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Korean Medication Algorithm for Depressive Disorder 2021, Fourth Revision: An Executive Summary

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Objective: In the 19 years since the Korean College of Neuropsychopharmacology and the Korean Society for Affective Disorders developed the Korean Medication Algorithm Project for Depressive Disorder (KMAP-DD) in 2002, four revisions have been conducted.
Methods: To increase survey efficiency in this revision, to cover the general clinical practice, and to compare the results with previous KMAP-DD series, the overall structure of the questionnaire was maintained. The six sections of the questionnaire were as follows: 1) pharmacological treatment strategies for major depressive disorder (MDD) with/without psychotic features; 2) pharmacological treatment strategies for persistent depressive disorder and other depressive disorder subtypes; 3) consensus for treatment-resistant depression; 4) the choice of an antidepressant in the context of safety, adverse effects, and comorbid physical illnesses; 5) treatment strategies for special populations (children/adolescents, elderly, and women); and 6) non-pharmacological biological therapies. Recommended first-, second-, and third-line strategies were derived statistically.
Results: There has been little change in the four years since KMAP-DD 2017 due to the lack of newly introduced drug or treatment strategies. However, shortened waiting time between the initial and subsequent treatments, increased preference for atypical antipsychotics (AAPs), especially aripiprazole, and combination strategies with AAPs yield an active and somewhat aggressive treatment trend in Korea.
Conclusion: We expect KMAP-DD to provide clinicians with useful information about the specific strategies and medications appropriate for treating patients with MDD by bridging the gap between clinical real practice and the evidence-based world.

KEY WORDS: Algorithm; Depressive disorder; Guideline; Pharmacotherapy.

INTRODUCTION

Nineteen years have passed since the first Korean Medication Algorithm Project for Depressive Disorder (KMAP-DD), the expert's consensus guideline with clinical evidence on the treatment of depressive disorder, was developed in 2002 [1]. Since then, three revisions have been conducted by the KMAP-DD executive committee within the Korean Society for Affective Disorders (KSAD) and the Korean College of Neuropsychopharmacology (KCNP): KMAP-DD 2006 [2], KMAP-DD 2012 [3], and KMAP-DD 2017 [4].

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Because depressive disorder is a heterogeneous disorder that has various symptoms, clinical courses, and outcomes, the KMAP-DD executive committee conducted a fourth revision in 2021 to assist clinicians with decisions on proper treatment strategies, to standardize the quality of pharmacological treatments as the definitive clinical guideline [5], and to reflect changes that have been made for several years in pharmacological practice in Korea.

We summarized the results of the fourth revision of Korean experts' opinions on the pharmacological treatment of patients with depressive disorder and compared the 4th revision results to those of the previous KMAP-DD, from 2017, 2012, and 2006; KMAP-DD 2002 was excluded due to questionnaire format and differences in the lists of antidepressants (ADs) and atypical antipsychotics (AAPs).

METHODS

The overall study design and method used in previous

Table 1. Comparison among the first (2006), second (2012), third (2017), and fourth (2021) revisions of the KMAP-DD

	First revision in 2006	Second revision in 2012	Third revision in 2017	Fourth revision in 2021
Depressive episode	Mild Moderate Non-psychotic severe Psychotic severe	Mild to moderate Non-psychotic severe Psychotic severe	Same as 2012	Same as 2017
AD dosage and duration of treatment	Present	Deletion	Change: duration of initial treatment and number of choosing AD as initial treatment	Same as 2017
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
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 Arrythmia Chronic pain (fibromyalgia, etc.)
Special population	Child only	Child and adolescent Elderly Women	Same as 2012	Child (up to primary school) Adolescent (up to high school) Elderly Women
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
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])

KMAP-DD, Korean Medication Algorithm for Depressive Disorder; AD, antidepressant; DBS, deep brain stimulation; DM, diabetes mellitus; ECT, electroconvulsive therapy; PDD, persistent depressive disorder; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VNS, vagal nerve stimulation.

revisions were maintained in this revision for the comparison across the KMAP-DD series. To obtain the experts' consensus, the executive committee composed a review committee, and the review committee completed the questionnaire (Table 1).

Review Committee

The composition criteria and qualifications of the review committee were similar to those of KMAP-DD 2012 and 2017. We recruited 143 Korean psychiatrists (97 adult psychiatrists and 46 child/adolescent psychiatrists) who were lifelong members of KCNP and KSAD, had more than 15 years of clinical experience in the field of psychiatry, and who had each published at least one paper related to mood disorders during the previous year or who have been running a mood clinic in their hospital. Psychiatrists for adult members worked in various clinical settings (university hospitals, n = 68; general and mental hospitals, n = 22; private psychiatric clinics, n = 7), and the child/adolescent psychiatrists worked in university hospitals (n = 29), general and mental hospitals (n = 6), and private psychiatric clinics (n = 11). All members of the review committee provided written informed consent for their participation in this survey. Of the 143 psychiatrists, 98 responded to our survey (response rate = 68.5%; adult = 67.0% [65/97], child/adolescent = 71.7% [33/46]). Respondents received a predetermined fee for their participation.

Questionnaire

The questionnaire included six sections and thirty three general questions, including 118 sub-items and 764 options. The six sections of the questionnaire were as follows: 1) pharmacological treatment strategies for mild-to-moderate, severe without psychotic features (non-psychotic severe episode), and severe episode with psychotic features (psychotic severe episode) (first to third step); 2) pharmacological treatment strategies for persistent depressive disorder (PDD) and depressive disorder subtypes; 3) consensus for treatment-resistant depression; 4) the choice of an antidepressant in the context of safety, adverse effects, and comorbid physical illnesses; 5) treatment strategies for special populations (children/adolescents, elderly, and women); and 6) non-pharmacological biological therapies (electroconvulsive therapy, ECT; repetitive transcranial magnetic stimulation, rTMS; etc.). The executive committee decided to exclude fluvoxamine due to lack of usage in Korea and include esketamine (nasal spray), a newer antidepressant approved for treatment-resistant depression (TRD) (Table 2). In this revision, the list of AAPs is the same as in 2017, including amisulpride, aripiprazole, blonanserin, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone.

Unlike previous surveys, children (primary school students and younger) and adolescents (middle and high school students) were investigated separately within the children/adolescents with depression group.

Rating Scale

The overall rating method was the same as before. Each treatment option was scored on a nine-point scale. Nine indicates extremely appropriate, 7–8 indicates usually

Table 2. Lists of drugs used in KMAP-DD 2021

Antidepressant	Agomelatine
	Bupropion
	Esketamine (nasal spray)[a]
	Mirtazapine
	SNRI (desvenlafaxine, duloxetine, milnacipran, venlafaxine)
	SSRI (escitalopram, fluoxetine, paroxetine, sertraline)[b]
	Tianeptine
	TCA (amitriptyline, clomipramine, imipramine, etc.)
	Vortioxetine[a]
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.
[a]Newly included in AD lists in this survey. [b]Fluvoxamine was deleted in AD lists.

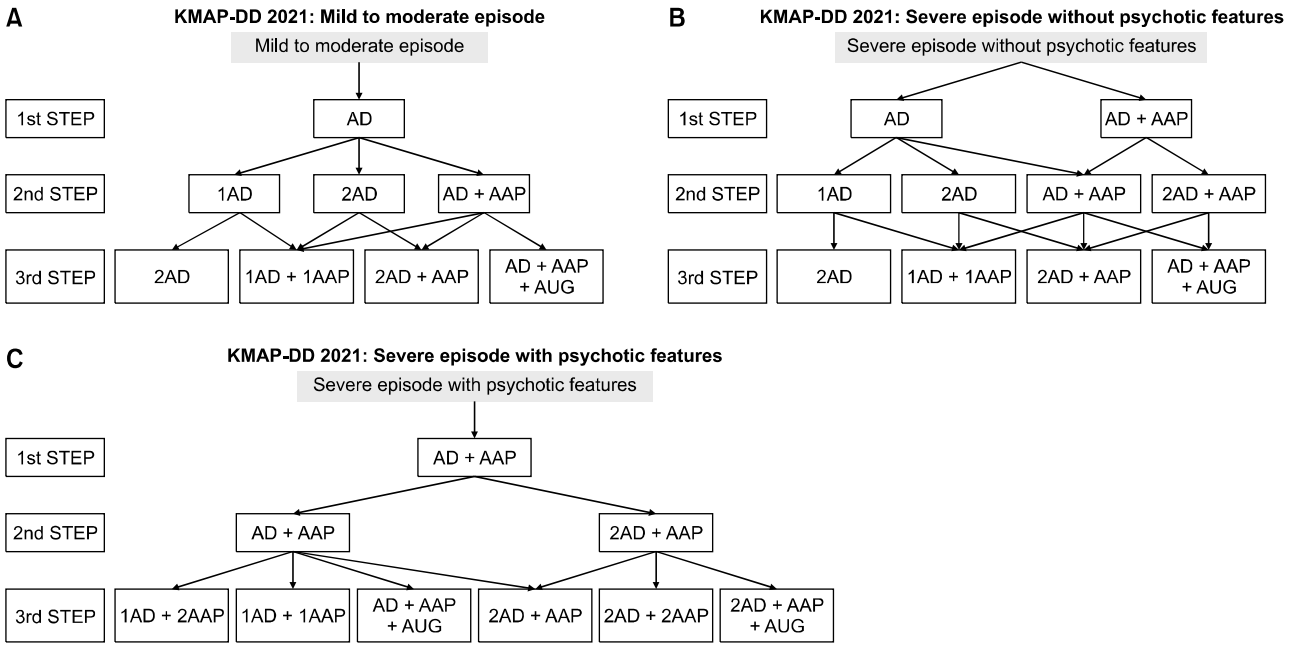

Fig. 1. The Korean Medication Algorithm for Depressive Disorder 2021.
KMAP-DD, Korean Medication Algorithm for Depressive Disorder; AD, antidepressants; AAP, atypical antipsychotics; AUG, augmenting agents.

appropriate, 4−6 indicates ambivalence about its appropriateness, 2−3 indicates usually inappropriate (a treatment the clinician would rarely use), and 1 indicates extremely inappropriate (a treatment the clinician would never use). Some questions had a numeric response instead of a rating. For example, "How long do you wait before switching ongoing AD or AAP?"

Data Analysis and Decision of Preference and Categories

Means and 95% confidence intervals (CI) of each question or option were calculated. We divided them into three categories according to the lowest score of 95% CI: first-line/preferred treatment, ≥ 6.5; second-line/reasonable treatment, < 6.5 and ≥ 3.5; and third-line/inappropriate treatment, < 3.5. Treatment of choice (TOC) was defined as an option that was rated at 9 points by 50% or more of the experts.

A chi-square test was used to confirm the presence or absence of consensus on each option/question. No significant difference between categories indicated lack of consensus.

The SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA) was used for the analyses of preference rankings and multiple responses.

Development of Treatment Guidelines and Algorithms

After the advisory committee and the executive committee discussed these results and reviewed the clinical evidence, considering Korean clinical situations, the executive committee drew up the fourth revised KMAP-DD algorithms (Fig. 1) and distributed KMAP-DD 2021 to psychiatrists and related experts in Korea.

Ethics

The present study was conducted according to the Declaration of Helsinki. The study protocol was approved by the Institutional Review or Ethics Committee at Wonkwang University (approved number: WKUH 2020-12-012). The revision process was funded entirely by KCNP and KSAD without external financial support.

RESULTS

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

Initial step strategies for depressive episode

For mild-to-moderate depressive episodes, AD monotherapy (95% CI 8.47−8.84) was recommended as the TOC. For non-psychotic severe episodes, AD mono-

Table 3. Initial and next step strategies for depressive disorder between the KMAP-DD 2021, 2017, 2012, and 2006

		KMAP-DD 2021		KMAP-DD 2017		KMAP-DD 2012		KMAP-DD 2006	
		1st line	2nd line	1st line	2nd line	1st line	2nd line	1st line	2nd line
Initial step treatment strategy									
Depressive episode									
Mild to moderate		AD monotherapy[a]	AD + AD AD + AAP[b]	AD monotherapy[a]	AD + AD AD + AAP AD + MS	AD monotherapy[a]	AD + AD AD + AAP	AD monotherapy[a]	AD + AD AD + AUG
Non-psychotic severe		AD monotherapy AD + AAP	AD + AD AD + MS AAP monotherapy	AD monotherapy AD + AAP	AAP monotherapy AD + AD AD + MS ECT	AD monotherapy	AD + AAP AAP monotherapy AD + AD ECT	AD monotherapy	AD + AD AD + AAP AD + AUG
Psychotic severe		AD + AAP[a]	AAP monotherapy AD + MS AD + AD[b] AD monotherapy[b]	AD + AAP[a]	ECT AAP monotherapy AD + TAP AD + MS AD monotherapy AD + AD	AD + AAP[a]	AD + TAP AAP monotherapy ECT AD + AD AD monotherapy	AD + AAP[a]	AD + TAP ECT AD + AD AD + AUG AD monotherapy AAP monotherapy
2nd step treatment strategies									
Mild to moderate	No response	Adding AAP Switching AD Adding AD	Adding AUG	Switching AD Adding AD Adding AAP	Adding AUG	Switching AD Adding other AD	Adding AAP AUG	Switching AD Adding other AD	Adding AUG Adding AAP
Non-psychotic severe	Partial response	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Adding AD Adding AAP	Switching AD AUG	Adding other AD Adding AAP	AUG Switching AD	Adding other AD AUG	Switching AD Adding AAP
Psychotic severe	Inadequate response	Adding AD Switching AAP	Adding AAP Switching AD Adding AUG	Switching AAP Adding AD Switching AD	Adding AAP AUG Adding TAP	Adding other AD Switching AAP Switching AD	Adding other AAP AUG Adding TAP	Adding AAP Switching AD Adding other AD	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.
[a]Treatment of choice (TOC), defined as an option that was rated at 9 points by 50% or more of the experts. [b]No consensus.

therapy and AD + AAP were the preferred first-line strategies (Table 4). For psychotic severe episodes, the AD + AAP combination was the TOC in all four KMAP-DD revisions.

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

When the patient is unresponsive to the initial AD monotherapy, adding AD or AAP and switching AD were preferred. With a partial response rather than 'no response' to AD monotherapy, adding AD or AAP was preferred. When unresponsive to the initial AD + AAP combination, switching AAP or AD and adding AD were preferred. With partial response to the initial AD + AAP, adding AD and switching AAP were preferred.

In general, changing ADs occurred among SSRIs, SNRIs, and mirtazapine, and adding ADs occurred among SSRIs, SNRIs, mirtazapine, bupropion, agomelatine, and vortioxetine, depending on the drug being used. Changing or adding AAPs occurred among aripiprazole, quetiapine, and olanzapine in the same way.

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

When there is inadequate response to the second-step treatment, adding another AAP or AD or changing AAP or AD were recommended. Adding augmentation drugs, such as buspirone, mood stabilizer, psychostimulant, and thyroid hormone, was preferred when there was an inadequate response to adding AAP to AD monotherapy for non-psychotic depression 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 psychotic depression.

AD Choices

Preferred AD for initial treatment

For mild-to-moderate depressive episodes, escitalopram (95% CI 8.3−8.7) was the TOC, and sertraline, desvenlafaxine, fluoxetine, venlafaxine, vortioxetine, duloxetine, mirtazapine, and paroxetine were recommended as first-line ADs. For non-psychotic severe episodes, escitalopram (95% CI 8.1−8.5) was the TOC, and desvenlafaxine, venlafaxine, sertraline, mirtazapine, fluoxetine, duloxetine, paroxetine, and vortioxetine were the first-line ADs. For psychotic severe episodes, escitalopram (95% CI 8.1−8.5) was the TOC, and venlafaxine, desvenlafaxine, sertraline, mirtazapine, fluoxetine, paroxetine, and duloxetine were recommended as the first-line ADs.

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

We asked the experts to choose three ADs when con-

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

Preference of atypical antipsychotics	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	
Amisulpride	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	7.6 (7.2−8.0)[a]	8.4 (8.2−8.6)[a,b]	8.3 (8.2−8.5)[a,b]	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	3.9 (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	2.6 (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	5.2 (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	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 (6.4−7.8)	8.0 (7.7−8.2)[a]	7.8 (7.6−8.0)[a]	7.9 (7.7−8.1)[a]	7.7 (7.4−8.0)[a]	8.1 (7.8−8.3)[a]	7.3 (6.9−7.7)[a]
Risperidone	4.7 (4.2−5.2)	6.8 (6.4−7.2)	5.3 (4.8−5.7)	6.7 (6.3−7.1)	6.0 (5.5−6.4)	7.3 (6.9−7.6)[a]	7.3 (6.9−7.7)[a]
Ziprasidone	4.3 (3.9−4.8)	5.7 (5.3−6.1)	5.1 (4.6−5.6)	5.9 (5.6−6.3)	5.7 (5.2−6.3)	6.5 (6.1−6.9)	6.5 (6.0−6.9)
Typical antipsychotics	2.3 (1.9−2.7)	3.4 (2.9−3.9)	2.9 (2.5−3.3)	4.0 (3.4−4.3)	3.2 (2.8−3.6)	4.5 (4.0−5.0)	4.8 (4.3−5.3)

Values are presented as mean (95% confidence interval).
[a]First-line drug:score of preference is 9 points. [b]Treatment of choice (TOC), defined as an option that was rated at 9 points by 50% or more of the experts. [c]No consensus.

sidering adverse effects, drug safety, and comorbid physical illness, respectively. 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, escitalopram, sertraline, 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.

AAP Choices

For non-psychotic severe episodes, aripiprazole was only first-line AAP, and quetiapine, olanzapine with no consensus, risperidone, ziprasidone, and amisulpride were recommended as second-line. However, for psychotic severe episodes, aripiprazole was the TOC, and quetiapine and olanzapine were recommended as first-line AAPs (Table 4).

Treatment Duration with Initial AD before Next Strategy

The reviewers were asked, "How long do you keep using the initial drug until the next strategic change, such as switching or adding, due to lack of efficacy?" With AD monotherapy for mild-to-moderate depressive episodes, their answer was a minimum 2.2 ± 0.9 − maximum 6.1 ± 2.3 weeks (no response: 2.2 − 4.3 weeks; partial response: 3.3 − 6.1 weeks). With AD monotherapy for non-psychotic severe episodes, the answer was 1.9 ± 0.8 − 5.2 ± 2.2 weeks (no response: 2.2 − 4.3 weeks; partial response: 2.9 − 5.2 weeks). With AD monotherapy for psychotic severe episodes, their answer was a minimum 1.7 ± 0.8 − maximum 4.8 ± 2.3 weeks (no response: 1.7 − 3.3 weeks; partial response: 2.6 − 4.8 weeks).

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

Treatment strategies for PDD

AD monotherapy with escitalopram was the TOC for PDD. AD + AAP, AD + AD, AD + mood stabilizer (MS), and AAP monotherapy were recommended as second-line strategies.

AD choice according to subtype of depressive episode

For patients with melancholic features, escitalopram was the TOC and desvenlafaxine, venlafaxine, sertraline, fluoxetine, duloxetine, mirtazapine, paroxetine, vortioxetine, and milnacipran were the first-line ADs. Agomelatine, bupropion, tianeptine, TCA, and esketamine (with no consensus) were second-line ADs.

For atypical features, escitalopram, desvenlafaxine, fluoxetine, sertraline, venlafaxine, duloxetine, vortioxetine, bupropion, paroxetine, milnacipran, and agomelatine were the first-line ADs. Mirtazapine, tianeptine, esketamine, and TCA were second-line ADs.

For seasonal patterns, escitalopram, sertraline, fluoxetine, desvenlafaxine, venlafaxine, duloxetine, paroxetine, vortioxetine, bupropion, and mirtazapine were the first-line ADs. Agomelatine, milnacipran, tianeptine, TCA, and esketamine (with no consensus) were second-line ADs.

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

For anxious distress, an AD + AAP combination or AD monotherapy were the initial treatment strategies. AD + AD, AD + MS, and AAP monotherapy were recommended as the second-line strategies. As an initial AD, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, desvenlafaxine, mirtazapine, and vortioxetine were preferred. Aripiprazole, olanzapine, and quetiapine were the first-line AAPs for anxious distress.

For mixed features, AD + AAP or AD + MS were the

Table 5. Initial treatment strategies and drugs of choice for anxious distress or mixed features in KMAP-DD 2017 and 2021

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

Definition for treatment resistant depression	Respondent
Failure to respond to two AD treatments of separate pharmacological AD class	13 (20.6)
Failure to respond to three AD treatments of separate pharmacological AD class	6 (9.5)
Failure to respond to two AD combination treatment	1 (1.6)
Failure to respond to two AD + one AAP combination treatment of pharmacological AD classes	28 (44.4)
Failure to respond to two AD + two AAP combination treatment	12 (19.0)
ECT should be considered for no longer responsive to medications.	2 (3.2)
Others	1 (1.6)
Total	62 (100)

Values are presented as number (%).
KMAP-DD, Korean Medication Algorithm for Depressive Disorder; AAP, atypical antipsychotic; AD, antidepressant; ECT, electroconvulsive therapy.

first-line strategies, and AAP, MS, or AD monotherapy were recommended as second-line strategies. As preferred ADs, escitalopram, sertraline, fluoxetine, bupropion, mirtazapine, desvenlafaxine, venlafaxine, and paroxetine were recommended, and as AAPs and MSs, aripiprazole, quetiapine, olanzapine, valproate, and lithium were recommended.

Criteria for TRD Chosen by Experts

Experts were asked about the proper criteria for TRD. The largest number of experts (44.4%) chose the criteria for TRD as "Failure to respond to two ADs + one AAP combination treatment". "Failure to respond to two AD treatments of separate pharmacological AD classes" was the second most answered (20.6%). "Failure to respond to two ADs + two AAPs combination treatment (19.0%)" and "Failure to respond to three AD treatments of separate pharmacological AD classes (9.5%)" were in the third and fourth place, respectively. As fifth place, "ECT should be considered for no longer responsive to medications" (3.2%), and surprisingly, "Failure to response to a two-AD combination treatment" (1.6%) was the least preferred (Table 6).

Treatment Strategies for Special Populations (Table 7)

Depressive disorder in children or adolescents

For more detailed results, the fourth revision separately surveyed the children (elementary school students) and adolescents (middle and high school students). There is no first-line treatment for disruptive mood dysregulation disorder (DMDD). AAP, or AD monotherapy, and AD + AAP were recommended as second-line treatment. Escitalopram and fluoxetine were the first-line ADs, aripiprazole was the TOC, and risperidone and valproate were the first-line AAP and MS, respectively. AD monotherapy was the TOC for mild-to-moderate episodes in children and the first-line treatment strategy for mild-to-moderate episodes in adolescents. AD monotherapy and AD + AAP were the first-line strategies for children and adolescents with non-psychotic severe episodes. AD + AAP were the TOC for children and adolescents with psychotic severe episodes.

As first-line AD, escitalopram and fluoxetine for children, and escitalopram, fluoxetine, and sertraline for adolescents with mild-to-moderate depressive episodes were preferred. For children and adolescents with psychotic or non-psychotic severe episodes, escitalopram, fluoxetine, and sertraline were preferred. Among AAPs, aripiprazole was the TOC for children and adolescents with psychotic severe episodes, and risperidone and quetiapine were the first-line treatment preferences for children with psychotic severe episodes.

Elderly patients with MDD

AD monotherapy was the TOC for elderly patients with mild-to-moderate depressive episodes. AD monotherapy and AD + AAP were the first-line strategies for non-psychotic severe episodes, whereas AD + AAP were the TOC for psychotic severe episodes. Moreover, escitalopram was the TOC for all three types of episodes. Aripiprazole as the TOC and quetiapine as the first-line AAP were recommended for psychotic severe episodes.

Women with depressive disorder

AD monotherapy was the first-line treatment strategy

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	1st line	2nd line	1st line	2nd line
Child and adolescent	Disruptive mood dysregulation disorder		-	AAP monotherapy AD + AAP AD monotherapy MS + AAP[b] MS monotherapy MS + AD[b]	Escitalopram Fluoxetine	Sertraline Bupropion Duloxetine	Aripiprazole[a] Risperidone Valproate	Quetiapine Paliperidone Amisulpride Olanzapine[b]
	MDD	Mild-to-moderate episode, child	AD monotherapy[a]	AD + AAP AAP monotherapy AD + AD AD + MS[b]	Escitalopram Fluoxetine	Sertraline Bupropion Duloxetine Paroxetine[b]		
		Mild to moderate episode, adolescent	AD monotherapy	AD + AAP AAP monotherapy AD + MS AD + AD[b]	Escitalopram[a] Fluoxetine Sertraline	Venlafaxine Duloxetine[b] Bupropion[b] Paroxetine[b] Desvenlafaxine[b] Agomelatine[b] Vortioxetine[b] Mirtazapine[b]		
		Non-psychotic severe episode, child	AD monotherapy AD + AAP	AD + AD AD + MS AAP monotherapy[b]	Escitalopram[a] Fluoxetine Sertraline	Bupropion Paroxetine[b] Duloxetine[b] Venlafaxine Desvenlafaxine[b]		Aripiprazole Quetiapineb Risperidone[b]
		Non-psychotic severe episode, adolescent	AD monotherapy AD + AAP	AAP monotherapy AD + MS AD + AD[b]	Fluoxetine[a] Escitalopram[a] Sertraline	Bupropion Paroxetine[b] Venlafaxine Duloxetine[b] Desvenlafaxine[b] Agomelatine[b] Vortioxetine[b]		Aripiprazole Quetiapine[b] Risperidone[b]
		Psychotic severe episode, child	AD + AAP[a]	AAP monotherapy AD + MS AD monotherapy[b] AD + AD[b]	Escitalopram fluoxetine Sertraline	Bupropion Mirtazapine Paroxetine[b] Venlafaxine[b] Desvenlafaxine[b] Duloxetine[b]	Aripiprazole[a] Risperidone Quetiapine	Amisulpride Olanzapine[b] Paliperidone[b]
		Psychotic severe episode, adolescent	AD + AAP[a]	AAP monotherapy AD + MS AD monotherapy[b] AD + AD[b]	Escitalopram[a] Fluoxetine Sertraline	Paroxetine[b] Venlafaxine Duloxetine[b] Bupropion[b] Desvenlafaxine[b] Vortioxetine[b] Mirtazapine[b]	Aripiprazole[a] Risperidone	Quetiapine Amisulpride Olanzapine[b] Paliperidone[b]

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 AD + AD AAP monotherapy AD + MS AD + STM	Escitalopram[a] Sertraline Desvenlafaxine Vortioxetine Duloxetine Venlafaxine Fluoxetine Mirtazapine Milnacipran	Paroxetine Agomelatine Bupropion Tianeptine		
		Non-psychotic severe episode	AD monotherapy AD+AAP	AD + AD AD + MS AAP monotherapy AD + STM	Escitalopram[a] Sertraline Desvenlafaxine Duloxetine Mirtazapine Vortioxetine Venlafaxine Fluoxetine Milnacipran Paroxetine	Agomelatine Bupropion Tianeptine Esketamine (nasal spray)[b] TCAs		
		Psychotic severe episode	AD + AAP[a]	AD monotherapy AD + MS AD + AD AD + STM AAP monotherapy[b]	Escitalopram[a] Sertraline Desvenlafaxine Duloxetine Mirtazapine Venlafaxine Vortioxetine Fluoxetine Milnacipran Paroxetine	Agomelatine Bupropion Tianeptine Esketamine (nasal spray)[b] TCAs	Aripiprazolea Quetiapine	Olanzapine Risperidone Paliperidone Blonanserin Amisulpride Ziprasidone

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
Women	Premenstrual dysphoric disorder		AD monotherapy[a]		Fluoxetine Escitalopram Sertraline Paroxetine Desvenlafaxine Venlafaxine	Duloxetine Vortioxetine Milnacipran Mirtazapine Agomelatine Bupropion Tianeptine TCA		
	MDD in pregnancy	Mild to moderate episode	AD monotherapy	AAP monotherapy AD + AAP[b] ECT[b]				
		Non-psychotic severe episode	AD monotherapy	AD + AAP AAP monotherapy ECT				
		Psychotic severe episode	ECT AD + AAP	AAP monotherapy AD monotherapy AAP + MS				
	Postpartum depression	Mild to moderate episode	AD monotherapy AD + AAP	AAP monotherapy AD + MS MS monotherapy MS + AAP[b] ECT[b]				
		Non-psychotic severe episode	AD + AAP	AD monotherapy AAP monotherapy AD + MS MS monotherapy AAP + MS ECT				
		Psychotic severe episode	AD + AAP[a]	AD monotherapy AAP monotherapy AD + MS MS monotherapy AAP + MS ECT				

AAP, atypical antipsychotics; AD, antidepressant; ECT, electroconvulsive therapy; MDD, major depressive disorder; MS, mood stabilizer; STM, psychostimulant; TAP, typical antipsychotics; TCA, tricyclic antidepressant.

[a]Treatment of choice (TOC), defined as an option that was rated at 9 points by 50% or more of the experts. [b]No consensus.

for premenstrual dysphoric disorder (PMDD). Fluoxetine, escitalopram, sertraline, paroxetine, desvenlafaxine, and venlafaxine were first-line ADs for PMDD. For MDD in pregnant women, AD monotherapy was recommended as the first-line treatment for mild-to-moderate and non-psychotic severe depression. However, AD + AAP and ECT were recommended for psychotic severe depression. For postpartum depression, AD monotherapy and AD + AAP were the first-line strategies for mild-to-moderate episodes, and AD + AAP were recommended as the first-line treatment for non-psychotic severe episodes. For psychotic severe episodes, AD + AAP were the recommended TOC.

Non-pharmacological Biological Treatment

Electroconvulsive therapy (ECT)

Ninety-two percent of experts considered ECT to be an MDD treatment modality, and 43.8% of experts were applying it for MDD in clinical practice. On average, one expert conducts ECT with 7.0 persons per year, with 2.8 sessions per patient per week, totaling 10.5 sessions per patient during one treatment plan. The first-line indications for ECT were urgent suicidal risks in patients regardless of psychotic features and nonresponsiveness on pharmacotherapy with moderate episodes or severe episodes in pregnant patients.

Indications for repetitive transcranial magnetic stimulation (rTMS)

Eighty-nine percent of experts considered rTMS an MDD treatment option, but only 40.6% apply it in clinical practice for MDD. On average, one expert conducts rTMS with 12.6 persons per year, with 3.4 sessions per patient per week, totaling 12.6 sessions per patient during one treatment plan. In Korea, MDD in pregnant patients was the first-line indication for rTMS.

Choice of complementary or novel agents

Transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS), deep brain stimulation (BDS), light therapy, and omega-3 were considered as second-line treatment options for MDD.

DISCUSSION

Compared to KMAP-DD 2017, there are no significant changes in KMAP-DD 2021. However, we confirmed the increased preference of AAPs in various depressive conditions and the criteria for TRD that was first investigated in this revision and compared these results with previous versions of KMAP and foreign guidelines for depressive disorder [5-7].

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 2017, 2012, and 2006. Also, AAP + AD combination as the first-line strategy for non-psychotic or psychotic severe depressive episodes was the same recommendation as in KMAP-DD 2017, while AD monotherapy was the only first-line strategy for non-psychotic severe episodes in KMAP-DD 2012, which implicated the increased preference of AAPs in Korea.

Foreign clinical guidelines recommended AD monotherapy instead of AD + AAP combination as the first-line strategy for non-psychotic severe episodes on the bases of a benefit-harm comparison about initially using AAP for depression [5-8] and lack of evidence that AAP as an initial treatment strategy for depression is superior to AD monotherapy [5].

However, given that the response rate of initial AD monotherapy was 40−60% [9,10], the remission rate of initial AD monotherapy was 20−30% [11,12], and that a recent meta-analysis showed that the AD + AAP combination is superior to AD monotherapy (response rate, odds ratio [OR] = 1.69, 95% CI = 1.46−1.95, $p < 0.00001$; remission rates, OR = 2.00, 95% CI = 1.69−2.37, $p < 0.00001$) [13], AD + AAP combination could also be a good choice as the first-line strategy for non-psychotic or psychotic severe depressive episodes.

The AD + AAP combination was recommended as the TOC for psychotic depression in KMAP-DD 2006, 2012, 2017, and 2021. Canadian Network for Mood and Anxiety Treatments (CANMAT) recommended AD + AAP for psychotic depression based on the finding that an

AD + AAP combination was superior to placebo 2 randomized controlled trials (RCTs), AD monotherapy (3 RCTs), and AAP monotherapy (4 RCTs) [5].

Next step: Second and third steps

As the next step after inadequate response to initial treatment, we should consider adding (combination or augmentation) or switching, after reevaluating the factors for the lack of response, such as inadequate dose, inadequate duration, and adherence. As the second step after an inadequate response to initial treatment, adding AD or AAP with a partial response and switching ongoing AD or AAP with no response to initial treatment is the same recommendation as in KMAP previous series and CANMAT 2016 [5]. Based on the most consistent evidence for efficacy of AAP in TRD, CANMAT recommended aripiprazole, quetiapine, and risperidone as adjunctive therapy with level I evidence [5].

AD Choice

Preferred AD as initial treatment

For mild-to-moderate episodes, escitalopram was the only TOC in 2021, while escitalopram and sertraline were the TOCs in 2017. Escitalopram was the TOC for psychotic and non-psychotic severe depressive episodes in 2021 as well as in 2017 in contrast with the KMAP-DD 2012, in which there was no TOC among the ADs.

Although no single AD has proven to be more effective than others [6], 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 antidepressants (range of ORs 1.19−1.96) [14]. Like these results, the preference of escitalopram for all severities of depressive episodes is the highest in Korea for more than 9 years.

The preference of vortioxetine, newly included in KMAP-DD 2021, for psychotic depression was as a second-line treatment in 2021. CANMAT 2016 recommended vortioxetine and agomelatine as well as SSRIs, SNRIs, bupropion, and mirtazapine as first-line [5]. But the preference of vortioxetine for psychotic depression was second-line in 2021. Also, the preference of agomelatine in Korea was second-line in KMAP-DD 2021 following 2017. This result reflects the Korean situation that agomelatine was first withdrawn in Korea in 2017 due to medical insurance issues with Korean government and then re-marketed in 2019. The preference of agomelatine has recently been increasing.

Esketamine (nasal spray), new and not yet widely used in Korea, was recommended as the second-line for non-psychotic or psychotic severe episodes, which suggests higher expectations for this drug as an emergent drug as well as an AD by Korean experts. The US Food and Drug Administration (FDA) approved esketamine (nasal spray) for TRD [15,16]. A recent meta-analysis including 8 double-blinded, randomized controlled trials and 1,488 patients showed that esketamine significantly improved the Montgomery Asberg depression rating scale (MADRS) total score compared to placebo starting from 2−4 hours after the first administration (standardized mean difference, −0.41 [95% CI = −0.58 to −0.25], $p < 0.00001$) [17], and this superiority was maintained until the end of the double-blinded period (28 days). Esketamine (nasal spray) has indication for suicidal ideation as well as TRD in Korea.

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

Due to a lack of evidence regarding this section, we mainly compare these results with previous KMAP-DD series. These results are almost the same in 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 and 2) mirtazapine for insomnia, GI trouble, and suicidal ideation.

A recent systemic review regarding AD and weight gain showed that SSRIs including fluoxetine increase mean weight while bupropion decreases the mean weight [18]. Most experts in Korea would have the same clinical experience.

The clear mechanism for orthostatic hypotension in the elderly is unknown but due to its commonality [19], it can be assumed that bupropion was recommended as the first-line to take into consideration both orthostatic hypotension and anticholinergic side effects. However, CANMAT 2016 found patients taking bupropion-XL had more headache and dry mouth, by as much as 28% and 34%, respectively, compared to other ADs. Therefore, careful

prescription of bupropion is needed due to headache and dry mouth [5].

For suicidality, SSRIs are related to nearly twice the risk (OR 1.92) of suicide and suicidal attempts among adolescents in observational studies [20]. The US FDA warned that all antidepressants are related with an increase in suicidality among children and adolescents, including young adults (18－24 years), during initial treatment [21].

During the investigation period of KMAP-DD 2021, esketamine had only been approved for TRD in Korea. As a result, Korean experts recommended mirtazapine rather than esketamine when considering suicidality. However, a recent meta-analysis as described above showed that esketamine had superiority over placebo in TRD and suicidal ideation (OR = 2.04, 95% CI = 1.37－3.05), but the groups did not statistically differ at 24 hours and day 28 [17]. With careful monitoring and assessment for suicidality at the beginning of AD treatment, particularly in children, adolescents, and young adults, esketamine is promising to protect against suicide.

When considering comorbid physical illness, escitalopram and sertraline were recommended as first- or second-line drugs for comorbidities of DM, thyroid disease, liver disease, renal disease, hypertension, seizure disorder, cardiovascular disease, cerebrovascular disease, parkinsonism, and arrhythmia. When choosing the initial AD, after all, it is reasonable to select drugs by considering various factors including socioeconomic condition, safety issues, clinical experience, and comorbid physical conditions, as well as efficacy at the same time.

AAP Choices

For 15 years, there was a high preference of aripiprazole for non-psychotic severe episodes and aripiprazole, quetiapine, and olanzapine for psychotic severe episodes (Table 4). With level I evidence, foreign guidelines recommended aripiprazole, quetiapine, olanzapine, brexpiprazole, and lurasidone as adjunctive, not as AAP monotherapy [5,6]. That is, Korean experts recommend AAP as a first step, but foreign guidelines recommend AAP as the second step. Brexpiprazole and lurasidone are currently not available in Korea.

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

We observed a shorter waiting duration between the initial and next-step treatment strategies, 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), and 2.2－4.3 weeks (2021). With no response to the initial treatment for severe psychotic episodes, waiting durations were 2.4－4.7 weeks (2012), 2.3－4.7 weeks (2017), and 1.7－3.3 weeks (2021). With a partial response to initial treatment for psychotic severe episodes, waiting durations were 3.4－6.9 weeks (2012), 3.4－6.5 weeks (2017), and 2.6－4.8 weeks (2021).

We observed a trend of shorter durations when there was no response than when there was a partial response to initial drugs, as was seen in previous KMAP series. This trend can also be seen in foreign guidelines. World Federation of Societies of Biological Psychiatry (WSFBP) 2017 [6] recommended that optimization be considered with an inadequate response to AD therapy for 2 weeks. In addition, CANMAT 2016 introduced 'early improvement', defined as > 20－30% reduction from baseline on a depression rating scale after 2－4 weeks, as a predictor for later outcomes and prognoses and recommended increasing AD dosage or switching AD when intolerable at 2－4 weeks [5].

Treatment Strategies for Persistent Depressive Disorder (dysthymia) and Strategies Specific to Subtype or Specifiers such as Mixed or Anxious Distress

Treatment strategies for PDD

The recommendation for AD monotherapy as the initial strategy was the same as that of KMAP-DD 2021, 2017, 2012, and 2006. 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

Little information about the most effective agents for the melancholic and atypical subtypes is available [22]. Compared to the result of escitalopram and venlafaxine being TOCs in 2017, only escitalopram was the TOC in 2021. The preference of desvenlafaxine increased in 2021 compared to 2017. Recent Australian and New

Zealand guidelines for major depression recommended venlafaxine and amitriptyline for melancholic types [22].

Atypical features and seasonal patterns

Mirtazapine was downgraded to a second-line treatment in 2021 after being a first-line treatment in 2017, which may reflect the selection of less sedative ADs considering atypical symptoms, such as hypersomnia and psychomotor retardation. Agomelatine was recommended as second-line in 2017 but was promoted to first-line in 2021, which seems to have considered the stimulation effect via blocking 5-HT2C of agomelatine and effect of improving hypersomnia through adjusting the sleep cycle [23].

For seasonal patterns, the first-line ADs in 2021 were the same as those recommended in 2017. These results were presumed to be a choice considering the (hypo)manic switching of seasonal patterns that can be related to bipolarity [24]; bupropion XR was approved for depressive patients with seasonal patterns in the US [25].

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

Preferred initial strategies for "with anxious distress" were AD + AAP or AD monotherapy both in 2017 and 2021. First-line ADs in 2017 were the same in 2021, except escitalopram was the TOC and vortioxetine was newly included as a first-line AD in 2021. Quetiapine was the only recommended first-line AAP for 'with anxious distress' in 2017, but aripiprazole and olanzapine as well as quetiapine were the first-line AAPs in 2021. This showed that AAPs are not limited to psychosis or bipolar disorder but are also used for comorbid anxiety or agitation.

For mixed features, both KMAP-DD 2017 and 2021 had the same first-line strategies (AAP + AD and AD + MS). Aripiprazole, quetiapine, olanzapine, valproate, and lithium were recommended as the first-line augmenting medications for mixed features. These recommended medications were consistent with previous trials [26] and similar to those for mixed state of bipolar disorder [27]. Despite the controversies about the criteria for mixed features in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [28, 29], it is reasonable that mixed features in depressive episodes itself can be interpreted as bipolarity.

The Consensus on the Definition of TRD

There is no universal criteria or definition of TRD, but it is most commonly defined as at least two failures of AD monotherapy with adequate dose, for 6-9 weeks during a major depressive episode [30]. We expected a similar answer from Korean experts; however, contrary to our expectation, among 6 questions, 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 combination treatment" was chosen the least, by 1.6% of experts.

"Treatment-resistance" can be defined when the treatment response is outside the boundaries of standard therapy. Of course, AAP is not literally an AD; however, a few AAPs demonstrated antidepressant efficacy in clinical trials with TRD [5,6], and CANMAT 2016 recommended quetiapine as one of the second-line ADs. Therefore, it is necessary to extend the criteria of TRD to include AAPs [5]. These results also demonstrated the Korean trend of using AAPs in an earlier step in treating depression, with increased preference for AAPs.

Treatment Strategies for Special Populations (Table 7)

Because it is ethically difficult to conduct RCTs with special populations, such as children, pregnant subjects, and elderly subjects with depression, experts' consensus could be useful. However, experts' experience is not always right, as evidence is not always right. Special populations with depression should be carefully treated according to an advantage-disadvantage evaluation.

Treatment strategy for children and adolescents

Disruptive mood dysregulation disorder (DMDD)

This section has been included since KMAP-2012. In this revision, more detailed results could be obtained by distinguishing between children (5 to 12 years old) and adolescents (13 to 17 years old) in MDD, except for disruptive mood dysregulation disorder (DMDD).

The prevalence of DMDD, newly introduced in DSM-5, among children and adolescents has been as much as 2−5% [31,32]; however, there was no first-line strategy for DMDD in KMAP-DD 2021. Korean experts cautiously recommended AAP monotherapy, AD + AAP, and AD monotherapy as a second-line treatment. Given that two key symptoms are severe recurrent temper out-

bursts and persistent irritability observable by others, a higher preference for AAPs rather than ADs was reasonable, although DMDD is a type of depressive disorder.

Among AAPs, aripiprazole was the TOC for DMDD. Preference for risperidone was increased to a first-line drug in 2021 after being a second-line drug in 2017. These changes are consistent with results on tic disorder in Korea: aripiprazole was preferred over risperidone in terms of side effects [33], and results of the effects of AAP on DMDD demonstrated the efficacy of risperidone [31,32].

Considering the risks associated with valproate for pregnant women [34, 35], experts were asked to consider their choice of mood stabilizer differently between male and female patients. Valproate was the first-line treatment for DMDD in men but a second-line treatment for DMDD in women.

Children and adolescents with major depression

Similar to the recommendations of KMAP-DD 2017 and 2012, AD monotherapy was recommended as the TOC for mild-to-moderate episodes in children and the first-line strategy for mild-to-moderate episodes in adolescents. AD monotherapy and AD + AAP combination were the first-line strategies for non-psychotic severe depression in children and adolescents, and AD + AAP was the TOC for psychotic severe depression in children and adolescents, which was the same as in KMAP-DD 2017.

Aripiprazole was the TOC and risperidone and quetiapine were the first-line treatments for psychotic severe depression in children and adolescents in 2021, while aripiprazole and risperidone were the first-line treatments in 2017. However, AAPs were not included in the treatment strategy of CANMAT 2016 for child/adolescent depression [36].

Caution should be paid to AD use in children and adolescents, because ADs may be associated with increased risk of suicide in adolescents [36] and with (hypo)manic switching in young patients with bipolarity [37]. As the first-line AD for children and adolescents with MDD, escitalopram, fluoxetine, and sertraline were recommended. A recent Cochrane review of 19 trials with subjects aged 6–18 years (n = 3,335) showed that fluoxetine was significantly more effective than placebo, and sertraline was also significantly effective with a small effect size [38]. CANMAT 2016 recommended fluoxetine rather than escitalopram as the second step after initial cognitive-behavioral therapy (CBT) or interpersonal therapy (IPT) and internet-based psychotherapy [36], while the preference for escitalopram seems to be higher than that of fluoxetine in Korea. It can be seen as a result of considering the superior efficacy of escitalopram on improving children and adolescents' function and symptoms compared to placebo [38-40], its effect during maintenance treatment [41], and favorable safety issues including drug-drug interactions via CYP450 2D6, 3A4 [42].

By risk-benefit evaluation, psychosocial intervention was recommended as the first step for mild depressive episodes in children/adolescents, but for more severe episodes or when initial psychosocial intervention for mild depressive episodes failed in children and adolescent, pharmacotherapy could be recommended as the first step [36].

Treatment strategy for elderly adults

According to big data analysis from the Korea Health Insurance Review and Assessment Service (HIRA), the number of patients treated for depression increased from 588,000 in 2014 to 681,000 in 2017, and among the 684,690 patients treated in 2018, 40% (n = 275,684) of them were over the age of 60 [43]. Unlike typical middle-aged depression, memory loss, fatigue, loss of appetite, insomnia, and pain, rather than depressed mood, are more common in elderly depression [44].

The recommendations for the first-line treatment strategies for each severity of episode in 2021 were the same as those in 2017: AD monotherapy for mild-to-moderate depressive episodes as TOC, AD + AAP and AD monotherapy for non-psychotic severe depression, and an AD + AAP combination for psychotic severe episodes.

Compared to KMAP-DD 2017, the preference of aripiprazole increased from first-line to the TOC in 2021. Adjunctive aripiprazole with various ADs [45] and aripiprazole augmentation for treatment-resistant depression was found to be effective for elderly depression [46]. Considering diabetes, hypertension, metabolic syndrome, the anticholinergic effect, and somnolence, aripiprazole was more highly preferred than other AAPs [47].

Due to lack of evidence for escitalopram, CANMAT [36] recommended duloxetine, mirtazapine, and nortriptyline instead of escitalopram as first-line ADs with level I evidence, while escitalopram was considered to be

the preferred AD by many clinicians including the Korean experts [48,49].

Despite clinical limitations in treating elderly depression, it is clear that certain factors, such as comorbid physical illnesses, drug-drug interaction, and decreased metabolism due to the aging effect, should be considered in treating depression in the elderly.

Treatment strategy for women with premenstrual dysphoric disorder or postpartum depression

According to HIRA data survey, among the 681,000 depressed patients in Korea in 2017, there were 450,000 female patients, twice as many as the males [43]. As in KMAP-DD 2012 and 2017, AD monotherapy was recommended as the TOC for PMDD; in particular, escitalopram was the TOC for PMDD in 2017, while fluoxetine, escitalopram, sertraline, paroxetine, desvenlafaxine, and venlafaxine were the recommended first-line drugs. That is, the preference for SSRIs is higher than for other ADs in treating PMDD, which is consistent with foreign research [50-52].

In treating pregnant women, as with older people and children and adolescents, we should evaluate the benefit-risk ratio. CANMAT 2016 recommends escitalopram and sertraline after initially applying CBT and IPT for mild-to-moderate major depressive disorder during pregnancy with level I evidence, but recommends pharmacotherapy alone or combined with CBT or IPT for severe depression during pregnancy [36]. The fact that AD monotherapy was recommended for mild-to-moderate and non-psychotic severe episodes while ECT or AD + AAP was recommended for psychotic severe episodes, in KMAP-DD 2021 reflects a careful choice of treatment strategies as in CANMAT 2016.

Changes in the recommendations for postpartum depression were that AD monotherapy was the TOC for mild-to-moderate episodes in 2017, while AD + AAP as well as AD monotherapy were the first-line strategies in 2021. In addition, an AD + AAP combination was recommended as first-line for severe episodes with/without psychotic features as in the previous version. For postpartum depression, CANMAT 2016 also recommends CBT and IPT as first-line and escitalopram and sertraline as second-line [36].

Non-pharmacological Biological Therapy

ECT, rTMS

ECT for non-psychotic severe MDD with self-harm or suicidal risk regardless of psychotic features and TMS for pregnant women were recommended as first-line. Most Korean experts consider ECT (92% in 2021 vs. 92.4% in 2017) and rTMS (89% in 2021 vs. 86.0% in 2017) to be good treatment strategies in line with recent evidence [53,54]. Compared to 44.3% in 2017, 43.8% of experts conduct ECT in 2021, while compared to 31.6% in 2017, 40.6% in 2021 have used rTMS in real practice.

For the treatment of MDD, CANMAT 2016 recommended ECT as a second-line treatment, and rTMS for patients who have had failed treatment, based on efficacy, tolerability, and safety, with at least 1 AD as a first-line treatment [55]. As with previous revisions, the executive committee recommended that ECT could be applied whenever depressed patients have potential suicidality or attempt at self-harm.

Alternative biological therapies

In Korea, these alternative therapies are less popular than ECT or rTMS. As second-line treatment strategies, the frequencies of use in 2021 of light therapy, omega-3 nutritional therapy, and tDCS combined with initial pharmacotherapy, which are complementary or novel agents, were 17.2% (vs. 27.8% in 2017), 18.8% (vs. 22.8% in 2017), and 7.8%, respectively, which currently indicates a low utilization rate. CANMAT 2016 recommended light therapy alone as a first-line treatment for seasonal MDD and as a second-line treatment for non-seasonal, mild-to-moderate MDD [51]. Although tDCS is less effective for TRD, the onset of its effect was faster than AD monotherapy with equal efficacy [56], and when adjuvant with AD, its efficacy was superior to AD monotherapy [57], and it is a relatively safe, non-invasive modality that can improve cognition in MDD patients [58,59].

Summary: Advantages and Limitations of KMAP-DD 2021

A main limitation is the characteristics of the experts' consensus guidelines. As stated in another paper [3], experts' consensus and evidence-based guidelines are not contradictory, but complementary. To do this, the executive committee published final guidelines through the

process of drawing opinions from experts and reviewing the results with clinical evidence.

Second, the review committee may have been too small (n = 94) to reach a valid consensus and to select a TOC. However, given that there are only 3,800 psychiatrists in Korea and given that the total lifelong membership of the KSAD is only 258, a sample of 94 psychiatrists may be not insufficient. Finally, we did not explore psychosocial approaches, which should be addressed in a future study.

In summary, a shortened waiting time between the initial and subsequent treatments, increased preference for AAPs, especially aripiprazole, and combination strategies with AAPs yield an active and somewhat aggressive treatment trend in Korea. To our knowledge, the KMAP-DD series is the only experts' consensus guideline in the world that has been updated and revised at regular intervals since 2002. Reminding one of the principles of KMAP development that this guideline cannot go beyond the physicians' clinical decision, we expect KMAP-DD to provide clinicians with useful information about the specific strategies and medications appropriate for treating patients with MDD by bridging the gap between clinical real practice and evidence-based world.

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The present manuscript is a secondary publication of our group's papers, which were already published in the Korean language.

Though we have already published the papers in Korea, we decided to present and share the results with English-speaking experts according to the conditions for acceptable secondary publications as stated in Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

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