

Korean Medication Algorithm for Depressive Disorder 2025, Fifth Revision: An Executive Summary

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Objective: Since its development in 2002 by the Korean College of Neuropsychopharmacology and the Korean Society for Affective Disorders, the Korean Medication Algorithm Project for Depressive Disorder (KMAP-DD) has undergone five revisions.

Methods: To improve survey efficiency, reflect general clinical practice, and facilitate comparisons with previous KMAP-DD revisions, the overall structure of the questionnaire was retained. The six sections of the questionnaire were as follows: 1) pharmacological treatment strategies for major depressive disorder with and without psychotic features; 2) pharmacological treatment strategies for persistent depressive disorder and other depressive disorder subtypes; 3) consensus on treatment-resistant depression; 4) selection of an antidepressant in consideration of safety, adverse effects, and comorbid physical conditions; 5) treatment strategies for special populations (children/adolescents, elderly, and women); and 6) non-pharmacological biological therapies. First-, second-, and third-line treatment recommendations were statistically derived.

Results: Compared to KMAP-DD 2021, only minor changes were noted, due to the limited introduction of new medications or treatment modalities. Nonetheless, notable shifts included an increased preference for atypical antipsychotics (AAPs), and higher preference of combination strategies involving AAPs and mood stabilizers, indicating a more proactive and intensive treatment trend in Korea.

Conclusion: KMAP-DD is expected to serve as a valuable clinical resource by providing expert consensus-based recommendations on specific treatment strategies and pharmacological options for major depressive disorders, thereby supporting the integration of real-world clinical practice with evidence-based medicine.

KEY WORDS: Algorithms; Guideline; Depressive disorder; Pharmacotherapy; Treatment guideline.

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INTRODUCTION

Major depressive disorder (MDD) is a common and chronic condition characterized by persistent depressive mood, somatic symptoms, cognitive dysfunction, and impairments in social, occupational functioning. According

to the World Health Organization, approximately 300 million people worldwide suffer from MDD, and it is projected to become the leading cause of disease burden by 2030 [1,2].

Pharmacotherapy plays a central role in the treatment of depression, and many countries have developed and implemented treatment guidelines tailored to their respective healthcare systems [3-6]. However, direct comparative studies evaluating treatment strategies or sequencing approaches are lacking, and clinical decision-making often depends on national insurance systems, individual physician experience, or personal preference. Although meta-analyses and systematic reviews—based primarily on randomized controlled trials (RCTs)—constitute the main body of evidence for pharmacological treatment guidelines, they may not adequately capture the complexities of clinical practice.

In response to these limitations, the first Korean Medication Algorithm for Depressive Disorder (KMAP-DD) was developed in 2002 [7]. Since then, the KMAP-DD executive committee within the Korean Society for Affective Disorders (KSAD) and the Korean College of Neuropsychopharmacology (KCNP) have conducted revision every 4 to 5 years to incorporate newly approved medications in Korea and recent research findings. Before this revision, four revisions have been published: KMAP-DD 2006 [8], KMAP-DD 2012 [9], KMAP-DD 2017 [10], and KMAP-DD 2021 [11]. The KMAP-DD is a consensus-based guideline developed through expert opinion, aimed at bridging the gap between evidence-based guidelines from other countries and the practical needs of clinical care in Korea, where locally generated clinical data remain limited.

In this article we present the results of the fifth revision of the Korean Medication Algorithm Project for Depressive Disorder and examine temporal trends in treatment preferences and strategies by comparing the current findings with those of previous revisions.

METHODS

To facilitate longitudinal comparison within the KMAP-DD series, overall study design and methodology used in previous revisions were retained in the current revision. Expert consensus was elicited through a systematic process in which the executive committee composed a review committee tasked with completing the questionnaire

(Table 1).

Review Committee

The selection criteria for the review committee members were consistent with those used in previous revisions of the KMAP-DD. To enhance the representativeness of the expert opinions and ensure a balanced view of real-world clinical practice in Korea, the number of review committee members from primary clinic was increased. We recruited 206 Korean psychiatrists (136 adult psychiatrists and 70 child/adolescent psychiatrists) who were lifetime members of KCNP and KSAD, had more than 15 years of clinical experience in psychiatry, and who had either published at least one paper related to mood disorders during the past year or were currently running a mood clinic in their hospital.

The review committee comprised 136 adult psychiatrists (92 from university or general hospitals, 18 from psychiatric hospitals, and 26 from private clinics) and 70 child/adolescent psychiatrists (42 from university or general hospitals, 16 from psychiatric hospitals, and 12 from private clinics). Of the 206 psychiatrists, 139 responded to our survey (response rate = 67.5%; adult = 71.3% [97/136], child/adolescent = 60% [42/70]). Respondents received a predetermined honorarium for their participation.

Questionnaire

The questionnaire consisted of six sections, comprising 34 items and 107 sub-items, with a total of 824 response options. The questionnaire consisted of six sections: 1) pharmacological treatment strategies for major depressive episodes, including mild-to-moderate, and severe episodes with or without psychotic features across the first to third treatment steps; 2) pharmacological treatment strategies for persistent depressive disorder (PDD) and other depressive disorder subtypes; 3) consensus for treatment-resistant depression (TRD); 4) selection of antidepressants (ADs) based on safety, adverse effect, and comorbid physical illnesses; 5) treatment strategies for special populations, including children/adolescents, older adults, and women; and 6) non-pharmacological biological therapies, such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and nutritional therapy (i.e. omega3, N-acetylcysteine, S-adenosyl methionine).

In this revision, the list of ADs and atypical antipsychotics (AAPs) remained the same as in the 2021 revision

Table 1. Comparison among the first (2006), second (2012), third (2017), fourth (2021), and fifth (2025) revisions of the Korean Medication Algorithm for Depressive Disorder

	First revision in 2006	Second revision in 2012	Third revision in 2017	Fourth revision in 2021	Fifth revision in 2025
Depressive episode	Mild Moderate Severe without psychotic features Severe with psychotic features	Mild to moderate Severe without psychotic features Severe with psychotic features	Same as 2012	Same as 2017	Same as 2021
AD dosage and duration of treatment	Present	Deletion	Change: duration of initial treatment and number of choosing AD as initial treatment	Same as 2017	Change: antipsychotic switch options according to previously used antipsychotic
Subtype	Dysthymia Minor depressive disorder Atypical features Melancholic features	Dysthymia Minor depressive disorder Atypical features Melancholic features Seasonal pattern	Dysthymia Minor depressive disorder Atypical features Melancholic features Seasonal pattern Mixed features Anxious distress	PDD (dysthymia) Atypical features Melancholic features Seasonal pattern Mixed features Anxious distress	Same as 2021
Comorbid physical illness	Absent	Newly added	DM Thyroid disease Liver disease Renal disease	DM Thyroid disease Liver disease Renal disease Hypertension Seizure disorder Cardiovascular disease Parkinson's disease Arrhythmia Chronic pain (fibromyalgia, etc.)	Same as 2021
Special population	Child only	Child and adolescent Elderly Women	Same as 2012	Child (up to primary school) Adolescent (up to high school) Elderly Women	Change in category Elderly - inclusion of atypical antipsychotic options for non-psychotic episode Women - inclusion of question regarding preferred antidepressant selection
Non-pharmacological biological therapy	ECT only	Including TMS Light therapy nutritional therapy, sleep deprivation, VNS, DBS as well as ECT	Same as 2012	ECT rTMS VNS DBS Light therapy Nutritional therapy tDCS	ECT rTMS VNS DBS Light therapy Nutritional therapy tDCS N-acetyl cysteine
Response rate of review committee	66.3% (67/101)	54.5% (67/123)	54.9% (79/144)	68.5% (98/143) (Adult 67.0% [65/97], child/adolescent 71.7%, [33/46])	67.5% (139/206) (Adult 71.3% [97/136], child/adolescent 60%, [42/70])

AD, antidepressant; DBS, deep brain stimulation; DM, diabetes mellitus; ECT, electroconvulsive therapy; PDD, persistent depressive disorder; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VNS, vagal nerve stimulation.

(Table 2). Unlike previous revisions, the present update included questions designed to guide the selection of alternative antipsychotics tailored to the agent currently in use, in cases where a change in medication was warranted.

Rating Scale

The rating methodology was identical to that used in previous editions. Each treatment option was rated on a nine-point scale: 9 = extremely appropriate; 7–8 = usually appropriate; 4–6 = uncertain or neutral; 2–3 = usually inappropriate (rarely used); and 1 = extremely inappropriate (never used). If reviewers were unable to assess a treatment option due to lack of clinical experience, they were instructed to select ‘q.’ For the questions on treatment duration, numerical responses were required instead of ratings. One open-ended question was included: “When considering AD monotherapy during pregnancy, please list your top three preferred ADs in order of preference, considering both efficacy and tolerability.”

Data Analysis and Decision of Preference and Categories

Means and 95% confidence intervals (CI) were calculated for each question or response option. Based on the lower bound of the 95% CI, treatments were categorized into three groups: first-line/preferred treatment (≥ 6.5), second-line/reasonable treatment (< 6.5 and ≥ 3.5), and third-line/inappropriate treatment (< 3.5). A treatment of choice (TOC) was defined as an option that received a rating of 9 from at least 50% of the reviewing experts.

A chi-square test was conducted to determine the pres-

ence or absence of consensus for each item or option. A non-significant difference among response categories was interpreted as an absence of consensus.

Basic descriptive statistics were calculated using built-in functions in Microsoft 365 (Microsoft Corp., 2024). Frequency analyses, including chi-square tests, were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp.). Statistical significance was set at $p < 0.05$.

Development of Treatment Guidelines and Algorithms

The results were discussed by the advisory and executive committees in the context of clinical evidence and the Korean clinical situation. Based on these discussions, the executive committee developed the fifth revised KMAP-DD algorithms (Fig. 1). KMAP-DD 2025 was subsequently published in book format and distributed to psychiatrists and relevant stakeholders across Korea.

RESULTS

Treatment Strategy for Acute Depression with or without Psychotic Features (Table 3)

Initial step strategies for depressive episode

AD monotherapy (95% CI 8.5–8.8) was recommended as TOC for mild-to-moderate depressive episodes. For severe episodes without psychotic features, AD monotherapy, AD + AAP combination, and AD + AD combination were identified as preferred first-line strategies. For severe episodes with psychotic features, AD + AAP com-

Table 2. Lists of drug options in KMAP-DD 2025

Antidepressant	Agomelatine
	Bupropion
	Esketamine (nasal spray)
	Mirtazapine
	SNRI (desvenlafaxine, duloxetine, milnacipran, venlafaxine)
	SSRI (escitalopram, fluoxetine, paroxetine, sertraline)
	Tianeptine
	TCA (amitriptyline, clomipramine, imipramine, etc.)
	Vortioxetine
Mood stabilizer	Carbamazepine, lamotrigine, lithium, valproate
Antipsychotics	Amisulpride, aripiprazole, blonanserin, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone
	Typical antipsychotics
Augmentation drugs	Buspirone, mood stabilizer, psychostimulant, thyroid hormone, etc.

KMAP-DD, Korean Medication Algorithm for Depressive Disorder; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; AD, antidepressant.

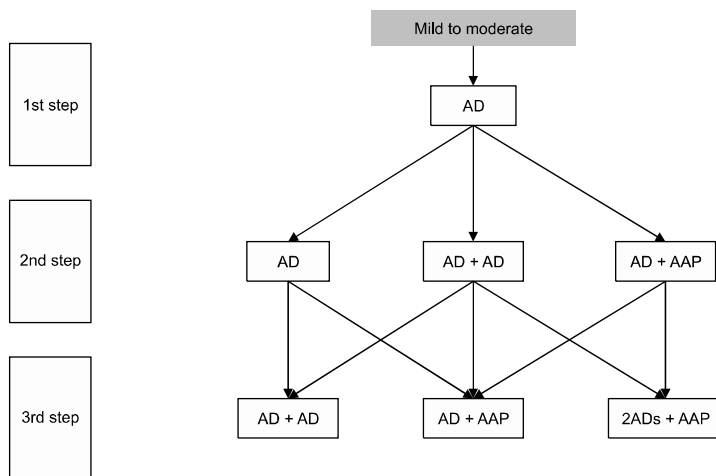
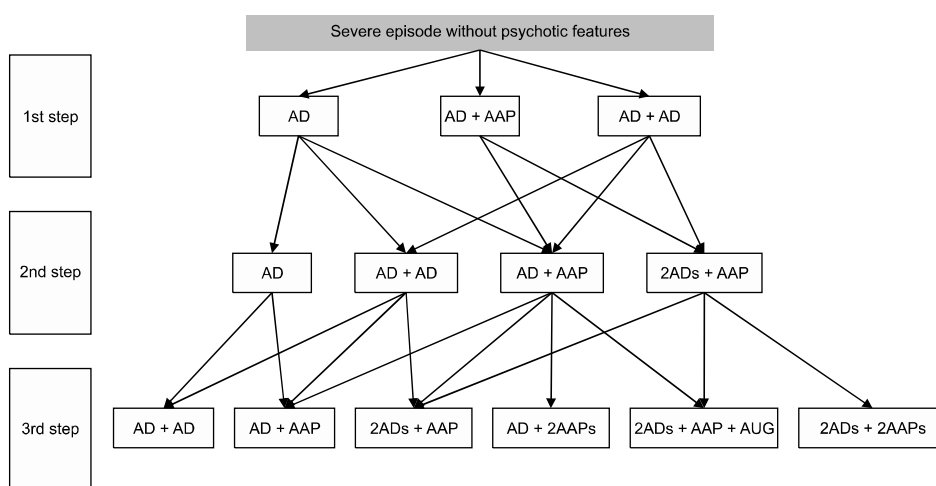
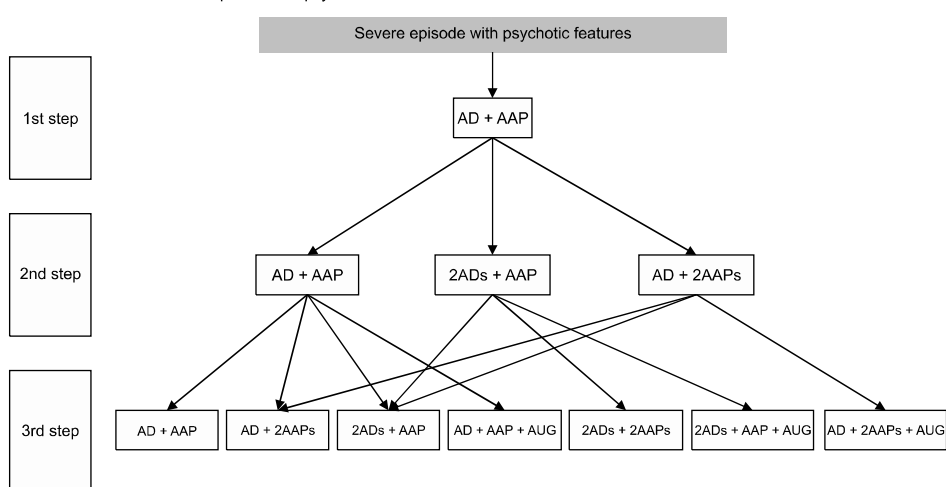
A KMAP-DD 2025: mild to moderate episode**B** KMAP-DD 2025: severe episode without psychotic features**C** KMAP-DD 2025: severe episode with psychotic features

Fig. 1. The Korean Medication Algorithm for Depressive Disorder 2025. KMAP-DD, Korean Medication Algorithm for Depressive Disorder; AD, antidepressant; AAP, atypical anti-psychotics; AUG, augmenting agent.

Table 3. Initial and next step strategies for depressive disorder between the KMAP-DD series

KMAP-DD 2025												KMAP-DD 2021		KMAP-DD 2017		KMAP-DD 2012		KMAP-DD 2006	
Initial step treatment strategy																			
Depressive episode	Mild to moderate episode	1st line	2nd line	1st line	2nd line	1st line	2nd line	1st line	2nd line	1st line	2nd line	1st line	2nd line	1st line	2nd line	1st line	2nd line		
		AD	AD + AD AD + AAP AD + MS	AD monotherapy ^a AD + AAP ^b	AD + AD AD + MS AAP monotherapy	AD monotherapy AD + AAP	AD + AD AD + MS AAP monotherapy	AD monotherapy AD + AAP	AD + AD AD + MS ECT	AD monotherapy AD + TAP AD + MS AD monotherapy AD + AD	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD + AD AD + AAP AD + AUG	AD + AD AD + AAP AD + AUG	
Severe episode without psychotic features	Severe episode with psychotic features	AD	AD + MS AAP	AD monotherapy ^b AD + AAP	AD + AD AD + MS AAP monotherapy	AD monotherapy AD + AAP	AD + AD AD + MS AAP monotherapy	AD monotherapy AD + AAP ^a AAP monotherapy AD + MS AD monotherapy ^b	AD monotherapy AD + AAP ^a AAP monotherapy AD + MS AD monotherapy ^b	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP AD + MS AD monotherapy AD + AD	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD monotherapy AD + AAP ^a AAP monotherapy AD + TAP ECT	AD + AD AD + AAP AD + AUG	AD + AD AD + AAP AD + AUG		
		2nd step treatment strategies																	
Mild to moderate episode	No response	Adding AAP Switching AD Adding AD	Adding AUG	Adding AAP Switching AD Adding AD	Adding AUG	Adding AAP Switching AD Adding AD	Adding AUG	Adding AAP Switching AD Adding AD	Adding AUG	Adding AAP Switching AD Adding AD	Adding AUG	Adding AAP Switching AD Adding AD	Adding AUG	Adding AAP Switching AD Adding AD	Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AD		
		Adding AAP Adding AD	Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AUG		
Severe episode without psychotic features	Partial response	Adding AAP Adding AD	Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG		
		Adding AAP Adding AD	Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG	Adding AAP Switching AD Adding AD	Adding AAP Switching AD Adding AUG		
Severe episode with psychotic features	Inadequate response	Adding AD Switching AAP Adding AAP Switching AD	Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG		
		Adding AD Switching AAP Adding AAP Switching AD	Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG		

KMAP-DD, Korean Medication Algorithm for Depressive Disorder; AAP, atypical antipsychotics; AD, antidepressant; ECT, electroconvulsive therapy; MS, mood stabilizer; TAP, typical antipsychotics; AUG, augmenting drug such as buspirone, mood stabilizer, psychostimulant, thyroid hormone, etc.

^aTreatment of choice, defined as an option that was rated at 9 points by 50% or more of the experts. ^bNo consensus.

bination (95% CI 8.6–8.9) was recommended as the TOC.

Second-step strategies when initial strategies yield no or partial response

When the patients were unresponsive to the initial AD monotherapy, adding AD or AAP and switching AD were preferred. In cases of partial response rather than no response to AD monotherapy, adding AD or AAP was preferred. When AD + AAP failed, switching the AAP or AD, and adding another AD were preferred. With partial response to the initial AD + AAP, adding AD or AAP, and switching AAP or AD were preferred.

When switching AD, recommendations varied based on the current agent in use. If a patient received selective serotonin reuptake inhibitors (SSRI), switching to a serotonin-norepinephrine reuptake inhibitors (SNRI) (95% CI 8.1–8.5) was recommended as the TOC; switching to another SSRI or to mirtazapine was also considered first-line strategy. In cases where SNRI was being used, switching to mirtazapine, another SNRI, or an SSRI were preferred first-line strategies. For patients being treated with mirtazapine, switching to SNRI (95% CI 8.1–8.5) was TOC; switching to an SSRI was first-line option. When switching from bupropion, SSRI (95% CI 8.1–8.5) and SNRI (95% CI 8.1–8.5) were both TOC; mirtazapine also recommended as first-line strategy. For patients on agomelatine, switching to SSRI (95% CI 8.2–8.5) or SNRI (95% CI 8.1–8.5) was TOC; mirtazapine and vortioxetine were also considered as first-line strategies. Finally, when switching from vortioxetine, SNRI (95% CI 8.1–8.5) and SSRI (95% CI 7.9–8.4) agents were TOC; mirtazapine was first-line option.

When adding the AD (excluding agents from the same pharmacological class), SSRI, SNRI, mirtazapine, and bupropion were first-line strategies. Also, vortioxetine was also a first-line strategy, especially when combined with agomelatine; conversely agomelatine was recommended as first-line strategy when combined with SSRI, SNRI, bupropion and vortioxetine.

Recommendations for switching AAP varied depending on the agent currently being used. For patients currently treated with aripiprazole, switching to quetiapine, olanzapine, or risperidone were first-line options. When olanzapine was being used, switching to aripiprazole, quetiapine, or risperidone were similarly recommended

as first-line strategies. When quetiapine was the current agent, aripiprazole, olanzapine, and risperidone were considered as first-line strategies. Paliperidone, amisulpride, ziprasidone, and blonanserin were considered second-line regardless of the previously administered AAP.

For augmenting AD with AAP, aripiprazole (95% CI 8.2–8.6) was the TOC. Quetiapine was first-line; olanzapine, risperidone, ziprasidone, amisulpride, and blonanserin were second-line.

When adding a second AAP, recommendations varied depending on the AAP currently in use. For patients receiving aripiprazole, adding quetiapine, olanzapine, and risperidone were recommended as first-line strategy. For those on olanzapine or quetiapine, adding aripiprazole (95% CI 8.0–8.4, 95% CI 8.2–8.6, respectively) was TOC. In case of using olanzapine, adding quetiapine or risperidone were considered as first-line strategies. For those on quetiapine, adding risperidone or olanzapine were recommended as first-line strategies. Paliperidone, amisulpride, ziprasidone, and blonanserin were considered second-line augmentation options regardless of the initial AAP being used.

Third-step strategies when second-step strategies have no or partial response

In cases of inadequate response to second-step treatment, adding another AAP or AD or changing AAP or AD were recommended. Augmentation drugs such as buspirone, mood stabilizers (MS), psychostimulants, and thyroid hormone were recommended as first-line strategies when there was an insufficient response either adding AD to AD + AAP combination (2AD + AAP) or changing AD or AAP to AD + AAP combination therapy for severe episodes without psychotic features, and when there was an inadequate response to either adding AD to an AD + AAP combination (2ADs + AAP) or switching or adding AAP to ongoing AD + AAP for severe episodes with psychotic features.

When considering augmentation drugs, lithium was a first-line option; lamotrigine, buspirone, and valproate were considered second-line options regardless of presence of psychotic features. Methylphenidate was considered a second-line strategy in severe episodes without psychotic features, whereas carbamazepine was recommended as a second-line strategy in severe episodes with psychotic features.

Antidepressant Choices

Preferred antidepressant for initial treatment

Regardless of severity and presence of psychotic features, escitalopram was recommended as the TOC. For mild-to-moderate depressive episodes, sertraline, fluoxetine, desvenlafaxine, venlafaxine, duloxetine, paroxetine, vortioxetine, and mirtazapine were first-line AD. For severe episodes without psychotic features, venlafaxine, sertraline, desvenlafaxine, mirtazapine, paroxetine, fluoxetine, and duloxetine were first-line AD. For severe episodes with psychotic features, sertraline, venlafaxine, desvenlafaxine, fluoxetine, mirtazapine, paroxetine, and duloxetine were recommended as first-line AD.

Antidepressant choice considering adverse effects, safety, or comorbid physical illness

We asked the experts to choose three ADs when considering adverse effects, drug safety, and comorbid physical illness. Considering adverse effects, bupropion, mirtazapine, and vortioxetine were preferred in terms of sexual dysfunction. For sedation and somnolence, bupropion, fluoxetine, and tianeptine; for weight gain, bupropion, fluoxetine, and vortioxetine; for insomnia, mirtazapine, paroxetine, and tricyclic antidepressants (TCAs); for gastrointestinal trouble, mirtazapine, tianeptine and bupropion; and for anticholinergic side effects, escitalopram, agomelatine, and vortioxetine were selected.

Regarding safety issues, for safety accidents such as falling or traffic accidents, bupropion, escitalopram, and fluoxetine; for serotonin syndrome, bupropion, tianeptine, and agomelatine; for orthostatic hypotension, bupropion, escitalopram, and mirtazapine; and for suicidal ideation, mirtazapine, bupropion, and agomelatine were chosen.

Regarding comorbid conditions, for diabetes mellitus (DM), escitalopram, sertraline and bupropion; for thyroid disease, escitalopram, sertraline and fluoxetine; for liver disease, escitalopram, sertraline, and tianeptine; for renal disease, escitalopram, sertraline, and tianeptine; for hypertension, escitalopram, sertraline, and tianeptine; for cardiovascular illness, sertraline, escitalopram, and tianeptine; for seizure disorder, escitalopram, sertraline, and tianeptine; for parkinsonism, escitalopram, sertraline, and bupropion; for arrhythmia, sertraline, escitalopram, and fluoxetine; and for chronic pain, duloxetine, milnacipran, and venlafaxine were preferred in the order listed above.

Atypical Antipsychotic Choices

For severe episodes without psychotic features, aripiprazole and quetiapine were the first-line AAPs, and olanzapine, risperidone, and ziprasidone were second-line. For severe episodes with psychotic features, aripiprazole (95% CI 8.3–8.6) and quetiapine (95% CI 8.1–8.5) were TOC, and olanzapine was recommended as first-line AAP, and risperidone, paliperidone, ziprasidone, amisulpride, and blonanserin were second-line (Table 4).

Treatment Duration with Initial Antidepressant before Next Strategy

The reviewers were asked about the duration of AD monotherapy before modifying the treatment strategy in cases of insufficient or non-response. For mild-to-moderate depressive episodes, in cases of minimal or no response, their answer was minimum of 2.4 ± 1.0 weeks to a maximum of 4.3 ± 2.0 weeks. If there was a partial response, the answer was 3.8 ± 0.8 to 6.9 ± 1.8 weeks. For severe episodes without psychotic features, the period ranged from 1.9 ± 0.8 to 3.6 ± 1.8 weeks for minimal response, and 3.1 ± 1.6 to 5.7 ± 3.5 weeks in cases of partial response. For severe episodes with psychotic features, their answer was a 1.8 ± 1.0 to 3.3 ± 2.0 weeks for minimal response, and 2.8 ± 1.6 to 5.2 ± 3.5 weeks for partial response.

Treatment Strategies for Persistent Depressive Disorder (Dysthymia) and Subtypes of Depression

Treatment strategies for persistent depressive disorder

AD monotherapy and AD + AAP were first-line treatments. AD + AD, AD + MS, and AAP monotherapy were second-line strategies. Escitalopram (95% CI 8.2–8.6) was TOC; all ADs except TCAs and tianeptine were first-line. TCAs and tianeptine were considered second-line.

Antidepressant choice according to subtype of depressive episode

For melancholic features, escitalopram, desvenlafaxine, venlafaxine, sertraline, fluoxetine, duloxetine, mirtazapine, paroxetine, vortioxetine, milnacipran, bupropion, and agomelatine were first-line AD; Tianeptine and TCAs were second-line AD. And esketamine (no consensus) was third-line drug.

For atypical features, escitalopram, sertraline, fluoxetine,

Table 4. Comparison of preference of antipsychotics in the Korean Medication Algorithm for Depressive Disorder

Preference of atypical antipsychotics	Fifth revision in 2025		Fourth revision in 2021, severe episode		Third revision in 2017, severe episode		Second revision in 2012, severe episode		First revision in 2006
	Without psychotic features	With psychotic features	Without psychotic features	With psychotic features	Without psychotic features	With psychotic features	Without psychotic features	With psychotic features	
Amisulpride	3.6 (3.2–4.0)	5.4 (5.0–5.8)	4.2 (3.7–4.7)	5.7 (5.3–6.2)	5.0 (4.6–5.5)	6.0 (5.6–6.3)	5.5 (5.0–5.9)	6.6 (6.1–7.0)	5.8 (5.3–6.2)
Aripiprazole	7.5 (7.2–7.8) ^a	8.5 (8.3–8.6) ^{ab}	7.6 (7.2–8.0) ^a	8.4 (8.2–8.6) ^{ab}	8.3 (8.2–8.5) ^{ab}	8.3 (8.1–8.5) ^a	7.9 (7.6–8.2) ^a	7.9 (7.6–8.2) ^a	6.3 (5.8–6.7)
Blonanserin	3.6 (3.2–3.9)	5.1 (4.7–5.5)	3.9 (3.5–4.4)	5.8 (5.3–6.2)	4.6 (4.2–5.0)	6.1 (5.7–6.5)	4.4 (3.7–5.1)	5.8 (5.1–6.4)	-
Clozapine	2.5 (2.2–2.9)	3.9 (3.5–4.4)	2.6 (2.2–3.1)	4.3 (3.8–4.8)	2.7 (2.3–3.1)	3.9 (3.4–4.3)	2.9 (2.4–3.4)	4.1 (3.6–4.6)	3.5 (3.0–4.0)
Olanzapine	5.6 (5.2–6.0)	7.6 (7.4–7.9) ^a	5.2 (4.6–5.7) ^c	7.3 (6.9–7.7) ^a	6.0 (5.6–6.4)	7.3 (7.0–7.7) ^a	6.6 (6.2–7.0)	7.6 (7.3–7.9) ^a	7.1 (6.7–7.5) ^a
Paliperidone	3.7 (3.3–4.1)	5.6 (5.2–6.1)	4.0 (3.5–4.6)	6.1 (5.6–6.6)	4.5 (4.1–5.0)	6.9 (5.6–6.5)	-	-	-
Quetiapine	6.9 (6.5–7.3) ^a	8.3 (8.1–8.5) ^{ab}	6.9 (6.4–7.8)	8.0 (7.7–8.2) ^a	7.8 (7.6–8.0) ^a	7.9 (7.7–8.1) ^a	6.0 (5.5–6.4)	7.3 (6.9–7.6) ^a	7.3 (6.9–7.7) ^a
Risperidone	4.8 (4.4–5.2)	6.8 (6.4–7.1)	4.7 (4.2–5.2)	6.8 (6.4–7.2)	5.3 (4.8–5.7)	6.7 (6.3–7.1)	5.7 (5.2–6.3)	6.5 (6.1–6.9)	6.5 (6.0–6.9)
Ziprasidone	4.1 (3.7–4.6)	5.5 (5.1–6.0)	4.3 (3.9–4.8)	5.7 (5.3–6.1)	5.1 (4.6–5.6)	5.9 (5.6–6.3)	3.2 (2.8–3.6)	4.5 (4.0–5.0)	4.8 (4.3–5.3)
Typical antipsychotics	2.0 (1.7–2.3)	3.2 (2.8–3.6)	2.3 (1.9–2.7)	3.4 (2.9–3.9)	2.9 (2.5–3.3)	4.0 (3.4–4.3)	-	-	-

Values are presented as mean (95% confidence interval).

-, not available.

^aFirst-line drug; maximum score of preference is 9 points. ^bTreatment of choice, defined as an option that was rated at 9 points by 50% or more of the experts. ^cNo consensus.

desvenlafaxine, venlafaxine, bupropion, duloxetine, and paroxetine were first-line AD. Mirtazapine, agomelatine, milnacipran, agomelatine, and tianeptine were second-line AD. TCAs and esketamine were third-line AD.

For seasonal patterns, escitalopram, sertraline, fluoxetine, desvenlafaxine, venlafaxine, duloxetine, bupropion, paroxetine, mirtazapine, and agomelatine were first-line AD. Vortioxetine, milnacipran, tianeptine, TCAs were second-line AD. And esketamine was third-line AD.

Treatment strategies for anxious distress specifiers and mixed features (Table 5)

For anxious distress, AD monotherapy and AD + AAP were first-line strategies. AD + AD, AD + MS, and AAP monotherapy were second-line strategies. For choosing AD, escitalopram, sertraline, paroxetine, desvenlafaxine, venlafaxine, mirtazapine, fluoxetine, and duloxetine were first-line AD. Aripiprazole, quetiapine, and olanzapine were first-line AAP or MS for anxious distress.

For mixed features, AD + AAP and AD + MS were first-line strategies, and AAP, AD, or MS monotherapy, AD + AD, and AD + AAP were recommended as second-line strategies. As first-line AD, escitalopram, sertraline, fluoxetine, bupropion, and paroxetine were recommended, and as first-line AAP and MS, aripiprazole, quetiapine, olanzapine, valproate, lithium, and lamotrigine were recommended.

Criteria for Treatment-Resistant Depression Chosen by Experts (Table 6)

Experts were asked to identify appropriate criteria for TRD. The most selected criteria was “Failure to respond to two ADs + one AAP combination treatment” (43.3%). The second most frequently chosen definition was “Failure to respond to two AD treatments of separate pharmacological AD classes” (20.6%), followed by “Failure to respond to two ADs + two AAPs” (17.6%) and “Failure to respond to three ADs of different classes” (5.2%). Less commonly endorsed were “ECT should be considered when no longer responsive to medications” and “Failure to respond to an AD + AD combination” (both 4.1%).

Treatment Strategies for Special Populations (Table 7)

Depressive disorder in children or adolescents

There is no first-line treatment for disruptive mood dys-

Table 5. Initial treatment strategies and drugs of choice for anxious distress or mixed features in KMAP-DD series

Subtype of depressive disorder	2025				2021				2017			
	Initial treatment strategies		AD		AAP or MS		Initial treatment strategies		AAP or MS		Initial treatment strategies	
	1st line	2nd line	1st line	2nd line	1st line	2nd line	1st line	2nd line	1st line	2nd line	1st line	2nd line
Anxious distress	AD monotherapy AD + AAP	AD + AD AD + MS AAP monotherapy	Escitalopram Sertraline Paroxetine Desvenlafaxine Venlafaxine Mirtazapine Fluoxetine Duloxetine		Aripiprazole Quetiapine Olanzapine	AD + AAP AD monotherapy	Escitalopram Fluoxetine Paroxetine Sertraline Venlafaxine Desvenlafaxine Mirtazapine Vortioxetine	AD + AD AD + MS AAP monotherapy	Aripiprazole Olanzapine Quetiapine	AD + AAP AD monotherapy	Escitalopram Fluoxetine Paroxetine Sertraline Duloxetine Venlafaxine Desvenlafaxine Mirtazapine	MS monotherapy AD + AD AD + MS AAP monotherapy AD + TAP AD + AAP Mirtazapine
Mixed features	AD + AAP AD + MS AD monotherapy MS monotherapy AD + TAP AD + AD	AAP monotherapy AD MS monotherapy AD + TAP AD + AD	Aripiprazole Quetiapine Olanzapine Valproate Lithium Lamotrigine		Escitalopram Sertraline Fluoxetine Bupropion Paroxetine	AD + AAP AD + MS AAP MS monotherapy AD monotherapy AD + AD AD + TAP	Escitalopram Sertraline Fluoxetine Bupropion Mirtazapine Desvenlafaxine Venlafaxine Paroxetine	AAP monotherapy MS AD monotherapy AD + AD AD + TAP	Aripiprazole Quetiapine Olanzapine Valproate Lithium	AD + AAP AD + MS AD monotherapy AD + TAP AD + AD ECT	Escitalopram Fluoxetine Sertraline Venlafaxine Bupropion Mirtazapine	Aripiprazole Quetiapine Valproate Olanzapine Lithium

KMAP-DD, Korean Medication Algorithm for Depressive Disorder; AAP, atypical antipsychotics; AD, antidepressant; MS, mood stabilizer; TAP, typical antipsychotics; ECT, electroconvulsive therapy.

Table 6. Consensus of clinical definition for treatment resistant depression in KMAP-DD 2021 and 2025

Definition for treatment resistant depression	2025		2021	
	Respondent	%	Respondent	%
Failure to respond to two AD treatments of separate pharmacological AD class	20	20.6	13	20.6
Failure to respond to three AD treatments of separate pharmacological AD class	5	5.2	6	9.5
Failure to respond to two AD combination treatment	4	4.1	1	1.6
Failure to respond to two AD + one AAP combination treatment of pharmacological AD classes	42	43.3	28	44.4
Failure to respond to two AD + two AAP combination treatment	17	17.6	12	19.0
ECT should be considered for no longer responsive to medications.	4	4.1	2	3.2
Others	5	5.1	1	1.6
Total	97	100	62	100

KMAP-DD, Korean Medication Algorithm for Depressive Disorder; AAP, atypical antipsychotic; AD, antidepressant; ECT, electroconvulsive therapy.

regulation disorder (DMDD). AD or AAP monotherapy, AD + AAP, MS monotherapy, MS + AAP, and AD + MS were recommended as second-line treatment. Escitalopram, fluoxetine, and sertraline were first-line AD, aripiprazole and risperidone were first-line AAP, and valproate was first-line MS for male, there was no first-line MS for female.

AD monotherapy was TOC for mild-to-moderate episodes in children (95% CI 8.4–8.8) and adolescents (95% CI 8.4–8.9). AD monotherapy and AD + AAP were first-line strategies for children with severe episodes without psychotic features. AD monotherapy (95% CI 7.5–8.4) was TOC, and AD + AAP was first-line treatment for adolescents with severe episodes without psychotic features. AD + AAP were TOC for children (95% CI 8.4–8.7) and adolescents (95% CI 8.4–8.8) with severe episodes with psychotic features.

For children patients, the selection of AD was consistent regardless of symptom severity or the presence of psychotic features. Fluoxetine was recommended as the TOC, while escitalopram and sertraline were first-line. For adolescent patients, escitalopram and fluoxetine were TOC, sertraline was first-line treatment regardless of severity or the presence of psychotic features. Among AAP, aripiprazole was first-line treatment for children and adolescents with severe episodes without psychotic features. For those with severe episodes with psychotic features, aripiprazole was TOC in both age groups. Risperidone was also recommended as a first-line option for children with severe episodes with psychotic features, while risperidone and quetiapine were preferred first-line treatments for adolescents with severe episodes with psychotic features.

Elderly patients with major depressive disorder

AD monotherapy (95% CI 8.4–8.7) was TOC for elderly patients with mild-to-moderate depressive episodes. AD monotherapy, AD + AAP and AD + AD were first-line strategies for severe episodes without psychotic features. Whereas AD + AAP (95% CI 8.4–8.6) was TOC, AAP monotherapy was first-line strategy for severe episodes with psychotic features. Escitalopram was TOC for all three types of episodes. Aripiprazole and quetiapine were first-line drug for severe episodes without psychotic features. Aripiprazole (95% CI 8.2–8.5) was TOC, quetiapine and olanzapine were first-line recommendations for severe episodes with psychotic features.

Women with depressive disorder

For premenstrual dysphoric disorder (PMDD), escitalopram, fluoxetine, sertraline, paroxetine, and desvenlafaxine were first-line AD. For MDD in pregnant women, AD monotherapy and rTMS was recommended as first-line treatment for mild-to-moderate and severe episodes without psychotic features. However, AD + AAP and ECT were recommended for severe episodes with psychotic features. For postpartum depression, AD monotherapy and AD + AAP were the first-line strategies for mild-to-moderate and severe episodes without psychotic features. For severe episodes with psychotic features, AD + AAP (95% CI 8.3–8.6) was TOC, and AAP monotherapy was first-line.

Non-pharmacological Biological Treatment

Electroconvulsive therapy

ECT was recommended as the TOC in patients with se-

Table 7. Treatment strategies for major depressive disorder in special populations

Special populations	Disorder	Severity of episode	Initial treatment strategies				AD		AAP or MS	
			1st line	2nd line	2nd line	2nd line	1st line	2nd line	1st line	2nd line
Child and adolescent	Disruptive mood dysregulation disorder		-	AAP monotherapy AD + AAP AD monotherapy MS + AAP MS monotherapy MS + AD	Escitalopram Fluoxetine Sertraline	Bupropion Agomelatine	Aripiprazole ^a Risperidone Valproate (male)	Quetiapine Olanzapine Paliperidone Lithium Lamotrigine Valproate (female)		
MDD	MDD	Mild-to-moderate episode, child	AD monotherapy ^a	AAP monotherapy AD + AAP AD + MS AD + AD ^b	Fluoxetine ^a Escitalopram Sertraline	Bupropion Agomelatine	-	-		
		Mild to moderate episode, adolescent	AD monotherapy ^a	AAP monotherapy AD + MS AD + AD ^b	Escitalopram ^a Fluoxetine ^a Sertraline	Bupropion Agomelatine Duloxetine Venlafaxine Vortioxetine	-	-		
		Severe episode without psychotic features, child	AD monotherapy AD + AAP	AD + MS AD + AD ^b AAP monotherapy ^b	Fluoxetine ^a Escitalopram Sertraline	Bupropion Agomelatine	Aripiprazole	Quetiapine Risperidone		
		Severe episode without psychotic features, adolescent	AD monotherapy ^a AD + AAP	AD + AD AD + MS AAP monotherapy	Fluoxetine ^a Escitalopram ^a Sertraline	Bupropion Agomelatine Venlafaxine Duloxetine Mirtazapine Paroxetine	Aripiprazole	Quetiapine Risperidone Olanzapine		
		Severe episode with psychotic features, child	AD + AAP ^a	AAP monotherapy AD monotherapy AD + MS ^b AD + AD ^b	Fluoxetine ^a Escitalopram Sertraline	Bupropion	Aripiprazole ^a Risperidone	Quetiapine Olanzapine Paliperidone Amisulpride		
		Severe episode with psychotic features, adolescent	AD + AAP ^a	AAP monotherapy AD + MS AD monotherapy ^b AD + AD ^b	Escitalopram ^a Fluoxetine Sertraline	Bupropion Agomelatine Duloxetine Mirtazapine Paroxetine	Aripiprazole ^a Risperidone Quetiapine	Olanzapine Paliperidone Amisulpride Lurasidone Blonanserin Ziprasidone		

Table 7. Continued 1

Special populations	Disorder	Severity of episode	Initial treatment strategies				AD		AAP or MS		
			1st line	2nd line			1st line	2nd line	1st line	2nd line	
Elderly	MDD	Mild to moderate episode	AD monotherapy ^a	AD + AAP		Escitalopram ^a	Agomelatine				
				AD + AD		Sertraline	Milnacipran				
				AAP monotherapy		Duloxetine	Paroxetine				
				AD + MS		Fluoxetine	Bupropion				
				AD + STM		Desvenlafaxine	Tianeptine				
							Mirtazapine				
							Venlafaxine				
							Vortioxetine				
							Escitalopram ^a	Paroxetine		Aripiprazole	Olanzapine
							Sertraline	Agomelatine		Quetiapine	Risperidone
						Duloxetine	Milnacipran		Ziprasidone		
						Desvenlafaxine	Bupropion		Paliperidone	Paliperidone	
						Venlafaxine	Tianeptine		Blonanserin	Blonanserin	
						Mirtazapine			Amisulpride	Amisulpride	
						Fluoxetine					
						Vortioxetine					
						Escitalopram ^a	Milnacipran		Aripiprazole ^a	Risperidone	
						Sertraline	Paroxetine		Quetiapine	Paliperidone	
						Duloxetine	Agomelatine		Olanzapine	Ziprasidone	
						Desvenlafaxine	Bupropion		Blonanserin	Blonanserin	
						Venlafaxine	Tianeptine		Amisulpride		
						Mirtazapine					
						Fluoxetine					
						Vortioxetine					

Table 7. Continued 2

Special populations	Disorder	Severity of episode	Initial treatment strategies				AD		AAP or MS	
			1st line	2nd line	1st line	2nd line	1st line	2nd line	1st line	2nd line
Women	Premenstrual dysphoric disorder	-	-	-	Escitalopram Fluoxetine Sertraline Paroxetine Desvenlafaxine	Venlafaxine Duloxetine Vortioxetine Milnacipran Mirtazapine Agomelatine Bupropion Tianeptine	-	-	-	-
MDD in pregnancy	Mild to moderate episode	Mild to moderate episode	AD monotherapy rTMS	AAP monotherapy AD + AD AD + AAP ^b ECT ^b tDCS	-	-	-	-	-	-
Postpartum depression	Severe episode without psychotic features	Severe episode without psychotic features	AD monotherapy rTMS	AD + AAP AAP monotherapy AD + AD tDCS	-	-	-	-	-	-
Postpartum depression	Severe episode with psychotic features	Severe episode with psychotic features	AD + AAP ECT	AAP monotherapy rTMS	-	-	-	-	-	-
Postpartum depression	Mild to moderate episode	Mild to moderate episode	AD monotherapy AD + AAP	AAP monotherapy AD + AD AD + MS MS + AAP	-	-	-	-	-	-
Postpartum depression	Severe episode without psychotic features	Severe episode without psychotic features	AD + AAP AD monotherapy	AAP monotherapy AD + AD AD + MS AD + AAP	-	-	-	-	-	-
Postpartum depression	Severe episode with psychotic features	Severe episode with psychotic features	AD + AAP ^a AAP monotherapy	MS monotherapy MS + AAP AD + MS AD monotherapy AD + AD	-	-	-	-	-	-

AAP, atypical antipsychotics; AD, antidepressant; ECT, electroconvulsive therapy; MDD, major depressive disorder; MS, mood stabilizer; STM, psychostimulant; TAP, typical antipsychotics; TCA, tricyclic antidepressant; tDCS, transcranial direct current stimulation; rTMS, repetitive transcranial magnetic stimulation; -, not available.

^aTreatment of choice, defined as an option that was rated at 9 points by 50% or more of the experts. ^bNo consensus.

vere episodes with psychotic features and acute suicidal risk. Also, ECT was first-line strategy for patients with severe episodes without psychotic features and acute suicidal risk, pregnant women with severe episodes with psychotic features, and patients with moderate depressive episode who failed to respond to pharmacotherapy.

ECT was a second-line strategy in patients with severe episodes without psychotic features who failed to respond to two ADs and in those with significant physical comorbidities. Among patients with severe episodes with psychotic features, ECT was also a second-line option in cases where there was inadequate response to combination treatment with AD and AAP, or in those with physical comorbidities.

Eighty-five percent of experts considered ECT as a treatment modality for MDD, and 36% of experts were applying it for MDD in clinical practice. On average, one expert conducts ECT with 5.0 persons per year, with 1.5 sessions per patient per week, totaling 9.6 sessions per patient during one treatment plan.

Indications for repetitive transcranial magnetic stimulation

Only for pregnant patients with severe episodes without psychotic features, rTMS was recommended as first-line strategy. And rTMS was a second-line strategy under the following conditions: for severe episodes without psychotic features when patients had no prior exposure to AD or had shown inadequate response to one AD; for severe episodes, when patients failed to respond to two ADs, presented with acute suicidal risk, or had physical comorbidities.

Ninety-five percent of experts considered rTMS an MDD treatment option, but only 43.3% apply it in clinical practice for MDD. On average, one expert conducts rTMS with 6.4 persons per year, with 1.7 sessions per patient per week, totaling 14.9 sessions per patient during one treatment plan.

Choice of complementary or novel agents

Transcranial direct current stimulation (tDCS) was considered as a second-line treatment for pregnant women with severe episodes without psychotic features. Except for this recommendation, tDCS, vagus nerve stimulation (VNS), deep brain stimulation (DBS), light therapy, N-acetyl cysteine (NAC) and omega-3 were considered as third-

line treatment options for MDD.

DISCUSSION

The treatment strategies in KMAP-DD 2025 were largely consistent with those of KMAP-DD 2021, with no substantial changes observed. However, we confirmed the increased preference of combination strategies involving various classes of medication, including AAP and MS. We compared these results with previous versions of KMAP-DD and foreign clinical guidelines for depressive disorders [3-6].

Treatment Strategies for Non-psychotic or Psychotic Depression

Initial step

As a first step, the preferred initial treatment strategy for non-psychotic depressive episodes was AD monotherapy regardless of the severity of the depressive episodes, as recommended in KMAP-DD 2021, 2017, 2012, and 2006. Also, AAP + AD combination as first-line strategy for severe episodes with or without psychotic features was the same recommendation as in KMAP-DD 2021. In mild-to-moderate depressive episodes, AD + MS was a second-line strategy, while a third-line strategy in KMAP-DD 2021. Similarly, AD + AAP, which had been a second-line strategy without consensus in KMAP-DD 2021, achieved consensus in the current revision, and was recommended as a second-line strategy in mild-to-moderate episodes. Additionally, in severe episodes without psychotic features, AD + AD was promoted from second-line to first-line strategy.

Given that the KMAP-DD is a consensus-based algorithm, the updated recommendation suggests an increasing tendency of combination therapies, AD and either AAP or MS, in mild-to-moderate depressive episodes. This trend may reflect growing clinical awareness of bipolarity features, such as bipolar depression or mixed features, during treatment for depressive episodes. Moreover, international studies have shown that as the severity of depression increases, the use of combination therapy becomes more common than AD monotherapy [12,13]. This trend appears to be reflected in Korean clinical practice as well, with an increasing tendency toward rapid and intensive treatment approaches for severe depressions.

This aligns with foreign clinical practice guidelines, which often recommend the addition of agents such as lithium or AAPs following an inadequate response to first-line AD monotherapy [14].

The AD + AAP combination has been consistently recommended in the KMAP-series for treatment of severe episodes with psychotic features, and the recommendation remained in the current revision. Notably, this recommendation is consistent with several foreign clinical guidelines, including those of Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 [3], the National Institute for Health and Care Excellence [6], and the Royal Australian and New Zealand depression treatment guideline [4].

Next step: second and third steps

The recommendation to add AD or AAP in cases of partial response, and to switch the ongoing AD or AAP in cases of no response to initial treatment, remains consistent with previous KMAP-DD revisions and CANMAT 2023 [3]. A key feature of the CANMAT 2023 is its differentiated approach based on the reason for inadequate outcome: switching is recommended when poor tolerability is an issue, while augmentation is preferred when the initial AD is well-tolerated but insufficiently effective. This aligns with the present findings, which similarly discourage switching in cases of poor response alone without tolerability issues.

Furthermore, based on the most consistent evidence supporting the efficacy of AAP in TRD, CANMAT 2023 recommends aripiprazole, quetiapine, olanzapine, and risperidone as adjunctive therapies, all supported by Level I evidence [3].

Antidepressant Choice

Preferred antidepressant as initial treatment

In the selection of an initial AD, escitalopram was recommended as the TOC regardless of the severity of the depressive episodes or the presence of psychotic features, consistent with the KMAP-DD 2021. This continued preference reflects clinicians' consideration of escitalopram's high selectivity for serotonin receptors, favorable tolerability profile, low potential for drug-drug interactions, and well-established efficacy [15].

Although no single AD has proven to be more effective than others [5], Cipriani and colleagues, who conducted

network analyses among 21 ADs, suggested that in head-to-head studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other ADs (range of odds ratios 1.19–1.96) [16]. A recent network meta-analysis comparing the efficacy and safety of 21 AD reported that, during maintenance treatment for MDDs, escitalopram was associated with a higher risk of relapse compared to other SSRIs such as sertraline and fluoxetine. This finding suggests that caution may be warranted when considering escitalopram for long-term treatment [17].

The preference of agomelatine and vortioxetine, newly included in KMAP-DD 2021, an overall increase in preference was observed in the selection of ADs for the treatment of depression. CANMAT 2023 recommended vortioxetine and agomelatine as well as SSRIs, SNRIs, bupropion, and mirtazapine as first-line [3]. But the preference of vortioxetine and agomelatine for psychotic depression was second-line in 2021 but these medications were promoted as first-line in 2025. This result reflects the Korean situation that agomelatine was first withdrawn in Korea in 2017 due to medical insurance issues with the Korean government and then re-marketed in 2019. Its use in clinical practice has expanded, and growing clinical experience appears to have contributed to increased recognition of its efficacy.

In KMAP-DD 2021, esketamine (nasal spray) was second-line for severe episodes with or without psychotic features. This indicated a relatively favorable view of esketamine as an augmentation or alternative strategy in TRD. But, in the current revision, the overall preference for esketamine declined. For severe episodes without psychotic features, esketamine was maintained as a second-line treatment option, but expert consensus was not reached. For psychotic severe episodes, esketamine was downgraded to a third-line option.

Despite its advantage of producing rapid AD effects in patients with TRD or those experiencing suicidal ideation [18], concerns regarding esketamine's safety may have influenced its reduced preference in the current revision. In the SUSTAIN-2 study—a multinational, multicenter, open-label trial assessing the safety and effectiveness of esketamine—subgroup analysis of Asian participants revealed a higher incidence of serious treatment-related adverse events, including suicidality and dissociative symptoms, compared to the general population [19,20]. Although

some reports have suggested that esketamine may be safely used in patients with psychotic features [21], there remains insufficient evidence supporting its safety in patients with current or past psychotic symptoms [22].

In addition to safety concerns, recent clinical trials conducted in East Asia have raised questions about its efficacy. A phase 2b randomized trial in Japan failed to demonstrate a statistically significant difference in depressive symptom reduction between esketamine and placebo groups, despite both groups showing numerical improvement on the Montgomery-Åsberg Depression Rating Scale (MADRS) scale [23]. Similarly, a phase 3 trial involving Chinese patients reported no significant difference in MADRS score change at 4 weeks between esketamine and placebo groups, although a transient AD effect was observed at 24 hours after administration [24].

Furthermore, in Korea, esketamine is not yet covered by the national health insurance, relatively high cost poses a substantial burden on patients. These findings collectively may have contributed to the decreased consensus and preference of esketamine observed in this revision.

Antidepressant choice considering adverse effects, safety, and comorbid physical illness

In the current revision, results were largely consistent with those from KMAP-DD 2021, 2017, and 2012. When considering adverse effects, the following ADs were recommended with higher preference: 1) bupropion for sexual dysfunction, sleepiness or sedation, weight gain, safety accidents, serotonin syndrome, and orthostatic hypotension; 2) mirtazapine for insomnia, GI trouble, and suicidal ideation; and 3) escitalopram for anti-cholinergic side effects.

A recent systemic review regarding AD and weight gain showed that all SSRIs except fluoxetine increase mean weight while bupropion and fluoxetine decreases the mean weight [25]. Most experts in Korea would have the same clinical experience.

Bupropion was favorably regarded due to its relatively advantageous profile in key side effect domains, including sexual dysfunction, sedation, safety accidents, serotonin syndrome, and orthostatic hypotension. This favorable side effect profile has been highlighted in CANMAT 2023 [3], and the current findings suggest that Korean clinicians similarly recognize these benefits in clinical practice.

When considering comorbid physical illness, escitalo-

pram was recommended as a first-line drug for comorbidities of DM, thyroid disease, liver disease, renal disease, hypertension, seizure disorder, and parkinsonism. Sertraline was recommended for cardiovascular disease and arrhythmia. These results are consistent with major international treatment guidelines, and the cardiovascular safety of sertraline has been confirmed in a recent cohort study [26].

Atypical Antipsychotic Choices

In KMAP-DD 2021, aripiprazole was the only first-line AAP for severe episodes without psychotic features. In the 2025 revision, quetiapine was promoted to a first-line option. Similarly, quetiapine was added as a TOC alongside aripiprazole for severe episodes with psychotic features. With level I evidence, foreign guidelines recommended aripiprazole, quetiapine, olanzapine, brexpiprazole, and lurasidone as adjunctive, not as AAP monotherapy [3]. That is, Korean experts recommend AAP as a first step, but foreign guidelines recommended AAP as the second step. Notably, lurasidone was excluded from evaluation in this revision due to limited clinical experience, as its introduction coincided with the survey period. It may be re-evaluated in future updates as its clinical use expands.

Treatment Duration with the Initial Antidepressant before the Next Strategy (Switching to or Adding Another Antidepressant, etc.)

We observed a similar waiting duration between the initial and next-step treatment strategies with the previous revision, such as augmentation, switching, or combination. With no response to the initial treatment for mild-to-moderate depressive episodes, waiting durations were 3.3–6.1 weeks (2006), 3.2–7.5 weeks (2012), 2.9–6.4 weeks (2017), 2.2–4.3 weeks (2021), and 2.4–4.3 weeks (2025). With no response to the initial treatment for severe episodes with psychotic features, waiting durations were 2.4–4.7 weeks (2012), 2.3–4.7 weeks (2017), 1.7–3.3 weeks (2021), and 1.8–3.3 weeks (2025). With a partial response to initial treatment for severe episodes with psychotic features, waiting durations were 3.4–6.9 weeks (2012), 3.4–6.5 weeks (2017), and 2.6–4.8 weeks (2021), 2.8–5.2 weeks (2025).

We observed a consistent trend of short waiting periods before modifying treatment when there was no response

to initial AD therapy, compared to cases with partial response—consistent with previous KMAP-DD series. A similar pattern is reflected in international guidelines. The World Federation of Societies of Biological Psychiatry [5] recommends considering treatment optimization after 2 weeks in the case of an inadequate response. Additionally, CANMAT 2023 introduced the concept of ‘early improvement’ defined as a $> 20\%$ reduction from baseline on a depression rating scale after 2 to 4 weeks, as a predictor of treatment outcome and prognosis [3]. Based on this, CANMAT 2023 recommended dose escalation or switching ADs when there is poor tolerability or insufficient response within that time frame.

Treatment Strategies for Persistent Depressive Disorder (Dysthymia) and Subtypes of Depression

Treatment strategies for persistent depressive disorder

In the current revision AD + AAP was promoted as a first-line treatment, alongside AD monotherapy. A review study has described the role of AAP in the treatment of MDD. The authors suggested that AAP may complement the limitations of traditional AD such as SSRIs and SNRIs, offering both sufficient AD efficacy and acceptable tolerability. They further emphasized the particular importance of AAPs in cases of treatment-resistant and recurrent depression [27]. The preference of escitalopram as initial AD was the TOC in 2021 while a first-line treatment in 2017.

Antidepressant choice according to subtypes

Melancholia

Compared with KMAP-DD 2017 and 2021, escitalopram and venlafaxine were TOC in 2017, while only escitalopram was the TOC in 2021. In the current revision, the TOC category was removed entirely, and most ADs are now recommended as first-line treatment options. Bupropion and agomelatine were promoted as first-line. Except for tianeptine and TCAs, nearly all ADs are now considered for first-line treatment. These results are consistent with CANMAT 2023, which also recommends most ADs—excluding TCAs—as first-line options for the treatment of melancholic depression [3].

Atypical features and seasonal patterns

Mirtazapine was promoted to a first-line treatment in 2025 after being downgraded to a second-line treatment in 2021. Except tianeptine and TCAs, all ADs were recommended as first-line treatment in the current revision. This result is also consistent with CANMAT 2023, which states that most ADs—excluding TCAs—can be considered first-line options for atypical depression [3].

For seasonal patterns, agomelatine and milnacipran were promoted to the first-line ADs in 2025. Agomelatine acts as an agonist at melatonin receptors MT1 and MT2, and its AD properties are associated with improvements in sleep and circadian rhythm regulation, suggesting potential efficacy in the treatment of seasonal depression [28,29].

Treatment strategies for anxious distress specifiers and mixed features

As in 2017 and 2021, both AD monotherapy and AD + AAP were recommended as first-line treatment for depression with anxious distress. First-line ADs in 2025 were mostly consistent with those in KMAP-2021. But vortioxetine was downgraded as second-line treatment. Aripiprazole, quetiapine, and olanzapine were all recommended as first-line AAP, consistent with KMAP-DD 2021. This suggested that AAPs are not limited to psychosis or bipolar disorder but are also used for comorbid anxiety or agitation. Some studies have demonstrated that AAPs are effective in depression with anxious distress [30,31].

For mixed features, KMAP-DD 2017, 2021 and 2025 maintained the same first-line strategies; AAP + AD and AD + MS. Among the first-line treatment strategies, AD + AAP was the most strongly preferred, while for second-line treatment, AAP monotherapy was more commonly preferred, whereas preference for AD + AD had notably low preference. Aripiprazole, quetiapine, olanzapine, valproate, lithium, and lamotrigine were recommended as the first-line augmenting medications for mixed features. Although the diagnostic criteria for mixed features in DSM-5 remain a subject of debate [32,33], mixed features during depressive episodes are often considered indicative of bipolar spectrum [34].

The Consensus on the Definition of Treatment-resistant Depression

In the current revision, results were similar with KMAP-

DD 2021. 44% of experts chose the criteria of TRD as “Failure to respond to two ADs + one AAP combination treatment.” “Failure to respond to a two-AD treatment of separate pharmacological AD class” was chosen by 20.6% of experts. And “Failure to respond to two ADs + two AAPs combination treatment” was chosen by 17.6% of experts. These findings also reflect a growing trend in Korea toward earlier use of AAP in the treatment of depression, as evidenced by the increased preference for AAP in recent treatment strategies.

There is no universal criteria or definition of TRD. According to a recent review, the definition of TRD remains inconsistent across studies, resulting in significant heterogeneity in both clinical and research settings. TRD is commonly regarded as a MDD in which patients fail to respond to two or more adequately dosed and appropriately administered AD treatments [35]. However, the use of AAP becomes increasingly common in the early stages of depression treatment, it may be necessary to expand the definition of TRD to include failure of treatment strategies involving AAP.

Treatment Strategies for Special Populations

Because conducting RCTs in special populations—such as children, pregnant women, and elderly patients with depression—is ethically and practically challenging, expert consensus can serve as a valuable supplement to limited evidence. However, expert experience is not always correct, just as evidence is not always conclusive. Therefore, the treatment of depression in special populations should be approached with caution, guided by a careful evaluation of the potential benefits and risks.

Treatment strategy for children and adolescents

In the previous revision, more detailed results into the treatment of MDD were obtained by distinguishing between children (ages 5–12) and adolescents (ages 13–17), except for DMDD. In the current revision, recent research findings and clinical experiences were incorporated, resulting in more refined and detailed recommendations for treatment strategies.

Disruptive mood dysregulation disorder

There was no first-line strategy for DMDD in KMAP-DD 2025, same as the previous revision. Korean experts recommended AAP monotherapy, AD + AAP, and AD mon-

otherapy as a second-line treatment, also consensus was reached on the MS + AAP, MS monotherapy, and MS + AD as a second-line. DMDD is characterized by recurrent temper outbursts and persistent irritability, the high preference for MS and AAP are likely attributable to these symptom characteristics.

For DMDD, escitalopram and fluoxetine remained first-line ADs, consistent with KMAP-DD 2021. Notably, sertraline, which was previously considered a second-line option in KMAP-DD 2021, was elevated to a first-line option in the current revision, reflecting increased clinical preference. In AAP, aripiprazole, which was TOC in KMAP-DD 2021, was recommended as a first-line agent together with risperidone in the current revision. This may reflect growing evidence for risperidone’s efficacy, particularly in combination regimens [36,37].

Considering the reproductive risks associated with valproate in women [38], the current revision maintained the approach adopted in the 2021 revision by assessing MS preferences separately by sex. Valproate was a first-line treatment for male but a second-line treatment for female. Both lamotrigine and lithium were recommended as second-line treatments for both male and female patients.

Children and adolescents with major depression

For both children and adolescents with mild to moderate depressive episodes, AD monotherapy was recommended as TOC. In cases of severe episodes without psychotic features, KMAP-DD 2025 recommended, for children, the same first-line treatments as KMAP-DD 2021: AD monotherapy and AD + AAP. For adolescents, while AD monotherapy was a first-line option in KMAP-DD 2021, it was elevated to TOC in KMAP-DD 2025. For severe episodes with psychotic features, as in KMAP-DD 2021, AD + AAP was recommended as TOC for both children and adolescents in the current revision.

In the current revision, fluoxetine replaced escitalopram as TOC in children, and sertraline was promoted to a first-line option. For adolescents, the preference for fluoxetine increased, and it was recommended as TOC. For severe episodes without psychotic features, fluoxetine was recommended as TOC in children. For severe episodes with psychotic features, fluoxetine was recommended as TOC in children, while both escitalopram and fluoxetine were recommended as TOC in adolescents. Fluoxetine showed increased preference across all clin-

ical situations, which may reflect consistent evidence from multiple studies supporting its efficacy in improving depressive symptoms. According to the American Academy of Child and Adolescent Psychiatry (AACAP) 2023 guidelines, fluoxetine is recommended as the AD with the strongest level of evidence for the treatment of MDD in adolescents [39].

In the selection of AAP for severe episodes without psychotic features, aripiprazole—previously a second-line treatment in KMAP-DD 2021—was upgraded to a first-line treatment for both children and adolescents in KMAP-DD 2025. For severe episodes with psychotic features, aripiprazole continued to be recommended as TOC for both age groups, consistent with KMAP-DD 2021, and quetiapine was also newly recommended as a first-line option in adolescents. However, AAP were not included in the treatment strategy of CANMAT 2016 for child/adolescent depression [40] and AACAP 2023 guideline [39].

Because AD may increase the risk of suicide in children and adolescents [41], caution should be paid to AD use in these age groups. Due to this potential risk, the AACAP 2023 guidelines recommend that [39], for mild to moderate depressive episodes, non-pharmacological psychotherapies such as cognitive behavioral therapy (CBT) or interpersonal therapy (IPT) should be implemented as first-line treatment. If symptoms do not improve or in cases of moderate to severe depression, pharmacological treatment with AD-fluoxetine (preferred) or escitalopram as second-line treatment. As third-line treatment, for severe depression or cases with insufficient response to monotherapy, combination therapy with both medication and psychotherapy is recommended.

Treatment strategy for elderly adults

For mild to moderate episodes of MDD in the elderly, AD monotherapy was recommended as TOC, consistent with the recommendations of KMAP-DD 2012, 2017, and 2021. This reflects the perception that monotherapy is a safer treatment option in the elderly, given the high prevalence of comorbid physical illnesses and the increased risk of drug-drug interactions due to polypharmacy commonly seen in this population [42]. For severe episodes without psychotic features, AD monotherapy, AD + AAP, and AD + AD were recommended as first-line options, AD + AD was promoted from a second-line in 2021. For severe episodes with psychotic features, AD + AAP was

TOC same as 2021, AAP monotherapy was promoted from a second-line in 2021 to first-line recommendation.

Compared to KMAP-DD 2021, the preference of olanzapine increased from second-line to first-line in 2025. Adjunctive olanzapine with sertraline [43] and olanzapine augmentation for TRD was found to be effective for elderly depression [44]. But, at the same time, olanzapine increases the risk of diabetes, hypertension, and metabolic syndrome, caution should be paid to use in these age group. Despite clinical limited evidence in treating elderly depression, it is essential to consider factors such as comorbid physical illnesses, potential drug-drug interactions, and age-related metabolic changes.

Treatment strategy for women with premenstrual dysphoric disorder or peripartum depression

In the current revision, escitalopram, fluoxetine, sertraline, paroxetine, and desvenlafaxine were the recommended first-line drugs for PMDD. That is, the preference for SSRI is higher than for other ADs in treating PMDD, which is consistent with foreign research [45,46]

In treating pregnant women, clinicians must carefully weigh the potential risks of medication exposure to the fetus against the risks of untreated maternal depression, which may include poor nutritional intake, inadequate prenatal care, and engagement in harmful behaviors such as smoking or alcohol use [47,48]. In the current revision, AD monotherapy was recommended as the first-line strategy for mild to moderate, and severe episodes without psychotic features during pregnancy. These results were consistent with those of previous studies that advocate for minimizing medication use during pregnancy [47,49]. A notable change from KMAP-DD 2021 is the inclusion of rTMS as a newly recommended first-line treatment. rTMS is gaining attention as a relatively safe biological treatment alternative for pregnant patients who have significant concerns about pharmacotherapy [50,51]. Its clinical utility appears to be reflected in the current revision. In case of severe episodes with psychotic features, AD + AAP and ECT were recommended as first-line treatment, consistent with KMAP-DD 2017 and 2021.

For postpartum depression, AD monotherapy and AD + AAP were recommended as first-line treatments for mild to moderate depressive episodes, consistent with the KMAP-DD 2021. Changes in the recommendations for postpartum depression were that AD + AAP was the only

first-line option for severe episodes without psychotic features in 2021, while AD + AAP as well as AD monotherapy were the first-line strategies in 2025. For postpartum depression, CANMAT 2016 also recommends CBT and IPT as first-line and escitalopram and sertraline as second-line [40].

Non-pharmacological Biological Therapy

Electroconvulsive therapy, repetitive transcranial magnetic stimulation

ECT was the TOC for severe episodes with psychotic features accompanied by acute suicidal risk. It was also recommended as a first-line strategy in cases of severe episodes without psychotic features with acute suicidal risk, in treatment-resistant severe episodes, and in pregnant women presenting with severe episodes with psychotic features. Notably, the preference for ECT has increased compared to the KMAP-DD 2021, reflecting growing clinical confidence in its effectiveness and safety in critical cases. Foreign guidelines also recommend ECT as a first-line option in cases where psychotic symptoms are present and the risk of suicide is high and pregnant women [3,4,6,40,52]. However, only 36% of Korean experts reported performing ECT, despite 85.7% indicating they would consider it—representing a decline from the results of KMAP-DD 2021, in which 92.4% considered ECT and 43.8% performed it. The number of procedures also decreased. These findings suggest that practical challenges—such as reimbursement issues, lack of appropriate facilities, and insufficient support from other medical specialties—have contributed to the limited implementation of ECT in clinical practice [53].

rTMS was recommended as a first-line treatment strategy for severe episodes without psychotic features during pregnancy. In the previous revision, there was no expert consensus on the use of rTMS for mild to moderate episodes, severe episodes without prior AD treatment, or severe episodes without psychotic features accompanied by acute suicidal risk. However, in the current revision, rTMS was recommended as a second-line strategy in all these cases, indicating an increased preference and recognition of rTMS as an efficient treatment option. Reflecting these results, the proportion of experts who considered using rTMS increased from 89.1% in 2021 to 95.4% in the current revision. Similarly, the proportion of experts who per-

formed rTMS also increased, from 40.6–43.3%. For the treatment of depression, CANMAT 2023 recommended rTMS for patients who have failed treatment, based on efficacy, tolerability, and safety, with at least 1 AD as a first-line treatment [3,52].

Alternative biological therapies

In Korea, these alternative therapies are less popular than ECT or rTMS. Light therapy, tDCS, VNS, DBS, NAC, and nutritional therapy (e.g., omega-3) were all considered third-line strategies, either as monotherapy or in combination. Notably, tDCS, light therapy, and omega-3—previously recommended as second-line options in KMAP-DD 2021—showed decreased preference in the current revision. CANMAT 2023 recommended light therapy alone as a first-line treatment for seasonal MDD mild depressive episode [3]. Although tDCS is less effective for TRD, the onset of its effect was faster than AD monotherapy with equal efficacy [54], and when adjuvant with AD, its efficacy was superior to AD monotherapy [55], and it is a relatively safe, non-invasive modality that can be administered at home [56]. Therefore, tDCS may serve as a supplementary treatment option in the future.

Summary: Advantages and Limitations of Korean Medication Algorithm for Depressive Disorder 2025

In summary, the treatment trend in Korea has become more active, characterized by short intervals between treatment steps, a rising preference for AAP, and an increased preference on combination strategies with MS and AAP. While preference of esketamine appears to decrease.

The main limitation of this study is that the treatment algorithm is largely based on expert opinion, which may not always consistent with existing evidence-based guidelines. While evidence-based approaches offer clear guidance, they may not fully capture the complexity of real-world clinical practice. In this context, expert consensus can serve as a meaningful bridge between evidence and real-world practice.

Given the variability in depressive symptoms and treatment responses across racial, genetic, and sociocultural backgrounds—and the limited clinical research involving Korean populations, this expert-opinion algorithm offers a valuable complement to international guidelines, addressing their limitations in Korean clinical settings.

To our knowledge, the KMAP-DD series remains the only expert consensus guideline for depressive disorders that have been regularly updated and revised since 2002. While it is important to acknowledge that KMAP-DD is not intended to override individual clinical judgment, it is designed to support clinicians by offering practical guidance on treatment strategies and medication choices. By bridging the gap between real-world clinical practice and evidence-based literature, KMAP-DD aims to serve as a valuable resource for managing patients with MDD in Korea.

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REFERENCES

- McCarron RM, Shapiro B, Rawles J, Luo J. *Depression. Ann Intern Med* 2021;174:ITC65-ITC80.
- Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, *et al.* Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal Transduct Target Ther* 2024;9:30.
- Lam RW, Kennedy SH, Adams C, Bahji A, Beaulieu S, Bhat V, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 update on clinical guidelines for management of major depressive disorder in adults: Réseau canadien pour les traitements de l'humeur et de l'anxiété (CANMAT) 2023 : mise à jour des lignes directrices cliniques pour la prise en charge du trouble dépressif majeur chez les adultes. *Can J Psychiatry* 2024;69:641-687.
- Malhi GS, Bell E, Singh AB, Bassett D, Berk M, Boyce P, *et al.* The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: major depression summary. *Bipolar Disord* 2020;22:788-804.
- Bauer M, Severus E, Möller HJ, Young AH; WFSBP Task Force

- on Unipolar Depressive Disorders. *Pharmacological treatment of unipolar depressive disorders: summary of WFSBP guidelines. Int J Psychiatry Clin Pract* 2017;21:166-176.
6. National Institute for Health and Care Excellence (NICE). *Depression in adults: treatment and management. NICE*;2022.
 7. Lee MS, Lim SW, Cha JH, Chung SK, Kim KS, Kasper S, et al. *The Korean Medication Algorithm for Major Depressive Disorder (KMA-MDD): report of the Korean Society of Depressive and Bipolar Disorders. Int J Psychiatry Clin Pract* 2006;10:186-194.
 8. Seo JS, Min KJ, Kim W, Seok JH, Bahk WM, Song HC, et al. *Korean Medication Algorithm for Depressive Disorder 2006 (I). J Korean Neuropsychiatr Assoc* 2007;46:453-460.
 9. Seok Seo J, Rim Song H, Bin Lee H, Park YM, Hong JW, Kim W, et al. *The Korean Medication Algorithm for Depressive Disorder: second revision. J Affect Disord* 2014;167:312-321.
 10. Seo JS, Bahk WM, Wang HR, Woo YS, Park YM, Jeong JH, et al. *Korean Medication Algorithm for Depressive Disorders 2017: third revision. Clin Psychopharmacol Neurosci* 2018;16:67-87.
 11. Seo JS, Bahk WM, Woo YS, Park YM, Kim W, Jeong JH, et al. *Korean Medication Algorithm for Depressive Disorder 2021, fourth revision: an executive summary. Clin Psychopharmacol Neurosci* 2021;19:751-772.
 12. Dold M, Bartova L, Mendlewicz J, Souery D, Serretti A, Porcelli S, et al. *Clinical correlates of augmentation/combination treatment strategies in major depressive disorder. Acta Psychiatr Scand* 2018;137:401-412.
 13. Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. *Combining antidepressants vs antidepressant monotherapy for treatment of patients with acute depression: a systematic review and meta-analysis. JAMA Psychiatry* 2022;79:300-312.
 14. Taylor RW, Marwood L, Oprea E, DeAngel V, Mather S, Valentini B, et al. *Pharmacological augmentation in unipolar depression: a guide to the guidelines. Int J Neuropsychopharmacol* 2020;23:587-625.
 15. Kirino E. *Escitalopram for the management of major depressive disorder: a review of its efficacy, safety, and patient acceptability. Patient Prefer Adherence* 2012;6:853-861.
 16. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. *Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet* 2018;391:1357-1366.
 17. Kishi T, Ikuta T, Sakuma K, Okuya M, Hatano M, Matsuda Y, et al. *Antidepressants for the treatment of adults with major depressive disorder in the maintenance phase: a systematic review and network meta-analysis. Mol Psychiatry* 2023;28:402-409.
 18. Wang SM, Kim NY, Na HR, Lim HK, Woo YS, Pae CU, et al. *Rapid onset of intranasal esketamine in patients with treatment resistant depression and major depression with suicide ideation: a meta-analysis. Clin Psychopharmacol Neurosci* 2021;19:341-354.
 19. Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, et al. *Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). J Clin Psychiatry* 2020;81:19m12891.
 20. Jeon HJ, Ju PC, Sulaiman AH, Aziz SA, Paik JW, Tan W, et al. *Long-term safety and efficacy of esketamine nasal spray plus an oral antidepressant in patients with treatment-resistant depression— an Asian sub-group analysis from the SUSTAIN-2 study. Clin Psychopharmacol Neurosci* 2022;20:70-86.
 21. Veraart JKE, Smith-Apeldoorn SY, Spijker J, Kamphuis J, Schoevers RA. *Ketamine treatment for depression in patients with a history of psychosis or current psychotic symptoms: a systematic review. J Clin Psychiatry* 2021;82:20r13459.
 22. Medeiros GC, Demo I, Goes FS, Zarate CA Jr, Gould TD. *Personalized use of ketamine and esketamine for treatment-resistant depression. Transl Psychiatry* 2024;14:481.
 23. Takahashi N, Yamada A, Shiraiishi A, Shimizu H, Goto R, Tominaga Y. *Efficacy and safety of fixed doses of intranasal Esketamine as an add-on therapy to oral antidepressants in Japanese patients with treatment-resistant depression: a phase 2b randomized clinical study. BMC Psychiatry* 2021;21:526.
 24. Chen X, Hou X, Bai D, Lane R, Zhang C, Canuso C, et al. *Efficacy and safety of flexibly dosed esketamine nasal spray plus a newly initiated oral antidepressant in adult patients with treatment-resistant depression: a randomized, double-blind, multicenter, active-controlled study conducted in China and USA. Neuropsychiatr Dis Treat* 2023;19:693-707.
 25. Moss L, Laudenslager M, Steffen KJ, Sockalingam S, Coughlin JW. *Antidepressants and weight gain: an update on the evidence and clinical implications. Curr Obes Rep* 2025;14:2.
 26. Ishtiak-Ahmed K, Musliner KL, Christensen KS, Mortensen EL, Nierenberg AA, Gasse C. *Real-world evidence on clinical outcomes of commonly used antidepressants in older adults initiating antidepressants for depression: a nationwide cohort study in Denmark. Am J Psychiatry* 2024;181:47-56.
 27. Han C, Wang SM, Kato M, Lee SJ, Patkar AA, Masand PS, et al. *Second-generation antipsychotics in the treatment of major depressive disorder: current evidence. Expert Rev Neurother* 2013;13:851-870.
 28. Pjrek E, Winkler D, Konstantinidis A, Willeit M, Praschak-Rieder N, Kasper S. *Agomelatine in the treatment of seasonal affective disorder. Psychopharmacology (Berl)* 2007;190:575-579.
 29. Lee KH, Han TS, Han C, Bahk WM, Lee SJ, Patkar AA, et al. *Additional clinical benefit of agomelatine treatment for major depressive disorder in naturalistic treatment setting. Clin Psychopharmacol Neurosci* 2023;21:594-598.
 30. Ravindran N, McKay M, Paric A, Johnson S, Chandrasena R, Abraham G, et al. *Randomized, placebo-controlled effectiveness study of quetiapine XR in comorbid depressive and anxiety disorders. J Clin Psychiatry* 2022;83:21m14096.

31. Lee SH, Lee KH, Han TS, Han C, Bahk WM, Lee SJ, et al. The potential role of aripiprazole augmentation for major depressive disorder with anxious distress in naturalistic treatment setting. *Clin Psychopharmacol Neurosci* 2024;22:370-375.
32. Koukopoulos A, Sani G, Ghaemi SN. Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV). *Br J Psychiatry* 2013;203:3-5.
33. Park YM. The mixed-features specifier of major depressive disorder in DSM-5: is it practical? *Psychiatry Investig* 2018;15:1009-1010.
34. Takeshima M, Inoue T. What Is the depressive mixed state?-associated factors beyond bipolarity. *Bipolar Disord* 2025;27:144-151.
35. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry* 2023;22:394-412.
36. Baweja R, Mayes SD, Hameed U, Waxmonsky JG. Disruptive mood dysregulation disorder: current insights. *Neuropsychiatr Dis Treat* 2016;12:2115-2124.
37. Benarous X, Consoli A, Guilé JM, Garny de La Rivière S, Cohen D, Olliac B. Evidence-based treatments for youths with severely dysregulated mood: a qualitative systematic review of trials for SMD and DMDD. *Eur Child Adolesc Psychiatry* 2017;26:5-23.
38. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al.; EURAP study group. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* 2011;10:609-617.
39. Walter HJ, Abright AR, Bukstein OG, Diamond J, Keable H, Ripperger-Suhler J, et al. Clinical practice guideline for the assessment and treatment of children and adolescents with major and persistent depressive disorders. *J Am Acad Child Adolesc Psychiatry* 2023;62:479-502.
40. MacQueen GM, Frey BN, Ismail Z, Jaworska N, Steiner M, Lieshout RJ, et al.; CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 6. Special populations: youth, women, and the elderly. *Can J Psychiatry* 2016;61:588-603.
41. Boaden K, Tomlinson A, Cortese S, Cipriani A. Antidepressants in children and adolescents: meta-review of efficacy, tolerability and suicidality in acute treatment. *Front Psychiatry* 2020;11:717.
42. Kok RM, Reynolds CF 3rd. Management of depression in older adults: a review. *JAMA* 2017;317:2114-2122.
43. Meyers BS, Flint AJ, Rothschild AJ, Mulsant BH, Whyte EM, Peasley-Miklus C, et al.; STOP-PD Group. A double-blind randomized controlled trial of olanzapine plus sertraline vs olanzapine plus placebo for psychotic depression: the study of pharmacotherapy of psychotic depression (STOP-PD). *Arch Gen Psychiatry* 2009;66:838-847.
44. Piel C, Quante A. Therapy strategies for late-life depression: a review. *J Psychiatr Pract* 2023;29:15-30.
45. Jespersen C, Lauritsen MP, Frokjaer VG, Schroll JB. Selective serotonin reuptake inhibitors for premenstrual syndrome and premenstrual dysphoric disorder. *Cochrane Database Syst Rev* 2024;8:CD001396.
46. Carlini SV, Deligiannidis KM. Evidence-based treatment of premenstrual dysphoric disorder: a concise review. *J Clin Psychiatry* 2020;81:19ac13071.
47. Eakley R, Lyndon A. Antidepressant use during pregnancy: knowledge, attitudes, and decision-making of patients and providers. *J Midwifery Womens Health* 2022;67:332-353.
48. Fischer Fumeaux CJ, Morisod Harari M, Weisskopf E, Eap CB, Epiney M, Vial Y, et al. Risk-benefit balance assessment of SSRI antidepressant use during pregnancy and lactation based on best available evidence - an update. *Expert Opin Drug Saf* 2019;18:949-963.
49. Tauqeer F, Moen A, Myhr K, Wilson CA, Lupattelli A. Assessing decisional conflict and challenges in decision-making among perinatal women using or considering using antidepressants during pregnancy-a mixed-methods study. *Arch Womens Ment Health* 2023;26:669-683.
50. Angeline S, Tiyaie B, Akosile W. Transcranial magnetic stimulation in pregnancy: efficacy, safety, and future implications for perinatal mental health care. *Brain Behav* 2025;15:e70304.
51. Ganho-Ávila A, Sobral M, Berg MLD. Transcranial magnetic stimulation and transcranial direct current stimulation in reducing depressive symptoms during the peripartum period. *Curr Opin Psychiatry* 2024;37:337-349.
52. Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, et al.; CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. *Can J Psychiatry* 2016;61:561-575.
53. Lee SH, Hyung WSW, Youn CE, Chi S, Youn H, Lee MS, et al. Trends in electroconvulsive therapy utilization in South Korea: health insurance review data from 2008 to 2018. *Psychiatry Investig* 2024;21:691-700.
54. Hejzlar M, Novak T, Bares M. Neurostimulation methods in the treatment of depression: a comparison of rTMS, tDCS, and venlafaxine using a pooled analysis of two studies. *Neuropsychiatr Dis Treat* 2021;17:1713-1722.
55. Brunoni AR, Valiengo L, Baccaro A, Zanão TA, de Oliveira JF, Goulart A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry* 2013;70:383-391.
56. Oh J, Jeon S, Ha TH, Myung W, Lee SH, Ko YH, et al. Effect of home-based self-administered transcranial direct stimulation in patients with mild to moderate major depressive disorder: a single-arm, multicenter trial. *Clin Psychopharmacol Neurosci* 2023;21:271-278.