophrenia treatment. While access to these drugs does not appear to be an issue, their cost may be prohibitive even for higher-income patients. Despite the uncertainty regarding their comparative effectiveness and cost-effectiveness, the panel is open to considering dopamine partial agonists as an alternative, resulting in a weak recommendation in favor of their use.

Background

Schizophrenia is a debilitating disorder that imposes a huge economic burden, particularly in the Philippines.[1] The choice of drugs vary considerably and depends on their efficacy and safety.[2] Serotonin-dopamine antagonists, including olanzapine, risperidone, quetiapine, and clozapine are some of the widely used antipsychotic agents with different efficacy and safety profile. Some guidelines recommend newer antipsychotic agents due to their improved efficacy and safety, particularly if the patient has poor response to older antipsychotic agents.[3] Majority of the available studies compared the newer agents to placebo, especially the more recently approved brexpiprazole and cariprazine.[4] As such, evidence directly comparing these dopamine partial agonists with the older antipsychotic agents for patients with schizophrenia is needed to adequately made recommendations regarding their use for these patients.

Evidence

We found nine RCTs that included a total of 3,153 patients with acute phase of schizophrenia. Four studies specifically mentioned the inclusion of patients with schizophrenia in acute

phase[5–8], while the rest of the studies included hospitalized patients with schizophrenia.[9–13] Only one study used cariprazine[8], while the rest of the studies compared aripiprazole to any of the serotonin-dopamine antagonists (risperidone, olanzapine, quetiapine). Majority of the studies looked into the symptom control using the Positive and Negative Syndrome Scale[5–10,12], while some studies included Brief Psychiatric Rating Scale scores, quality of life, and adverse effects as outcomes of interest. Currently, there are no ongoing studies relevant to the topic.

Benefits and risks

Dopamine partial agonists did not show significant difference compared to serotonin dopamine antagonists in symptom control as measured by total positive and negative syndrome scale, positive symptom scale, negative symptom scale, and brief psychiatric rating scale, with the outcome on quality of life as inconclusive. Adverse events, particularly extrapyramidal (EPS)-related symptoms and weight were also comparable between the two groups.

There was an observed lack of large, high-quality RCTs assessing the effect of dopamine partial agonists compared to serotonin-dopamine antagonists for patients with acute-phase of schizophrenia. The available studies used aripiprazole mainly, other studies employing other serotonin dopamine antagonists such as brexpiprazole and cariprazine compared to any serotonin-dopamine antagonists were minimal to lacking. Different studies also employed different measurements of symptom control.

Table Q10.1. Summary of findings: dopamine partial agonist compared to serotonin-dopamine antagonist for acute schizophrenia.

Outcomes	No. of patients (studies)	Effect Estimate (95%CI)	Interpretation	Certainty of Evidence
Positive and Negative Syndrome Scale Total	1134 (5 RCTs)	MD 3.21 higher (-0.31 to 6.73)	Equivalent	Low[a,b] ⊕⊕◯◯
Positive Symptom Scale	495 (4 RCTs)	MD 1.29 higher (-0.83 to 3.41)	Equivalent	Very low[a,b,c] ⊕◯◯◯
Negative Symptom Scale	495 (4 RCTs)	MD 0.03 higher (-1.15 to 1.21)	Equivalent	Very low[a,b,c] ⊕◯◯◯
Brief Psychiatric Rating Scale	371 (2 RCTs)	MD 0.44 higher (-1.99 to 2.87)	Equivalent	Low[b,c] ⊕⊕◯◯
Quality of Life	33 (1 RCT)	MD 1.59 lower (-9.58 to 6.40)	Inconclusive	Very low[b,d] ⊕◯◯◯
EPS-related events	1426 (4 RCTs)	OR 0.99 (0.60 to 1.63)	Equivalent	Moderate[a] ⊕⊕⊕◯
Significant weight gain (≥7% from baseline)	1704 (4 RCTs)	OR 0.46 (0.15 to 1.44)	Equivalent	Low[a,c] ⊕⊕◯◯
Explanation a. serious inconsistency; b. serious imprecision; c. serious risk of bias; d. very serious risk of bias				

Certainty of the evidence

Of the nine studies, three had high risk of bias due to unclear risk of randomization, absence of blinding to both participants and outcome assessor.[5,9,10] Four studies had unclear risk of allocation concealment and with absence also of blinding.[10–13] The inconsistency and imprecision, in addition to risk of bias contributed to downgrading of evidence from low to very low for the critical outcomes of symptom control and moderate to low certainty of evidence for safety outcomes due to serious risk of bias and inconsistency.

Recommendations from other groups

Table Q10.2. Recommendations from other groups.

Name of Group	Recommendation	Certainty of Evidence, Strength of Recommendation
European Psychiatric Association[3] Treatment of cognitive impairment in schizophrenia 2022	Second-generation antipsychotics are recommended for their favorable cognitive profile compared to first-generation antipsychotics. For patients with cognitive impairment who are treated with a first-generation antipsychotic, a switch to a second-generation antipsychotic should be considered. No clear superiority of a single second-generation antipsychotic over other molecules of the same category has currently been found regarding cognitive outcomes	Grade A
American Psychiatric Association[14] Treatment of Patients with Schizophrenia 2020	Patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects.	Class Ia
National Institute for Health and Care Excellence[2] Psychosis and schizophrenia in adults: prevention and management 2014	For people with first episode psychosis offer oral antipsychotic medication in conjunction with psychological interventions. The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Provide information and discuss the likely benefits and possible side effects of each drug.	-

Other considerations

There were no studies found investigating the cost effectiveness of the use of dopamine partial agonists compared to serotonin dopamine antagonists for patients with acute schizophrenia. No evidence was also found assessing patient values and preference related to this topic as well as acceptability, equity implications, and local feasibility.

References

1. Verma A, Pruthi J, Krishna A, Rai MK, Rao A. EE109 A Systematic Review of Cost of Schizophrenia Treatment and the Potential Role of Long Acting Injectables in Easing Economic Burden: A Perspective from 5 Asian Nations. *Value Health*. 2022 Jul 1;25(7):S356.

2. Psychosis and schizophrenia in adults: prevention and management | Guidance | NICE. 2014 Feb 12 [cited 2025 Mar 3]; Available from: https://www.nice.org.uk/guidance/cg178

3. Vita A, Gaebel W, Mucci A, Sachs G, Barlati S, Giordano GM, et al. European Psychiatric Association guidance on treatment of cognitive impairment in schizophrenia. *Eur Psychiatry J Assoc Eur Psychiatr.* 2022 Sep 5;65(1):e57.

4. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *The Lancet.* 2019 Sep 14;394(10202):939–51.

5. McQuade RD, Stock E, Marcus R, Jody D, Gharbia NA, Vanveggel S, et al. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *J Clin Psychiatry.* 2004;65 Suppl 18:47–56.

6. Hatta K, Sato K, Hamakawa H, Takebayashi H, Kimura N, Ochi S, et al. Effectiveness of second-generation antipsychotics with acute-phase schizophrenia. *Schizophr Res.* 2009 Aug 1;113(1):49–55.

7. Fleischhacker WW, McQuade RD, Marcus RN, Archibald D, Swanink R, Carson WH. A Double-Blind, Randomized Comparative Study of Aripiprazole and Olanzapine in Patients with Schizophrenia. *Biol Psychiatry.* 2009 Mar 15;65(6):510–7.

8. Durgam S, Starace A, Li D, Migliore R, Ruth A, Németh G, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. *Schizophr Res.* 2014 Feb;152(2–3):450–7.

9. Maat A, Cahn W, Gijsman HJ, Hovens JE, Kahn RS, Aleman A. Open, randomized trial of the effects of aripiprazole versus risperidone on social cognition in schizophrenia. Eur *Neuropsychopharmacol.* 2014 Apr 1;24(4):575–84.

10. Liemburg E, Aleman A, Bous J, Hollander K, Knegtering H. An Open Randomized Pilot Trial on the Differential Effects of Aripiprazole versus Risperidone on Anhedonia and Subjective Well-Being. *Pharmacopsychiatry.* 2011 Mar 22;44:109–13.

11. McCue RE, Waheed R, Urcuyo L, Orendain G, Joseph MD, Charles R, et al. Comparative effectiveness of second-generation antipsychotics and haloperidol in acute schizophrenia. *Br J Psychiatry J Ment Sci.* 2006 Nov;189:433–40.

12. Cheng Z, Yuan Y, Han X, Yang L, Cai S, Yang F, et al. An open-label randomised comparison of aripiprazole, olanzapine and risperidone for the acute treatment of first-episode schizophrenia: Eight-week outcomes. *J Psychopharmacol* (Oxf). 2019 Oct 1;33(10):1227–36.

13. Jindal KC, Singh GP, Munjal V. Aripiprazole versus olanzapine in the treatment of schizophrenia: a clinical study from India. *Int J Psychiatry Clin Pract.* 2013 Feb;17(1):21–9.

14. Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtabai R, et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *Am J Psychiatry.* 2020 Sep;177(9):868–72.

Guideline Question 11: Should long-acting injectable antipsychotics be used as an alternative to oral antipsychotic monotherapy among patients with schizophrenia in the acute phase?

Recommendation 11.

We suggest the use of long-acting injectable antipsychotics as an alternative to oral antipsychotic monotherapy in the treatment of adults with schizophrenia in the acute* phase.

Strength of Recommendation: Weak
Certainty of Evidence: Low

***Remarks:** The acute phase of schizophrenia is defined as the period of an acute psychotic episode. This phase begins with a new onset or acute exacerbation of symptoms and lasts until symptoms are reduced to a level considered to be the patient's expected "baseline." (APA, 2010)

Justification

Findings from two eligible studies—one lasting 10 weeks and another lasting 12 months—suggest that LAIs are non-inferior to oral antipsychotics in overall symptom improvement, including positive and negative symptom domains. However, social functioning outcomes were inconclusive due to variations in assessment tools.

Despite these findings, the panel identified key limitations in the evidence base that led to a weak recommendation. First, the available studies primarily evaluated second-generation LAIs, while first-generation LAIs are more commonly used in the Philippines. The lack of direct evidence comparing first-generation LAIs to oral monotherapy in the acute phase limited the applicability of the findings to local practice. Second, while LAIs may improve adherence, they were associated with higher dropout rates due to inefficacy and non-adherence, as well as an increased risk of extrapyramidal symptoms. Lastly, the certainty of evidence ranged from low to moderate, further limiting confidence in the findings.

Given these factors, the panel reached a consensus on issuing a weak recommendation for LAIs as an alternative to oral antipsychotic monotherapy in the acute phase of schizophrenia. LAIs may be particularly beneficial for patients with frequent relapses, as they help reduce the burden of daily medication adherence. A footnote has been added to clarify the definition of "acute phase" based on established guidelines. Future guideline updates should consider expanding the evidence review to include open-label studies, studies involving first-generation LAIs, and research on stabilized patients experiencing acute exacerbations. Additionally, efforts should be made to update pricing information for both innovator and generic versions of all antipsychotic medications discussed, as well as data on the availability of paliperidone LAI in government institutions.

Background

Schizophrenia is a complex disease that results from dysfunction within the brain, leading to a wide range of symptoms and variable outcomes over the course of the illness.[1,2] The acute exacerbation of schizophrenia, characterized by a marked worsening of symptoms[2], often leads to a state of acute psychosis, which can cause significant disruptions in social, occupational, and personal functioning. During this acute phase, treatment becomes increasingly challenging, as patients may exhibit reduced responsiveness to medications, necessitating a more refined and intensive approach to care.[3]

Over the years, the shift from first-generation antipsychotics (FGAs) to second-generation antipsychotics (SGAs) has brought about significant changes in treatment regimens, with the introduction of long-acting injectables (LAIs) offering a promising alternative to oral formulations.[4]Oral antipsychotics have been traditionally used but this rely on patient adherence that may lead to poor outcomes and an increased risk of relapse (guidelines). In contrast, LAIs offer the advantage of reducing the burden of daily medication adherence and have the potential to improve long-term treatment outcomes.[4]

However, despite the potential benefits of LAIs, the evidence comparing their efficacy and safety to oral antipsychotics remains mixed, with varying findings across studies.[4] This highlights the need to critically review and synthesize existing evidence regarding the use of LAIs versus oral antipsychotics, particularly in terms of symptom control, functional recovery, and adverse effect profiles.

Evidence

A network meta-analysis (NMA) comparing the efficacy, acceptability and side effects of long-acting injectable to oral antipsychotics involving patients acutely ill with schizophrenia was retrieved and used in this review.[5] There were 115 RCTs using second-generation antipsychotics (SGA) in their LAI or oral forms that were eligible for inclusion in this NMA, however 3 studies were found to have unusable data. There were two direct head to head comparisons of LAI to oral antipsychotics included and were used for the purposes of this review.

In the study by Keks et al. done last 2007, 618 patients diagnosed with schizophrenia or schizoaffective disorder were enrolled to compare the efficacy and safety of long-acting injectable risperidone with oral olanzapine tablets.[6] Inclusion criteria specified that patients were to have been hospitalized or required medical attention for an acute exacerbation of psychosis apart from experiencing an acute exacerbation in the previous 2 years. There were 318 patients randomized to the risperidone LAI group and 300 to the olanzapine oral group. However, there were only 378 patients, 164 in the risperidone LAI and 214 in the olanzapine oral group, who were included in the per-protocol analysis of short-term efficacy outcome as assessed using the Positive and Negative Syndrome Scale (PANSS) over a 13-week period. Other outcomes assessed included long-term efficacy, evaluated through PANSS scores over a 12-month period,and at long-term end-point, as well as changes in PANSS factor scores, including positive and negative symptoms and depression. Additional measures included treatment adherence, and the incidence of adverse events. Assessments were done at baseline, week 5, 9, 13 25, 37, 53, and at end-point.

The study by Xiao et al. in 2022 enrolled 436 Chinese patients experiencing acute episodes of schizophrenia to evaluate the efficacy and safety of aripiprazole once-monthly (AOM) compared

to daily oral aripiprazole.[7] Participants were randomly assigned to receive either AOM at a dose of 400 mg (n=218) or oral aripiprazole at doses ranging from 10 to 20 mg daily (n=218) over a 12-week period. The severity of schizophrenia was assessed using the PANSS scale at baseline, week 10, and 12. Other measures included treatment adherence and adverse events related to antipsychotics such as EPS and weight gain.

There are no ongoing studies evaluating the use of long-acting injectable antipsychotics as an alternative to oral antipsychotic monotherapy among patients with schizophrenia in the acute phase.

Benefits and risks

Although LAIs were similarly effective to oral antipsychotics, there was no significant difference in overall symptom improvement as measured by PANSS, including its positive, negative, and depressive symptom domains, as well as social functioning over both short- and long-term periods. Responder rates also did not differ significantly. However, there were fewer dropouts due to inefficacy and non-adherence with aripiprazole LAI compared to its oral formulation. Regarding safety outcomes, patients on risperidone LAI experienced significantly more extrapyramidal symptoms than those on olanzapine oral antipsychotics. No significant differences were observed in the frequency of severe adverse events, weight gain, or anticholinergic side effects among the studied antipsychotics.

Table Q11.1. Summary of findings for short-term efficacy outcomes.

Efficacy outcomes	No. of participants (studies)	Effect estimate (95%CI)	Interpretation	Certainty of evidence
Change in overall symptoms (PANSS)	696 (2 RCTs)	MD 1.05 points (-1.13 to 3.24)	Equivalent	Very low[a,b] ⊕◯◯◯
Positive symptoms	319 (1 RCT)	MD -0.60 points (-1.40 to 0.30)	Equivocal	Moderate[c] ⊕⊕⊕◯
Negative symptoms	319 (1 RCT)	MD 0.20 points (-1.00 to 1.40)	Equivocal	Moderate[c] ⊕⊕⊕◯
Social functioning	319 (1 RCT)	MD -0.5 points (-2.70 to 1.70)	Equivocal	Low[b] ⊕⊕◯◯
Responder rate	319 (1 RCT)	OR 2.20 (1.00 to 4.70)	Equivocal	Low[b] ⊕⊕◯◯
Explanation a. serious risk of bias; b. very serious imprecision c. serious impreision				

Table Q11.2. Summary of findings for long-term efficacy outcomes.

Efficacy outcomes	No. of participants (studies)	Effect estimate (95%CI)	Interpretation	Certainty of evidence
Change in overall symptoms (PANSS)	361 (1 RCT)	MD 0.20 points (-3.40 to 3.80)	Equivalent	Very low[a,c] ⊕◯◯◯
Positive symptoms	361 (1 RCT)	MD -0.40 points (-1.50 to 0.70)	Equivocal	Low[a,b] ⊕⊕◯◯

Negative symptoms	361 (1 RCT)	MD 0.30 points (-0.70 to 1.40)	Equivocal	Low[a,b] ⊕⊕◯◯
Depressive symptoms	361 (1 RCT)	MD 0.6 points (0.10 to 1.20)	Equivocal	Low[a,b] ⊕⊕◯◯
Clinical improvement	361 (1 RCT)	OR 1.38 (0.84 to 2.26)	Equivocal	Very low[a,c] ⊕◯◯◯
Explanation a. serious risk of bias; b. serious imprecision; c. very serious imprecision				

Table Q11.3. Summary of findings for short-term safety outcomes

Safety outcomes	No. of participants (studies)	Effect estimate (95%CI)	Interpretation	Certainty of evidence
Dropouts due to any reasons	436 (1 RCT)	RR 1.11 (0.81 to 1.53)	Equivocal	Moderate[c] ⊕⊕⊕◯
Dropouts due to inefficacy and non-adherence	436 (1 RCT)	RR 2.27 (1.15 to 4.50)	Favors aripiprazole oral	High ⊕⊕⊕⊕
Dropout due to adverse events	436 (1 RCT)	RR 0.86 (0.29 to 2.51)	Equivocal	Low[d] ⊕⊕◯◯
Severe adverse events	434 (1 RCT)	OR 1.15 (0.41 to 3.22)	Equivocal	Low[d] ⊕⊕◯◯
Anticholinergic adverse event	434 (1 RCT)	OR 1.71 (0.92 to 3.17)	Equivocal	Low[d] ⊕⊕◯◯
Extrapyramidal symptoms	434 (1 RCT)	OR 0.69 (0.47 to 1.01)	Equivocal	Moderate[c] ⊕⊕⊕◯
Weight gain	434 (1 RCT)	OR 1.03 (0.63 to 1.68)	Equivocal	Moderate[c] ⊕⊕⊕◯
Prolactin	434 (1 RCT)	MD -6.20 ng/mL (-13.22 to 0.82)	Equivocal	Low[d] ⊕⊕◯◯
Explanation c. serious imprecision; d. very serious imprecision				

Table Q11.4. Summary of findings for long-term safety outcomes

Safety outcomes	No. of participants (studies)	Effect estimate (95%CI)	Interpretation	Certainty of evidence
Dropouts due to any reasons	547 (1 RCT)	RR 0.94 (0.75 to 1.17)	Equivocal	Very low[a,b] ⊕◯◯◯
Dropouts due to inefficacy and non-adherence	547 (1 RCT)	RR 0.55 (0.27 to 1.14)	Equivocal	Low[a,c] ⊕⊕◯◯

Dropout due to adverse events	547 (1 RCT)	RR 0.77 (0.30 to 1.96)	Equivocal	Low[a,c] ⊕⊕◯◯
Severe adverse events	547 (1 RCT)	OR 1.36 (0.74 to 2.53)	Equivocal	Very low[a,b] ⊕◯◯◯
Extrapyramidal symptoms	532 (1 RCT)	OR 1.95 (1.27 to 3.00)	Favors oral olanzapine	Moderate[a] ⊕⊕⊕◯
Weight gain	532 (1 RCT)	OR 0.66 (0.34 to 1.28)	Equivocal	Low[a,c] ⊕⊕◯◯
Explanation a. serious risk of bias; b. very serious imprecision c. serious imprecision				

Certainty of the evidence

Of the 2 studies, the study by Keks et al had high risk of bias due to high risk in blind outcome assessment and missing outcomes.[6] The study by Xiao and colleagues had unclear risk of randomization and allocation concealment as these were not clearly reported in the study.[7] The risk of bias summary is shown in Appendix 4. Overall certainty of evidence was downgraded to very low because of these serious risks of bias, the wide confidence interval, and small number of events recorded in some of the outcomes of interest.

Recommendations from other groups

Different guidelines define acute psychosis across different stages of schizophrenia. The Canadian guidelines categorizes schizophrenia into distinct stages, distinguishing the management of first-episode psychotic disorder from acute exacerbation, relapse prevention, and maintenance treatment.[2] In cases of acute exacerbation, following an adjustment or initiation of antipsychotic medication, treatment should be continued for at least four weeks unless significant tolerance issues arise. This recommendation is graded as Level D, based on a modified adaptation from the Scottish Intercollegiate Guidelines Network (SIGN), drawing primarily from non-analytic studies and expert consensus.[2] The transition to a long-acting injectable (LAI) formulation may be considered in cases where nonadherence is a concern.

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) categorizes schizophrenia into distinct stages, grouping acute psychosis management under clinical stage 2, which includes first-episode psychotic disorder, acute and early recovery phases.[1] In these cases, second-generation antipsychotics (SGAs) are preferred over first-generation antipsychotics (FGAs) based on consensus-based recommendations, where evidence was weak or lacking, with no explicit preference for long-acting injectable (LAI) or oral antipsychotics (OAPs). Acute relapse can also occur in patients with established schizophrenia (stages 3b or 3c).[1] For these cases, the guidelines recommend an initial sequential trial of two antipsychotic medications, one of which should be an SGA. If these trials fail, clozapine should be considered. The use of LAI antipsychotic medication is advised in cases of poor adherence, provided it aligns with the patient's preference, a decision based on evidence from systematic reviews evaluation.

The American Psychiatric Association (APA) 2020 guideline on the management of schizophrenia in adults recommends that patients with schizophrenia be treated with an antipsychotic medication and monitored for both effectiveness and side effects (Level 1A evidence).[8] Regarding the use of long-acting injectable (LAI) antipsychotics, the guideline

suggests their consideration for patients with a history of poor or uncertain adherence or based on patient preference (Level 2B evidence), without specific regard to the clinical stage of illness.

Table Q11.5. Summary of Recommendations from Other Groups

Group or Agency	Recommendation	Strength of Recommendation Certainty/Quality of Evidence
American Psychiatry Association (APA) 2020[4]	Patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects	Level 1A
	Patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence	Level 2B
Canadian Journal of Psychiatry[2]	Continue after an increase or change of antipsychotic medication in response to acute exacerbation. A switch to LAI strategy in possible nonadherence.	Modified from SIGN Grade D
The Royal Australian and New Zealand College of Psychiatry (RANZCP)[1]	Second-generation antipsychotic agents should be used in preference to first-generation antipsychotic agents (Stage 2)	Consensus-based recommendation (N/A)
	If there has been poor or uncertain adherence, or it is the individual's preference, long-acting injectable antipsychotic medication should be considered(Stage 3b or 3c)	EBR - I

Other considerations

Resource implications

Currently there is a paucity of data in the economic evaluation of using LAI as an alternative to oral antipsychotics in the acute phase of schizophrenia in the Philippines. Therefore additional considerations should be placed on the availability and cost of these medications. Table 3 and table 4 summarizes the available antipsychotics in the Philippines and their corresponding unit prices and monthly expenditures for treatment.

Table Q11.6. Price list of available LAI antipsychotics in the Philippines.

Drug	Preparation	Dose	Unit price	Monthly expenditure
SGA				
Aripiprazole	400 mg/mL	Once every 4 weeks	6313[9]	6313

Paliperidone	100 mg/ mL	Once every 4 weeks	7473.40[9]	747
FGA				
Haloperidol	50 mg/mL (as decanoate)	Once every 4 weeks	889.80[10]	889.80
Fluphenazine decanoate	25 mg/ml	Once every 2 to 4 weeks	74.18[10]	148.36
Flupentixol decanoate	20 mg/ml	Once every 2 to 4 weeks	378.40[10]	756.8

Table Q11.7. Price list of available oral antipsychotics in the Philippines.

Drug	Preparation	Dose	Unit price	Monthly price
FGA				
Haloperidol	5 mg tablet	2 to 3 times daily	26.89[9]	2420.21
SGA				
Aripiprazole	10 mg per capsule	Once daily	59.54[10]	1786.2
Olanzapine	10 mg per tablet	Once daily	29.29[11]	878.7
Quetiapine	25 mg per tablet	Twice daily	17.50[9]	1050
Risperidone	2 mg per tablet	Once daily	26.21[9]	786.3

Stakeholder values, preferences and acceptability

There is no data on stakeholder's values, preferences, and acceptability on the use of LAI as an alternative to oral antipsychotic monotherapy among those with schizophrenia in the acute phase. In the 2012 Adherence in Schizophrenia (ADHES) survey in the Philippines, which involved interviews with 71 psychiatrists, found that the most common strategy for addressing non-adherence—reported by 27% of respondents—was switching patients to long-acting antipsychotics.[12] However, the survey did not explore the stages of schizophrenia of the involved patients.

Equity and feasibility

Currently, no data is available on Filipino adults' values and preferences including equity and acceptability of LAI as an alternative to oral antipsychotic monotherapy among those with schizophrenia in the acute phase. A post-marketing surveillance survey conducted in the Philippines from November 2017 to December 2019 evaluated the safety and efficacy of once-monthly aripiprazole injection for schizophrenia, bipolar disorder, and schizoaffective disorder[13]. Among the respondents, 79.9% had schizophrenia. However, the survey did not specify the stage of schizophrenia in these patients. While the drug was generally considered safe and effective, 25% of patients discontinued treatment for various reasons.

References

1. Royal Australian and New Zealand College of Psychiatrists. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Aust N Z J Psychiatry.* 2016;50(5):410-72. doi:10.1177/0004867416641195.

2. Canadian Psychiatric Association. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry.* 2017;62(9):604-16. doi:10.1177/0706743717720448.

3. Barnes TRE, Drake R, Paton C, Cooper SJ, Deakin B, Ferrier IN, et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from the British Association for Psychopharmacology. *J Psychopharmacol.* 2020;34(1):3-78. doi:10.1177/0269881119889296.

4. Baden LR, Swaminathan S, Angarone M, Blouin G, Camins BC, Casper C, et al. Prevention and treatment of cancer-related infections, version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* [Internet]. 2019 Jun;17(6):590–634. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6598776/

5. Wang D, Schneider-Thoma J, Siafis S, Qin M, Wu H, Zhu Y, et al. Efficacy, acceptability and side-effects of oral versus long-acting injectables antipsychotics: Systematic review and network meta-analysis. *Eur Neuropsychopharmacol.* 2024;83:11-18. doi:10.1016/j.euroneuro.2024.03.003.

6. Keks NA, Ingham M, Khan A, Karcher K. Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder: Randomised, controlled, open-label study. *Br J Psychiatry.* 2007;191:131-9. doi:10.1192/bjp.bp.105.017020.

7. Xiao L, Zhao Q, Li A, Sun J, Wu B, Wang L, et al. Efficacy and safety of aripiprazole once-monthly versus oral aripiprazole in Chinese patients with acute schizophrenia: a multicenter, randomized, double-blind, non-inferiority study. *Psychopharmacology (Berl)*. 2022;239(1):243-251. doi:10.1007/s00213-021-06044-x.

8. Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtabai R, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. *Am J Psychiatry.* 2020;177(9):868-72. doi:10.1176/appi.ajp.2020.177901

9. National Center for Mental Health. Public Bidding for the Supply and Delivery of Drugs and Medicines (Service Patients) CY 2023: List of Items. ITB No. 003-2023. Published November 8, 2022. Available from: https://ncmh.gov.ph/images/pdf/bids/itb-003-2023-list.pdf

10. Jose R. Reyes Memorial Medical Center. Pharmacy Fees and Charges 2024. Available from: https://jrrmmc.gov.ph/images/Fees_and_Charges/2024/Pharmacy.pdf

11. Department of Health (Philippines). 2024 Drug Price Reference Index (DPRI) Booklet [Internet]. Updated October 21, 2023. Available from: https://dpri.doh.gov.ph/downloads/DPRI-2024-Booklet-asofOctober21.pdf

12. Vicente B, Hembra M, Sionzon M, Benedicto E. Survey on the adherence of patients with schizophrenia as assessed by selected psychiatrists in the Philippines - ADHES data. *Philipp J Psychiatry.* 2013;35(2):3-13.

13. Dalisay R, Cruz A, Perey F, Quibod B. Long-acting injectable antipsychotics for adherence: The Philippine experience. *Philipp J Psychiatry*. 2024;5(1):8-10.

Guideline Question 12: Should long-acting injectable antipsychotics be used versus oral antipsychotic monotherapy in patients with schizophrenia in the chronic or residual phase?

Recommendation 12.	
We recommend the use of long-acting injectable antipsychotics instead of oral antipsychotic monotherapy in the treatment of patients with schizophrenia in the chronic or residual phase.	
Strength of Recommendation:	Strong
Certainty of Evidence:	Very low

Justification

Despite the low to very low certainty of evidence, the panel issued a strong recommendation based on the advantage of LAIs over oral antipsychotic monotherapy in reducing hospitalization risk, their comparable safety profile, and their role in improving medication adherence, which remains a major challenge in the management of chronic schizophrenia. Poor adherence to oral antipsychotics is strongly linked to relapse and hospitalization, making LAIs a more reliable option, particularly for patients with frequent relapses. This recommendation also aligns with previous guidelines, including the 2017 Clinical Treatment Guidelines, which acknowledged the role of LAIs in maintenance therapy.

Challenges to implementing this recommendation include cost and accessibility, as LAIs may be less affordable and less widely available than oral antipsychotics, especially in low-resource settings. Expanding access through government-funded programs and cost-reduction strategies is critical. Additionally, there may be variable preferences across patients and providers, which highlights the need for shared decision-making and education on LAI benefits. Future research should focus on strengthening the evidence base with direct comparisons of LAIs and oral antipsychotics in chronic-phase schizophrenia, real-world studies, and cost-effectiveness analyses to inform implementation strategies.

Background

Schizophrenia affects approximately 24 million people worldwide. According to the 2017 Global Burden of Disease report by the World Health Organization, roughly 1 in 500 Filipinos suffer from schizophrenia, a prevalence of 0.2% of the population.[1]

Schizophrenia is a complex, chronic condition characterized by symptoms of delusions, hallucinations, disorganized speech or behavior and impaired cognitive ability. Because of its relatively early onset and chronic course, this mental health disorder is disabling for many of the patients afflicted with it and their families affecting their health, well-being and functioning including the surrounding environment.[2,3]

Treatment of symptoms with antipsychotics is a mainstay in the management of schizophrenia. The primary goal of antipsychotic treatment is to alleviate symptoms and restore the patient's normal functioning, followed by maintenance therapy to prevent symptom recurrence, reduce

hospitalizations, and improve quality of life.[4] However, nonadherence to antipsychotics has been a major issue on the effective management of schizophrenia. Risk factors identified included illness factors such as lack of insight; service factors such as lack of therapeutic alliance and ease of access; caregiver factors which includes stigma, patient factors such as attitudes to medications and illness and medication factors which includes effectiveness, side effects, dosing frequency and financial cost to patient.[5] Medication non-adherence in schizophrenia patients ranges from 20-89% with a reported median non-adherence rate to oral antipsychotics to be as high as 55%.[6]

Long-acting injectable (LAI) antipsychotics were an important step in addressing the medication related risk factors to relapse management in schizophrenia by eliminating the need for daily dosing through biweekly or monthly injections enhancing compliance and has been shown to improve clinical outcomes and quality of life.[7,8] Currently, however, clinical practice guidelines only recommend LAIs for patients who prefer such treatment or have history of poor or uncertain adherence.[9,10]

Evidence

No direct evidence was found investigating the effect of long-acting injectables (LAIs) compared to oral antipsychotics (OAPs) as treatment in chronic phase schizophrenia. However, one meta-analysis of 137 studies (RCTs, cohorts, and pre-post studies) looked into this comparison using LAIs over OAPs as maintenance treatment for schizophrenia. For this review, only randomized controlled trials were included in the analysis and this was used as indirect evidence for this review.

One systematic review and meta-analysis of 137 studies (n=397,319) covering three study designs was retrieved for this review. This study compared long-acting injectable antipsychotics versus oral antipsychotics for the maintenance treatment of schizophrenia across three study designs: randomized control trials (32 studies, n=8577), cohort studies (65 studies, n=377,447) and pre-post studies (29 studies, n=11295). Primary outcomes reviewed was risk of hospitalization, relapse, stabilization of symptoms and treatment response. Secondary outcomes measured included were classed by relevance to effectiveness, efficacy, and safety or adverse events. For this review, only randomized controlled trials were included in the analysis.

No ongoing studies regarding LAIs in specific populations of schizophrenic patients in the maintenance or chronic phase.

Benefits and risks

LAIs were associated with a lower risk of hospitalization compared to OAPs but showed no significant difference in relapse risk, symptom stabilization, or treatment response. The occurrence of movement disorders, metabolic disorders, gastrointestinal issues, and serious adverse events was similar between both treatment regimens. However, LAIs were linked to a higher risk of depression and anxiety as adverse events. Despite this, overall discontinuation rates due to adverse events did not differ significantly between LAIs and OAPs.

Table Q12.1. Summary of findings: efficacy outcomes.

Efficacy outcomes	No. of studies	Pooled effect (95% CI)	Interpretation	Certainty of Evidence
Hospitalization	18 RCTs	RR 0.83 (0.72, 0.95)	Favors LAI	Low[a,b] ⊕⊕◯◯
Relapse	27 RCTs	RR 0.89 (0.77, 1.02)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Stabilization of symptoms	3 RCTs	RR 0.99 (0.96, 1.04)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Treatment response	5 RCTs	RR 0.90 (0.78, 1.04)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Explanation a. serious risk of bias; b. serious indirectness; c. serious imprecision				

Table Q12.2. Summary of findings: adverse events.

Safety outcomes	No. of studies	Pooled effect (95% CI)	Interpretation	Certainty of Evidence
Discontinuation of antipsychotic due to AE	4 RCTs	RR 1.11 (0.84 to 1.46)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Akathisia	15 RCTs	RR 1.19 (0.94 to 1.49)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Extrapyramidal symptoms	8 RCTs	RR 1.27 (0.94 to 1.71)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Tardive dyskinesia	6 RCTs	RR 0.54 (0.20 to 1.43)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
SAE overall	12 RCTs	RR 0.97 (0.81 to 1.16)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Death	14 RCTs	RR 0.80 (0.42 to 1.51)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Suicidal ideation	10 RCTS	RR 0.94 (0.70 to 1.26)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Suicidal attempt	7 RCTs	RR 1.02 (0.56 to 1.86)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Death by suicide	8 RCTs	RR 0.93 (0.29 to 3.01)	Inconclusive	Very Low[a,b,c] ⊕◯◯◯
Explanation a. Serious risk of bias; b. serious indirectness; c. serious imprecision				

Certainty of the evidence

Overall certainty of evidence was deemed very low for all outcomes measured in this review due mainly to issues of indirectness, risk of bias including unclear selection bias (26 studies), allocation concealment issues (26 studies), issues on blinding of participants and personnel (21 studies) as well outcome assessors (15 studies), issues on incomplete assessment of outcomes (13 studies), heterogeneity and imprecision due to wide confidence intervals.

Recommendations from other groups

Table Q12.3. Recommendations from other groups

Group	Recommendation
American Psychiatric Association 2020 Practice Guideline for the Treatment of Patients with Schizophrenia	APA suggests that patients receive treatment with long acting injectable antipsychotic medications if they prefer such treatment or if they have a history of poor or uncertain adherence. (Grade 2B)
National Institute for Health and Care Excellence 2014 Psychosis and Schizophrenia in adults: prevention and management	Consider offering depot/long-acting injectable antipsychotic medications to people with psychosis or schizophrenia: - Who would prefer such treatment after an acute episode - Where avoiding covert non-adherence to antipsychotic medication is a clinical priority within the treatment plan.

Other considerations

Resource implications

Among varying sub-types of populations with schizophrenia in the United States, the initiation of LAI antipsychotics were associated with higher per-patient-per-year pharmacy costs (MD $5603 95% CI, $3799 to $7407) however was offset by lower per-patient-per-year medical cost (MD -$5404, 95% CI, -$7745 to $-3064). In this meta-analysis, the use of LAI antipsychotics were associated with improved medication adherence with clinical benefit of reduced hospitalizations and admissions compared with OA. The lower medical costs then offsets the higher pharmacy costs, however there is no significant difference in total healthcare costs between the two regimens.[11]

There are no cost effectiveness studies in the Philippines, however it has been inferred that the use of LAIs (specifically paliperidone LAI) can avert polypharmacy and therefore can reduce treatment costs around Php 470,000 ($4700) per annum if all patient in a specialty hospital will be shifted to LAI.[12] There are only a few LAIs in the country available. Paliperidone 150mg LAI is priced at Php 7,437.40 to Php 10,714.25, Aripiprazole 400mg LAI is priced at Php 6,313.00 to Php 9,517.85, both lower limits of the prices suggested by a specialty hospital in the county.[13,14]

Stakeholder values, preferences and acceptability

There were no studies retrieved on Filipino patients' values, preferences and acceptability on LAIs over oral antipsychotics.

Equity and feasibility

There were also no available studies on equity and feasibility of LAIs over oral antipsychotics in the country.

References

1. World Health Organization. Philippines WHO Special Initiative for Mental Health Situational Assessment CONTEXT [Internet]. 2020. Available from:

https://www.who.int/docs/default-source/mental-health/special-initiative/who-special-initiative-country-report---philippines---2020.pdf?sfvrsn=4b4ec2ee_8

2. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: Overview and Treatment Options. *Pharmacy and Therapeutics* [Internet]. 2014 Sep;39(9):638. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4159061/

3. Fitzgerald HM, Shepherd J, Bailey H, Berry M, Wright J, Chen M. Treatment Goals in Schizophrenia: A Real-World Survey of Patients, Psychiatrists, and Caregivers in the United States, with an Analysis of Current Treatment (Long-Acting Injectable vs Oral Antipsychotics) and Goal Selection. *Neuropsychiatric Disease and Treatment.* 2021 Oct;Volume 17(17):3215–28.

4. Hany M, Rehman B, Azhar Y, Chapman J. *Schizophrenia* [Internet]. NIH.gov. StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539864/

5. Haddad P, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. *Patient Related Outcome Measures.* 2014 Jun;5(5):43.

6. Guo J, Lv X, Liu Y, Kong L, Qu H, Yue W. Influencing factors of medication adherence in schizophrenic patients: a meta-analysis. *Schizophrenia* [Internet]. 2023 May 15;9(1):1–8. Available from: https://www.nature.com/articles/s41537-023-00356-x

7. Lin CH, Chen FC, Chan HY, Hsu CC. Time to rehospitalization in patients with schizophrenia receiving long-acting injectable antipsychotics or oral antipsychotics. *International Journal of Neuropsychopharmacology.* 2019 Jul 1;

8. Boyer L, Falissard B, Nuss P, Collin C, Duret S, Rabbani M, et al. Real-world effectiveness of long-acting injectable antipsychotic treatments in a nationwide cohort of 12,373 patients with schizophrenia-spectrum disorders. *Molecular Psychiatry* [Internet]. 2023 Jul 21;1–8. Available from: https://www.nature.com/articles/s41380-023-02175-z

9. American Psychiatric Association. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *American Psychiatric Association.* 2020 Aug 31;3.

10. National Institute for Health and Care Excellence (NICE). Psychosis and Schizophrenia in adults: Prevention and Management [Internet]. 2014. Available from: https://www.nice.org.uk/guidance/cg178/resources/psychosis-and-schizophrenia-in-adults-

11. Lin D, Thompson-Leduc P, Ghelerter I, Nguyen H, Lafeuille MH, Benson C, et al. Real-World Evidence of the Clinical and Economic Impact of Long-Acting Injectable Versus Oral Antipsychotics Among Patients with Schizophrenia in the United States: A Systematic Review and Meta-Analysis. *CNS Drugs.* 2021 Apr 28;35.

12. Alinea AA, Abelardo C, Amiel, Cochon KL, Guevarra JP. Clinical experience with paliperidone palmitate in a specialty hospital in the Philippines: A short report [Internet]. 2022. Available from: https://www.researchgate.net/publication/358203360_Clinical_experience_with_paliperidone_palmitate_in_a_specialty_hospital_in_the_Philippines_A_short_report

13. National Center for Mental Health. Public Bidding for the Supply and Delivery of Drugs and Medicines (Service Patients) CY 2023: List of Items. ITB No. 003-2023. Published November 8, 2022. Available from: https://ncmh.gov.ph/images/pdf/bids/itb-003-2023-list.pdf

14. Department of Health (Philippines). 2024 Drug Price Reference Index (DPRI) Booklet [Internet]. Updated October 21, 2023. Available from: https://dpri.doh.gov.ph/downloads/DPRI-2024-Booklet-asofOctober21.pdf

8. Guideline implementation and applicability

Guideline Implementation

This Clinical Practice Guideline aims to support the delivery of safe, evidence-based, and contextually appropriate pharmacologic care for Filipino adults diagnosed with anxiety disorders, depressive disorders, bipolar disorder, and schizophrenia.

To enable adoption, the Philippine Psychiatric Association (PPA) will disseminate this guideline through:

- A condensed summary version for quick reference
- Treatment algorithms, decision flowcharts, and prescribing checklists
- Inclusion in training programs and residency curricula for psychiatrists and general practitioners
- Continuing Professional Development (CPD) activities and case-based learning modules
- Integration with electronic health records, institutional protocols, and digital platforms

The CPG will be submitted to the DOH Practice Guidelines Clearinghouse and endorsed through national specialty society meetings and interdisciplinary conferences. Patient-facing versions and simplified guides will also be considered to support shared decision-making and treatment literacy among individuals with mental health conditions and their caregivers.

Dissemination and Knowledge Translation

- **Formal Launch**: National roll-out with professional societies, training institutions, and DOH.
- **Knowledge Translation Platforms**: Webinars, online CME, and open-access posting of summaries, algorithms, and tools on PPA and DOH websites.
- **Policy Integration**: Alignment with procurement and formulary decisions to ensure recommended therapies are available and affordable.

Implementation efforts will prioritize reaching both specialist and primary care providers across varied health system levels, recognizing the decentralization of mental health care delivery under the Mental Health Act.

Implementation Tools and Practical Guidance

To complement the evidence-based recommendations, this guideline provides practical strategies, tools, and resources to support clinicians, health facilities, and policymakers in applying the recommendations consistently and equitably across diverse Philippine settings.

Clinical Algorithms and Decision Support

- **Algorithms and Pathways**: Summaries of first-line, second-line, and alternative pharmacologic options, including titration and relapse-prevention strategies, will be developed.
- **Decision Support Tools**: Where electronic medical record (EMR) systems exist, checklists or prompts (e.g., suicide risk assessment for depression) may be embedded. In resource-limited areas, pocket cards, clinic posters, and mobile-friendly algorithms will be disseminated.

- **Case Discussions**: Departmental case conferences and morbidity/mortality reviews can highlight the value of guideline-concordant care.

Education, Training, and Peer Influence

- **Capacity-Building Modules**: Structured training for psychiatrists and other mental health professionals (primary care physicians, nurses, mhGAP-trained providers) will cover evidence, practical application, and monitoring. Modules may be integrated into residency programs, CME activities, and DOH-supported workshops.

- **Peer Champions**: Influential psychiatrists and department heads will be engaged as "guideline champions" to model and promote adoption. Peer dialogue during conferences and case reviews will encourage consistent use.
- **Integration in Professional Activities**: The Philippine Psychiatric Association (PPA) will continue embedding guideline content in scientific meetings, conferences, and residency curricula, ensuring widespread awareness and familiarity.

Practical Reference Tools

- **Summary Tables and Prescribing Aids**: Quick-reference tables with recommended drugs, dose ranges, monitoring requirements, and comparative cost data (based on local procurement prices).
- **Strength of Recommendations**: Highlighting priority interventions based on certainty of evidence.
- **Formats**: Disseminated as pocket cards, PDFs, and smartphone-ready files via PPA and DOH channels.

Patient and Family Engagement

- **Educational Materials**: Patient-friendly handouts, translated into Filipino and other local languages, explaining medication benefits, side effects, and adherence strategies.
- **Family Empowerment**: Guidance for families on supporting adherence, recognizing relapse signs, and participating in shared decision-making, aligned with cultural norms of family involvement.

Adaptability and Feedback

- **Feedback Loops**: Mechanisms for clinicians to share barriers (e.g., lack of psychotherapy resources). The guideline group will respond with interim advisories or adaptations (e.g., recommending alternative therapies or structured psychoeducation where CBT is unavailable).
- **Living Document**: Updates and advisories will be issued as evidence and practice contexts evolve.

Facilitators and Barriers to Guideline Application

During guideline development, the Steering Committee and Technical Working Group identified potential facilitators and barriers through feedback from psychiatric practitioners, primary care providers, pharmacists, and patient advocates, as well as reference to recent implementation experience from mental health programs.

Facilitators:

- Availability of commonly recommended medications in the Philippine National Drug Formulary (PNDF)
- Presence of psychiatrists and trained mental health professionals in academic and tertiary centers
- Increasing public awareness and advocacy for mental health
- Legal framework established under the Mental Health Act of 2018
- Existing partnerships between the PPA, DOH, and PhilHealth

Barriers:

- Uneven access to medications in geographically isolated and disadvantaged areas
- Limited inclusion of second-line or newer medications in institutional formularies or PhilHealth coverage
- Financial burden from out-of-pocket medication costs in non-subsidized settings
- Limited mental health training among primary care physicians and generalists
- Persistent stigma affecting health-seeking behavior and treatment continuity

These factors influenced both the strength of recommendations and practical implementation guidance. For instance, where medications were not routinely available or feasible, recommendations were made conditional (weak) despite supporting evidence. The panel also gave greater weight to interventions that are listed in the PNDF or available through public sector procurement.

Resource Implications

Resource and cost considerations were included as part of the GRADE Evidence-to-Decision (EtD) framework for each recommendation. The Guideline Development Group consulted a range of sources including:

- Drug acquisition costs from public and private hospital pharmacies
- Listings from the PNDF
- PhilHealth reimbursement policies for inpatient and outpatient psychiatric care

Examples of key cost-related findings include:

- Long-acting injectable antipsychotics (LAIs) are significantly more expensive than oral antipsychotics, although they may reduce relapse and hospitalization rates
- Second-generation antidepressants (e.g., vortioxetine, agomelatine) are often not available in public hospitals and may pose cost barriers in private practice
- Intranasal esketamine, while approved, remains prohibitively expensive for routine use

While formal health economic modeling was not conducted, this real-world cost information was central to determining recommendation strength, especially when comparing interventions with similar efficacy but differing availability or affordability.

Monitoring and Auditing Criteria

To promote accountability and continuous improvement in mental health care, the following monitoring and evaluation criteria are proposed to assess adherence to guideline recommendations and measure their clinical impact.

Impact Indicators:

- Clinical symptom severity scores (e.g., using validated psychiatric rating scales)
- Medication adherence rates (e.g., refill rates, discontinuation)
- Hospital readmission rates due to relapse or non-adherence
- Patient and caregiver satisfaction with treatment plans

These indicators will be piloted in selected public and private psychiatric facilities, with monitoring to be conducted at least annually. Data sources may include health facility records, pharmacy data, and digital health systems. The PPA will work in collaboration with the Department of Health (DOH) to refine and integrate these metrics into national mental health service audits and reporting frameworks.

- **Suggested Metrics**:
    - % of schizophrenia patients initiated on long-acting injectables when indicated.
    - % of major depressive disorder patients prescribed guideline-concordant first-line therapy.
    - Treatment discontinuation rates due to adverse events.

- **Use of Data**: Facilities can adapt these indicators for local audit, performance monitoring, and resource planning.

Guideline Updating

This CTG will be formally reviewed and updated by the Philippine Psychiatric Association (PPA) every three (3) years, with the next scheduled update in 2028, or earlier if warranted by emerging clinical evidence, significant policy changes, or feedback from clinical implementation.

The PPA Steering Committee, in collaboration with the Department of Health (DOH), will initiate an update in response to:

- New large-scale trials, meta-analyses, or high-quality systematic reviews
- Revisions to major international guidelines (e.g., APA, NICE, WHO)
- Regulatory changes (e.g., FDA or PNDF updates) involving drug approvals or withdrawals
- Reimbursement policy changes under PhilHealth
- Evolving patient preferences, values, or health system capacity
- Practice variation or knowledge gaps identified through audit or feedback

All updates will follow the methodology outlined in the 2018 DOH Manual for Clinical Practice Guideline Development, using either a de novo or adolopment approach depending on the availability of pre-existing high-quality recommendations. The GRADE framework and Evidence-to-Decision (EtD) process will be used throughout.

9. Guideline Development Group

Steering Committee

No.	Name	Area of expertise	Affiliation	Geographical Location	Sex	COI
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7	Mark Dale S. Imbag, MD	General Medicine	Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines	NCR	M	A
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Consensus Panel

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Anxiety Disorder						
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3	Fernando Zion A. Soriano, MD, DSBPP, FPPA	Psychiatry	Veterans Memorial Medical Center, University of the East - Ramon Magsaysay Memorial Medical Center, Inc.	NCR	M	A
4	Richardson dR Mojica, MC, PhD (hc/c)	Lived experience	#MentalHealthPH/ St. Dominic College of Asia	Cavite	M	A
5	Daisy C. Daquilanea, MD DPBP FPPA (Life)	Psychiatry	Western Visayas Medical Center; Healthway QualiMed Hospital	Iloilo City	F	A
Bipolar Disorder						
6	Aisa Katrina V. Francisco-Masacupan, MD, FPPA	Psychiatry, Consultation-Liaison Psychiatry	Philippine Psychiatric Association, SPMC-Institute of Psychiatry and Behavioral Medicine, Davao Doctors Hospital	Davao City	F	A
7	Constantina M. Ocampo, MD, FPPA	Psychiatry	National Center for Mental Health	NCR	F	A
8	Kenneth Ross P. Javate, MD, MBA, MSc, FPPA, FPSCAP	General Psychiatry; Child and Adolescent Psychiatry	The Medical City, Ateneo School of Medicine and Public Health	NCR	M	B
9	Rodelen C. Paccial, MD, MPH, MA, PhD, RPsy, DSBPP, FPPA	Psychiatry, Public Mental Health	Mariveles Mental Wellness and General Hospital	Cavite, Bataan	M	B
10	Jardine S. Sta. Ana, MD, FPAFP	Family and Community Medicine	Department of Family and Community Medicine, UP-PGH	NCR	M	A
Depression						

No.	Name	Area of expertise	Affiliation	Location	Sex	COI Assessment
11	Japhet G. Fernandez de Leon, MD, FPPA (Life), FPSCAP	Adult, Child & Adolescent Psychiatry	Past Chair, West Visayas State University Medical Center Department of Psychiatry	Iloilo City	F	A
12	Robert Gerard O. Kelemen, MD, FPPA	Psychiatry	Mariveles Mental Wellness and General Hospital	Bataan	M	A
13	Christine Joyce A. Villero, MD, DSBPP	Psychiatry	Center for Behavioral Science Out Patient Department B. Rodriguez St., Cebu City	Cebu	F	A
14	Barbara Amity N. Flores, MD	Hospice and Palliative Care	FEU-NRMF, Manila Doctors Hospital, Veterans Memorial Medical Center		F	A
15	Kevin Miko M. Buac, M.D.	General Practice; Mental Health Advocacy; Public Health	#MentalHealthPH	Zamboanga City	M	A
Schizophrenia						
16	Melissa Paulita Mariano, MD, MSc, FPPA	Psychiatry	University of the East Ramon Magsaysay Memorial Medical Center, Inc.	NCR	F	B
17	Maria Jecyl Radam, MD, FPPA, FPCAM	Psychiatry Addiction Medicine	Philippine Psychiatric Association; Philippine College of Addiction Medicine; Philippine College of Psychopharmacology (PPsych); Philippine Mental Health Association (PMHA)	Cebu	F	B
18	Elizabeth Rondain, MD, FPPA	Psychiatry	Makati Medical Center	NCR	F	A
19	Arabelle Coleen P. Ofina, MD, FPAFP, FPSHPM	Family and Community Medicine	Philippine Academy of Family Physicians (PAFP)	NCR	F	B