Review
https://doi.org/10.9758/cpn.2017.15.3.199
Clinical Psychopharmacology and Neuroscience 2017;15(3):199-209
pISSN 1738-1088 / eISSN 2093-4327

Korean Medication Algorithm for Depressive Disorder: Comparisons with Other Treatment Guidelines

Hee Ryung Wang[1], Won-Myong Bahk[1], Jeong Seok Seo[2], Young Sup Woo[1], Young-Min Park[3], Jong-Hyun Jeong[4], Won Kim[5,6], Se-Hoon Shim[7], Jung Goo Lee[8,9,10], Duk-In Jon[11], Kyung Joon Min[12]

[1]Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, [2]Department of Psychiatry, Konkuk University School of Medicine, Chungju, [3]Department of Psychiatry, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang, [4]Department of Psychiatry, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, [5]Department of Psychiatry, Inje University Seoul Paik Hospital, Inje University School of Medicine, Seoul, [6]Stress Research Institute, Inje University, Seoul, [7]Department of Psychiatry, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, [8]Department of Psychiatry, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, [9]Paik Institute for Clinical Research, Inje University, Busan, [10]Department of Health Science and Technology, Graduate School of Inje University, Busan, [11]Department of Psychiatry, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, [12]Department of Psychiatry, Chung-Ang University College of Medicine, Seoul, Korea

In this review, we compared recommendations from the Korean Medication Algorithm Project for Depressive Disorder 2017 (KMAP-DD 2017) to other global treatment guidelines for depression. Six global treatment guidelines were reviewed; among the six, 4 were evidence-based guidelines, 1 was an expert consensus-based guideline, and 1 was an amalgamation of both evidence and expert consensus-based recommendations. The recommendations in the KMAP-DD 2017 were generally similar to those in other global treatment guidelines, although there were some differences between the guidelines. The KMAP-DD 2017 appeared to reflect current changes in the psychopharmacology of depression quite well, like other recently published evidence-based guidelines. As an expert consensus-based guideline, the KMAP-DD 2017 had some limitations. However, considering there are situations in which clinical evidence cannot be drawn from planned clinical trials, the KMAP-DD 2017 may be helpful for Korean psychiatrists making decisions in the clinical settings by complementing previously published evidence-based guidelines.

KEY WORDS: Depressive disorder; Expert consensus; Guideline; KMAP-DD 2017; Therapy.

INTRODUCTION

Depression is a common psychiatric disorder characterized by frequent recurrence and is associated with morbidity and mortality.[1)] Since the introduction of first-generation antidepressants, such as monoamine oxidase inhibitors (MAOI), and tricyclic antidepressants (TCAs), pharmacotherapy including antidepressants, has been a mainstream treatment strategy for depression.[1)] During the past several decades, there has been great progress in the development of newer generation antidepressants possessing various modes of action and accumulated clinical experience in the use of pharmacotherapeutic agents for treating depression.[2-5)]

Despite this progress in the use of antidepressant medications, a significant portion of patients with depression experience an inadequate response to the standard antidepressant therapy.[6,7)] To overcome this challenge in the treatment of depression, there have been many clinical trials to investigate better treatment strategies for treatment-resistant individuals. In addition, there have been many studies investigating predictors of treatment outcomes, such as early treatment improvement,[8)] characteristics of the depressive episode,[9)] patient characteristics,[10,11)] and more. Clinicians should consider accumulated research findings when choosing a relevant treatment strategy in various clinical practice scenarios, which increases the need for the development of treatment guidelines. To date, many treatment guidelines for depres-

Received: November 29, 2016 / Revised: December 5, 2016
Accepted: December 6, 2016
Address for correspondence: Won-Myong Bahk, MD, PhD
Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10 63-ro, Yeongdeungpo-gu, Seoul 07345, Korea
Tel: +82-2-3779-1250, Fax: +82-2-780-6577
E-mail: wmbahk@catholic.ac.kr

sion have been published. The most commonly used guidelines are either evidence- or on consensus-based. Whichever guideline is used, it is important to consider various culture-specific characteristics of depression, patient-related factors and differences in clinical environments, such as health care policy and the prevailing medical insurance system. Thus, the development of treatment guidelines that consider specific cultural or practical issues in different countries is necessary. In Korea, to meet this clinical need, the Korean Medication Algorithm Project for Major Depressive Disorder (KMAP-MD 2002) was developed based on an expert consensus from Korean psychiatrists experienced in treating depression. After 6 years, the KMAP-MD 2002 was revised to the Korean Medication Algorithm Project for Depressive Disorder 2006 (KMAP-DD 2006) to reflect changes in the use of medication for treating depression during the intervening years.[12] A second revision was performed in 2012 and the Korean Algorithm Project for Depressive Disorder 2012 (KMAP-DD 2012) was released.[13] Since the KMAP-DD 2012 was published, there have been significant changes, such as the approval of newer antidepressants in Korea and new study results regarding pharmacotherapy for depression. Thus, we performed a third revision of the KMAP-DD 2012 guideline to create the Korean Medication Algorithm Project for Depressive Disorder 2017 (KMAP-DD 2017).

There have been various global major guidelines published for use in clinical practice, such as the National Institute for Health and Clinical Excellence Guideline on the Treatment of Depression (NICE),[14] the American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition (APA),[15] the Canadian Network for Mood and Anxiety Treatments Clinical Guidelines for the Management of Major Depressive Disorder in Adults (CANMAT),[16] and the World Federation Societies of Biological Psychiatry Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care (WFSBP).[17] When the KMAP-DD 2012 was published, we compared the recommendations of the KMAP-DD 2012 with those of several global guidelines to identify similarities and differences across all guidelines.[18] Since that time, several global guidelines also performed revisions to reflect new findings in the pharmacotherapy of depression.[16,17,19] Additionally, new guidelines, such as the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders, have been published.[20] Thus, we aimed to compare the recommendations of these updated global guidelines with those of the KMAP-DD 2017 to supplement any KMAP-DD 2017 weaknesses and to direct future revisions of the Korean Medication Algorithm Project.

TREATMENT GUIDELINES FOR COMPARISON

The American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition (APA)[15]

The American Psychiatric Association published an evidence-based guideline for depression in 1993. This first edition was revised into the Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Second Edition. In 2010, the second revision, the Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition was published.[15]

Canadian Network for Mood and Anxiety Treatments Clinical Guidelines for the Management of Major Depressive Disorder in Adults (CANMAT)[16]

The Canadian Network for Mood and Anxiety Treatments and the Canadian Psychiatric Association collaborated to publish evidence-based guidelines for depression in 2001. These guidelines were revised in 2009.[21] The most recent revised version was published in 2016.[16] The most current version of the guidelines is composed of six sections; one section specifies the guidelines for "Pharmacological Treatments"[16] and another includes guidelines for "Special populations: Youth, Women, and the Elderly."[22]

The National Institute for Health and Clinical Excellence Guideline on the Treatment of Depression (NICE)[14]

The National Institute for Health and Clinical Experience first published the NICE guideline in 2004, an evidence-based guideline drawn from a comprehensive literature review. The second edition was published in 2010.[14]

The Texas Medication Algorithm Project Procedural Manual: Major Depressive Disorder Algorithms (TMAP)[23]

The Texas Department of Mental Health and Mental Retardation and Texas University published an expert-consensus based guideline, the TMAP, in 1999. The second edition was revised and published in 2008.[23]

World Federation Societies of Biological Psychiatry Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care (WFSBP)[17,19]

The World Federation of Societies of Biological Psy-

chiatry published an evidence-based guideline, the WFSBP, in 2002. The second edition was revised and published in 2007.[24] After a systematic literature search to reflect new findings in pharmacotherapy, an updated version was published in 2013,[17] and again in 2015.[19] The 2013 update[17] involved guidelines on the acute and continuation treatment of depression, and the 2015 update concerned maintenance treatment for major depressive disorder.[19]

Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for Mood Disorders[20]

The Royal Australian and New Zealand College of Psychiatrists developed the Mood Disorders clinical practice guideline for clinical management of mood disorders, published in 2015.[20] This guideline encompasses both evidence-based and expert consensus-based recommendations (CBRs). When sufficient evidence exists, the Mood Disorder Committee formulates evidence-based recommendations according to the Australian National Health and Medical Research Council levels of evidence for intervention studies.[20] When there is little evidence for recommendations, the Mood Disorders Committee performed thorough discussion and came to an agreement, called CBR. The characteristics of the above-mentioned six treatment guidelines are summarized in Table 1.

DEVELOPMENT OF THE KMAP-DD 2017

The KMAP-DD 2017 is an expert consensus-based guideline. For the third revision of the Korean Medication Algorithm, the same revision framework used for the KMAP-DD 2012 was used. In the KMAP-DD 2017, the questionnaire is composed of many of the same questions asked in the KMAP-DD 2012, with some modifications. Question items regarding treatment strategies for newer subtypes of depression which newly appear in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; e.g., with mixed features, and with anxious distress), those for Disruptive Mood Dysregulation Disorder (DMDD), which also newly appear in the DSM-5, were added to reflect changes in treatment strategies after the DSM-5 was published. In addition, questions were added to the section on special populations (the elderly, women, children and adolescents). The survey consists of 51 questionnaires, and includes 8 parts. A nine-point scale from the RAND corporation[13] was applied to assess the adequacy of each treatment option. Each treatment option was classified into three categories based on the lower confidence interval: 6.5 or greater for first-line treatment, 3.5-6.5 for second-line, and lower than 3.5 for third-line. The first-line option that was scored as a "9" by at least 50% of the experts was termed a "treatment of choice (TOC)". More detailed information is available in the KMAP-DD 2017.[25]

COMPARISONS OF TREATMENT OPTIONS ACROSS TREATMENT GUIDELIENS

Initial Treatment for Depressive Disorder

In the KMAP-DD 2017, for a mild to moderate episode of nonpsychotic depression, antidepressant monotherapy was preferred as the TOC. For severe episodes without psychotic features, both antidepressant monotherapy and augmentation of an atypical antipsychotic agent with an antidepressant were preferred as the first-line treatment.

Table 1. Characteristics of global treatment guidelines for depressive disorder

Organization	Publication date	Audience	Methodology
Korean Medication Algorithm Project for Depressive Disorder 2017	2017	Psychiatrists	Expert consensus
American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition	2010	Psychiatrists Primary care physicians	Evidence-based
Canadian Network for Mood and Anxiety Treatments	2016	Psychiatrists	Evidence-based
National Institute for Health and Clinical Excellence	2009	Psychiatrists Primary care physicians	Evidence-based
Texas Medication Algorithm Project	2008	Psychiatrists Primary care physicians	Expert consensus
World Federation of Societies of Biological Psychiatry	2013, 2015	Psychiatrists Primary care physicians	Evidence-based
Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders	2015	Psychiatrists, Psychologists, Physicians	Amalgamating both evidence-based and expert consensus-based

For psychotic depression, the augmentation of an atypical antipsychotic agent with an antidepressant was preferred as the TOC. For severe episodes, with or without psychotic features, selective serotonin reuptake inhibitors (SSRIs), excluding fluvoxamine, serotonin-norepinephrine reuptake inhibitors (SNRIs), excluding milnacipran, and mirtazapine were preferred as the TOC or first-line treatments. Regarding the choice of an atypical antipsychotic agent for severe episodes with psychotic features, aripiprazole was chosen as the TOC. Quetiapine and olanzapine were preferred as the first-line treatments. Risperidone, blonanserin, paliperidone, amisulpride, ziprasidone, and typical antipsychotic agents were chosen as the second-line treatments. Most guidelines, such as the APA,[15] WFSBP,[17] TMAP[23] and CAMNAT,[16] recommend monotherapy with a second-generation antidepressant as the first-line treatment for nonpsychotic depression. In addition, in most of the recently published guidelines, such as the WFSBP,[17] Australian and New Zealand guideline[20] and CANMAT,[16,22] psychotherapeutic approaches, including psychoeducation, self-management, or other psychological approaches, are recommended over pharmacotherapy for relatively mild depression. However, in the KMAP-DD 2017, for severe episodes without psychotic features, augmentation of an atypical antipsychotic agent with an antidepressant is recommended as the first-line treatment, along with antidepressant monotherapy. These findings contrast with those in other guidelines, where they did not recommend atypical antipsychotic agents as the first-line for initial treatment of nonpsychotic depression (Table 2). This reflects a relatively higher preference by Korean psychiatrists for atypical antipsychotic agents for treating severely depressed mood without psychotic features, since the use of quetiapine and aripiprazole as adjunctive therapy for depression in Korea was approved.

Second Step Treatment in Cases of Inadequate Response to Initial Treatment

In the KMAP-DD 2017, for cases of nonpsychotic depression with no response to the initial treatment strategy, switching antidepressants, adding another antidepressant, or augmenting the initial antidepressant with an atypical antipsychotic agent were chosen as the first-line treat-

Table 2. Initial strategies for pharmacological treatment for major depressive disorder across practice guidelines

Guideline	1st-line treatment	Next intervention
Korean Medication Algorithm Project for Depressive Disorder 2017 (nonpsychotic depression)	• Mild to moderate episode: AD monotherapy • Severe episode without PF: AD monotherapy AD+AAP	• Mild to moderate episode: AD+AD AD+AAP AD+MS • Severe episode without PF: AAP monotherapy AD+MS ECT
Korean Medication Algorithm Project for Depressive Disorder 2017 (psychotic depression)	AD+AAP	ECT AAP monotherapy AD+TAP AD+MS AD monotherapy AD+AD
American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition	• Nonpsychotic: AD monotherapy • Psychotic: AD+AP, ECT	–
Canadian Network for Mood and Anxiety Treatments	SSRI, SNRI, agomelatine, bupropion, mirtazapine, vortioxetine	TCA, quetiapine, trazodone, moclobemide, selegiline, levomilnacipran, vilazodone
National Institute for Health and Clinical Excellence	AD monotherapy	–
Texas Medication Algorithm Project	• Nonpsychotic: AD monotherapy • Psychotic: AD+AP, ECT	–
World Federation of Societies of Biological Psychiatry	SSRI, other newer antidepressants	TCA, MAOI
Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders	SSRI, NaSSA, bupropion, SNRIs, NARI, agomelatine, vortioxetine	TCA, MAOI

AAP, atypical antipsychotic agent; AD, antidepressant; AP, antipsychotic agent; ECT, electroconvulsive therapy; MAOI, monoamine oxidase inhibitor; MS, mood stabilizer; NARI, noradrenaline reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; PF, psychotic features; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TAP, typical antipsychotic agent; TCA, tricyclic antidepressant.

ment. In cases of partial response to the initial treatment strategy, adding another antidepressant and augmenting the initial antidepressant with an atypical antipsychotic agent were chosen as the first-line treatment. When switching antidepressants, switching to another antidepressant from a different pharmacological class among SSRIs, SNRIs, or mirtazapine was preferred. When adding another antidepressant, adding one from a different pharmacological class among SSRIs, SNRIs, mirtazapine or bupropion was preferred. When augmenting an antipsychotic agent, aripiprazole or quetiapine was preferred. For psychotic depression, in cases of inadequate response to initial treatment, switching the atypical antipsychotic agent, adding another antidepressant, or switching the antidepressant were chosen as the first-line treatment. When adding or switching an antidepressant, adding or switching to another antidepressant from a different pharmacological class among SSRIs, SNRIs, or mirtazapine was preferred. These results are broadly consistent with other treatment guidelines, particularly recently published guidelines. In the WFSBP,[17] in cases of insufficient response to initial treatment, switching to another antidepressant, either within the same or from a different pharmacological class, adding another antidepressant from a different pharmacological class, and augmenting the antidepressant with lithium, an atypical antipsychotic agent or thyroid hormones were recommended. Among these strategies, the WFSBP states that augmentation with quetiapine, aripiprazole and lithium are most preferred. The CANMAT recommended aripiprazole (level 1), quetiapine (level 1), and risperidone (level 1) as the first-line adjunctive medications for non-response or partial response to an initial treatment strategy.[16] It recommended brexiprazole (level 1), lithium (level 2), modafinil (level 2), olanzapine (level 1), and triiodothyronine (level 2) as the second-line adjunctive medications. In the Australian and New Zealand guidelines,[20] augmenting with lithium or an atypical antipsychotic agent was recommended with level 1 evidence. It did not recommend buspirone, pindolol or the routine use of psychostimulants, due to unconvincing or insufficient evidence. However, in the TMAP,[23] augmenting with an atypical antipsychotic agent was recommended at later steps in cases showing inadequate response. This difference in recommendations regarding the use of atypical antipsychotics between the TMAP and other guidelines (the WFSBP, CANMAT, and Australian and New Zealand guidelines) appears to be a result of the year the guidelines were published; that is, the TMAP was published relatively earlier than the other guidelines. Thus, recently, as the evidence for augmenting with atypical antipsychotic agents in treating treatment resistant depression increased and accumulated, the more current guidelines (e.g., the WFSBP, CANMAT, and Australian and New Zealand guidelines) reflected this new evidence for the effectiveness of atypical antipsychotic agents (Table 3).

In terms of augmentation with other agents, such as mood stabilizers or lithium, the KMAP-DD 2017 recommends augmenting with mood stabilizers or lithium as the second-line, in cases of inadequate response to initial treatment. Compared with recommendations of the KMAP-DD 2012, the preference for augmenting with mood stabilizers or lithium decreased, while the preference for atypical antipsychotic agents increased. This finding in the KMAP-DD 2017 is consistent with that of the CANMAT,[16] the most recently published guideline (published in 2016), where lithium was recommended as the second-line in cases of inadequate response to initial treatment. However, in other guidelines, such as the WFSBP and the Australian and New Zealand guidelines, both atypical antipsychotics and lithium are recommended as first-line augmenting agents. To date, there has been little evidence for direct comparison between augmentation with atypical antipsychotic agents and lithium or other augmenting agents.[26] Further studies directly comparing the efficacy and tolerability between augmentation with atypical antipsychotics or other agents, such as lithium or mood stabilizers, are needed.

Third Step Treatment in Cases of Inadequate Response to Second Step Treatment

The KMAP-DD 2017 recommends third step treatment in cases of inadequate response to second step treatment. For nonpsychotic depression, adding an antidepressant from a different pharmacological class, augmenting with an atypical antipsychotic agent, switching atypical antipsychotic agents, or adding other augmenting agents, such as lithium, anticonvulsants, psychostimulants, or thyroid hormone, were recommended. The preference for each augmenting agent was not assessed separately. Most guidelines, except for the TMAP, did not separately recommend second or third step; instead, they recommended alternative strategies in case of failure to respond adequately to initial treatment. The TMAP recommended augmentation with MAOIs, lamotrigine, or dopamine agonists at this step.[23]

Table 3. Treatment strategies for partial or non-response to initial treatment

Guideline	1st-line treatment	Next intervention
Korean Medication Algorithm Project for Depressive Disorder 2017 (nonpsychotic depression)	· Non-response: Switching AD, Adding AD, Adding AAP · Partial response: Adding AD, Adding AAP	· Non-response: Adding AUG · Partial response: Switching AD, Adding AUG
Korean Medication Algorithm Project for Depressive Disorder 2017 (psychotic depression)	Switching AAP, Adding AD, Switching AD	Adding AAP, Adding AUG, Adding TAP
American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition	Optimizing the initial treatment Changing to a different treatment Augmenting and Combining treatment	–
Canadian Network for Mood and Anxiety Treatments	· Switching to a second-line or third-line antidepressant · Switching to antidepressant with superior efficacy · Adding an adjunctive medication (aripiprazole, quetiapine, risperidone)	· Second-line adjunctive medications: brexpiprazole, bupropion, lithium, mirtazapine, modafinil, olanzapine, triiodothyronine · Third-line adjunctive medications: TCAs, ziprasidone, methylphenidate, lisdexamfetamine
National Institute for Health and Clinical Excellence	· Nonresponse: increase the dose of initial AD, switch to another AD · Partial response: switch to another AD	–
Texas Medication Algorithm Project	· Nonpsychotic: augmenting another agent, switching to another AD, combination treatment, MAOI, TCA, TCA+lithium · Psychotic: TCA or SNRI combination with AP, lithium augmentation, switch to another AP	–
World Federation of Societies of Biological Psychiatry	· Switching from an SSRI to venlafaxine or tranylcypromine · Combination of an SSRI with an inhibitor of presynaptic autoreceptors (e.g., mirtazapine) · Adding lithium to ongoing antidepressant · Augmenting thyroid hormones · Augmenting quetiapine or aripiprazole	–
Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders	· Combine pharmacotherapy and psychological therapy · Increase dose of antidepressant medication · Augment antidepressant medication with lithium and/or antipsychotic medication · Combine antidepressants · rTMS	–

AAP, atypical antipsychotic agent; AD, antidepressant; AP, antipsychotic agent; AUG, other augmenting medications (lithium, anticonvulsants, buspirone, pindolol, psychostimulant, ketamine, thyroid hormone, etc); MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TAP, typical antipsychotic agent; TCA, tricyclic antidepressant; rTMS, repetitive transcranial magnetic stimulation.

Maintenance Treatment

In the KMAP-DD 2017, when symptom remission occurs after the augmentation of an antidepressant and an antipsychotic agent, the majority of clinicians prefer to maintain the antidepressant for at least 19.8 weeks to a maximum of 46.8 weeks for the first depressive episode. For the second depressive episode, the majority of clinicians prefer to maintain the antidepressant for at least 34.8 weeks to a maximum of 78.4 weeks. For the third and subsequent episodes, the majority of clinicians prefer to maintain the antidepressant for at least 41.8 weeks to a maximum of 88.9 weeks. The dose of antidepressant used during the maintenance phase was 75% of the dose used during the acute phase. With regard to antipsychotic agents, the majority of clinicians prefer to maintain the antipsychotic agent for at least 13.1 weeks to a maximum of

31.3 weeks for the first depressive episode. For the second episode, the antipsychotic agent was maintained for at least 21.6 weeks to a maximum of 49.8 weeks. For third and subsequent episodes, the antipsychotic agent was maintained for at least 28.8 weeks to a maximum of 59.6 weeks. The dose of antipsychotic agents during the maintenance phase was 50% of that used during the acute phase.

In the WFSBP,[17,19] the recommendation for maintenance treatment was divided into two separate phases, 'continuation treatment' and 'maintenance treatment'. During the continuation treatment, it was recommended that medication used during the acute phase should be used for at least 6 to 9 months with the same dose used during the acute phase. For patients with three or more previous depressive episodes and with a history of a high rate of recurrences, longer-term maintenance should be considered. The WFSBP stated that maintenance treatment for 3 years is usually appropriate for most recurrent patients. However, maintenance for more than 3 years or for an indefinite period could be considered among patients with a greater risk for recurrence. The CANMAT[16] recommended that, after symptom remission, maintenance treatment could be extended for 2 years or beyond in the presence of risk factors for recurrence based on level 3 and 4 evidence. Risk factors suggested by the CANMAT include frequent, recurrent, severe or chronic episodes, presence of comorbid psychiatric or other medical conditions, presence of residual symptoms, and difficult-to-treat episodes. The Australian and New Zealand guideline[20] recommends that antidepressants should be maintained for at least one year after an initial episode with the same dose used during the acute phase. In addition, it recommends the antidepressant should be maintained for at least 3 years for recurrent episodes with consensus-based evidence.

Pharmacologic Treatment for Persistent Depressive Disorder and Each Depression Subtype

Pharmacologic treatment for persistent depressive disorder

In the KMAP-DD 2017, antidepressant monotherapy was preferred as the TOC for persistent depressive disorder. Among antidepressants, escitalopram was preferred as the TOC, and fluoxetine, paroxetine, sertraline, duloxetine, milnacipran, venlafaxine, desvenlafaxine, bupropion, and mirtazapine were chosen as first-line treatments. In the APA[15] and NICE[14] guidelines, antidepressant monotherapy was also recommended as the first line for dysthymic disorder. The CANMAT[16] stated that fluoxetine, paroxetine, sertraline, moclobemide, and imipramine have been most found to be effective drugs. The CANMAT also emphasized chronic disease management, with a focus on functional improvement or quality of life rather than an emphasis on symptom remission for patients with persistent depressive disorder.[16]

Pharmacologic treatment for melancholic features

In the KMAP-DD 2017, escitalopram and venlafaxine were preferred as the TOC for melancholic features. Fluoxetine, paroxetine, sertraline, duloxetine, milnacipran, desvenlafaxine, and mirtazapine were chosen as the first-line treatments. The WFSBP[17] stated that some evidence exists that venlafaxine, amitriptyline and clomipramine are more efficacious than SSRIs in treating patients with severe melancholic features. However, in the CANMAT,[16] it was stated that there are no differences in efficacy between SSRIs, SNRIs, and TCAs.

Pharmacologic treatment for atypical features

In the KMAP-DD 2017, escitalopram, venlafaxine, sertraline, duloxetine, bupropion, desvenlafaxine, fluoxetine, mirtazapine, and milnacipran were chosen as the first-line treatments. In the WFSBP,[17] irreversible MAOIs could be more beneficial for patients with atypical features. However, the CANMAT[16] stated that there were no significant differences in efficacy among first-line antidepressants.

Pharmacologic treatment for depression with a seasonal pattern

In the KMAP-DD 2017, escitalopram, sertraline, venlafaxine, duloxetine, fluoxetine, desvenlafaxine, paroxetine, mirtazapine, bupropion, and milnacipran were chosen as the first-line treatments for depression with a seasonal pattern. The CANMAT[16] stated that there were no significant differences in efficacy among first-line antidepressants. The APA guideline[15] recommends extended release bupropion for depression with a seasonal pattern. The NICE guideline[14] mentioned the efficacy of light therapy, despite limited evidence.

Pharmacologic treatment for depression with mixed features

In the KMAP-DD 2017, the treatment options for mixed features were newly included to reflect the changes after the publication of the DSM-5. For mixed features,

augmentation of an antidepressant with an atypical antipsychotic agent, and augmentation of an antidepressant with mood stabilizer were chosen as the first-line treatment. Among antidepressants, escitalopram, sertraline, mirtazapine, fluoxetine, bupropion, and venlafaxine were chosen as the first-line. Among antipsychotic agents or mood stabilizers, aripiprazole, quetiapine, valproate, or olanzapine were chosen as the first-line. The CANMAT[16] stated that, to date, there were no trials that used DSM-5 criteria for mixed features; however, monotherapy with lurasidone or ziprasidone were found to be efficacious for major depressive episodes with mixed symptoms.

Pharmacologic treatment for depression with anxious distress

In the KMAP-DD 2017, the treatment options for individuals with depression with anxious distress were also newly included to reflect changes in the DSM-5. For depression with anxious distress, antidepressant monotherapy was chosen as the first-line treatment. Among antidepressants, escitalopram, paroxetine, sertraline, mirtazapine, venlafaxine, desvenlafaxine, duloxetine, and fluoxetine were chosen for first-line treatments. In the WFSBP,[17] it stated that patients with prominent anxiety symptoms could be beneficially treated with SSRIs, venlafaxine or TCAs. It also stated that clinicians should start at lower doses and increase the dose slowly for individuals with prominent anxiety symptoms. The CANMAT[16] mentioned there were no difference in efficacy between SSRIs, SNRIs, and bupropion. It also stated that using antidepressants with proven efficacy among individuals with generalized anxiety disorder could be considered for depression with anxious distress.

Special Populations

Child and adolescent depression

In the KMAP-DD 2017, the treatment options for DMDD, which first appeared in the DSM-5, were evaluated. For initial treatment for DMDD, there was no first-line treatment. Monotherapy with an atypical antipsychotic agent, augmentation of an antidepressant with an atypical antipsychotic agent, antidepressant monotherapy, mood stabilizer monotherapy, augmentation of mood stabilizer with an atypical antipsychotic agent, and augmentation of an antidepressant with mood stabilizer were chosen as the second-line treatments. Among mood stabilizers, there was also no first-line treatment selected. Valproate, lithium, and lamotrigine were selected as the second-line treatments. Among atypical antipsychotic agents, aripiprazole was selected as the first-line treatment; risperidone and quetiapine were selected as the second-line. Among antidepressants, escitalopram was selected as the first-line treatment. Fluoxetine, sertraline, fluvoxamine, venlafaxine, desvenlafxine, bupropion, mirtazapine, agomelatine were selected as the second line. To date, there are no guidelines that provide recommendations for DMDD; thus, we cannot directly compare the recommendations of the KMAP-DD 2017 with those of other guidelines. Similarly, no formal clinical trials of patients with DMDD have been performed. The only randomized controlled trial among patients with severe mood dysregulation found no beneficial efficacy of lithium compared with a placebo.[27] Given this dearth of information regarding treatment strategies for DMDD, the expert CBRs in the KMAP-DD 2017 could provide valuable guidelines. However, they should be further assessed for their utility in clinical practice.

In the KMAP-DD 2017, for mild to moderate depressive episodes among children and adolescents, antidepressant monotherapy was selected as the TOC. Among antidepressants, escitalopram and fluoxetine were selected as first-line treatments. For severe episodes, antidepressant monotherapy and augmentation of an antidepressant with an atypical antipsychotic agent were selected as the first-line. Among antidepressants, escitalopram and fluoxetine were selected as the first-line treatments. For severe episodes with psychotic features, augmentation of an antidepressant with an atypical antipsychotic agent was selected as the first-line treatment. Among antidepressants, fluoxetine and escitalopram were selected as the first-line treatments, and among atypical antipsychotic agents, aripiprazole and risperidone were selected as the first-line treatments. In the CANMAT,[16] for treatment of major depression among children and youth, cognitive-behavioral therapy (CBT) or interpersonal therapy (IPT) was suggested as the first-line treatment. Fluoxetine, escitalopram, sertraline or citalopram were chosen as the second-line. Venlafaxine or TCAs were selected as the third-line. In the Australian and New Zealand guideline,[20] due to evidence regarding a small increased risk of SSRIs inducing suicidality among younger individuals, it advised that the risks and benefits should be thoroughly assessed. When prescribing antidepressants, the guidelines recommended that clinicians closely monitor the worsening of suicidality among younger individuals, especially in the early treatment period.[20]

Pharmacologic treatment of geriatric depression

In the KMAP-DD 2017, antidepressant monotherapy was selected as the TOC for mild to moderate depressive episodes among elderly patients. Among antidepressants, escitalopram was selected as the TOC. Sertraline, fluoxetine, duloxetine, milnacipran, venlafaxine, desvenlafaxine, and mirtazapine were selected as the first-line treatments. For severe episodes without psychotic features, both antidepressant monotherapy and augmentation of an antidepressant with an atypical antipsychotic agent were selected as the first-line treatment. For severe with psychotic features, augmentation of an antidepressant with an atypical antipsychotic agent was selected as the first-line treatment. Among antidepressants, escitalopram was selected as the TOC, and among atypical antipsychotics, aripiprazole was selected as the TOC, with quetiapine as the first-line treatment. These recommendations are consistent with other guidelines. The APA guideline[15] recommends SSRIs and SNRIs preferentially due to the vulnerability of elderly patients to orthostatic hypotension or other side effect profiles. In the WFSBP,[17] it also mentions that elderly adults are more vulnerable to adverse events, such as cardiovascular side effects, and thus, SSRIs and newer antidepressants are generally preferred over TCAs. The CANMAT[22] recommends duloxetine, mirtazapine, and nortriptyline as the first-line treatment with level 1 evidence. It also recommends bupropion, escitalopram, desvenlafaxine, duloxetine, sertraline, venalafaxine and vortioxetine as the first-line treatments with level 2 evidence.

Pharmacologic treatment for depression in women

Premenstrual dysphoric disorder (PMDD)

In the KMAP-DD 2017, antidepressant monotherapy was selected as the TOC for PMDD. Among antidepressants, escitalopram was selected as the TOC. Fluoxetine, paroxetine, sertraline, duloxetine, and desvenlafaxine were selected as the first-line treatments.

Pharmacological treatment during pregnancy

In the KMAP-DD 2017, treatment strategies were recommended separately for pregnancy and for the postpartum period. During pregnancy, antidepressant monotherapy was the first-line treatment for nonpsychotic depression. For psychotic depression during pregnancy, both augmentation of an antidepressant with an atypical antipsychotic agent and electroconvulsive therapy (ECT) were selected as the first-line treatments. In the WFSBP,[17] ECT was recommended as the first-line strategy, particularly during the first trimester. In the Australian and New Zealand guideline,[20] it stated that SSRIs during pregnancy could be associated with a small risk of fetal abnormalities (especially paroxetine), pulmonary hypertension in newborns and withdrawal syndrome. In the CANMAT,[22] for mild to moderate depression, CBT and IPT were recommended as the first-line treatment. Citalopram, escitalopram and sertraline are recommended as the second-line treatments. The CANMAT recommended bupropion, desvenlafaxine, duloxetine, fluoxetine, fluvoxamine, mirtazapine, TCAs, venlafaxine and ECT as the third-line treatments.[22]

Pharmacologic treatment for postpartum depression

In the KMAP-DD 2017, for mild to moderate depressive episodes during the postpartum period, antidepressant monotherapy was selected as the TOC. For severe without psychotic features, both antidepressant monotherapy and augmentation of an antidepressant with an atypical antipsychotic agent were selected as the first-line treatment. For psychotic depression during the postpartum period, augmentation of an antidepressant with an atypical antipsychotic agent was selected as the TOC. The CANMAT recommended CBT and IPT as the first-line treatment for mild to moderate postpartum depression with level 1 evidence.[22] It recommended citalopram, escitalopram, sertraline and a combination of SSRIs and CBT or IPT as the second-line treatments with level 2 evidence. For severe postpartum depression, the CANMAT recommended citalopram, escitalopram, and sertraline as the first-line treatments.[22] It also stated that ECT could be considered as a first-line treatment for severe depression, especially among individuals with psychotic symptoms.[22]

Choosing Antidepressants in Specific Situations

In the KMAP-DD 2017, bupropion was preferred when there is a concern for sedation, serotonin syndrome and sexual dysfunction. When weight gain was a concern of interest, fluoxetine or bupropion were recommended. Mirtazapine was preferred when there was a concern for sleep disturbance or gastrointestinal trouble. Escitalopram was preferred when there was a concern for anticholinergic side effects, uncontrolled blood pressure, seizure, and arrhythmia. The APA[15] and CANMAT[16] guidelines mentioned that SSRIs or SNRIs could be more related to sexual dysfunction compared to bupropion, mirtazapine and moclobemide. The APA[15] recommended EKG or vital sign monitoring during the use of TCAs or

SNRIs. It mentioned that an SSRI was preferred when patients had cardiovascular problems. The APA[15] also mentioned that bupropion should be used with caution when there was comorbid seizure disorder, because of its potential to lower seizure threshold. The WFSBP[17] mentioned that SNRIs, such as venlafaxine and duloxetine, showed more frequent side effects compared to SSRIs, such as escitalopram and sertraline. It also mentioned that agomelatine had a similar prevalence of sexual side effects compared to placebo.[17] Recently published guidelines, such as the WFSBP,[17] the Australian and New Zealand guideline,[20] and the CANMAT,[16] contained precautions about side effects related to the use of SSRIs that were thought to be relatively safe, such as agitation, altering platelet function, risk for syndrome of inappropriate antidiuretic hormone secretion, and QTc prolongation, especially related to high doses of citalopram and escitalopram.

Non-pharmacologic Therapy

Electroconvulsive therapy (ECT)

The KMAP-DD 2017 recommended ECT as the first-line treatment for severe depression with a high risk of suicide, severe depression in pregnant women, and moderate depressive episodes with no response to pharmacotherapy. This is consistent with other guidelines. In the WFSBP, ECT was recommended as the first-line treatment in cases of severe psychotic depression, severe retarded depression, treatment refractory depression, or in situations when medication was contraindicated, such as pregnancy, or when rapid symptom relief is required, such as with high suicide risk or refusal to eat.[17] In the Australian and New Zealand guideline, ECT was preferred as the first-line in cases of suicide risk, catatonic or psychotic depression, or severe melancholic depression.[20]

Repetitive transcranial magnetic stimulation (rTMS)

The KMAP-DD 2017 did not recommend rTMS as the first-line treatment for depression. Rather, it was recommended as a second-line treatment in cases of moderate or severe depression with inadequate response to initial treatment, severe depression with physical problems, severe depression in pregnant women or severe depression with suicide risk. In other guidelines, such as the WFSBP,[17] APA,[15] and NICE,[14] it was mentioned that there was insufficient evidence for the efficacy of rTMS to recommend its use in standard settings.

Complementary and alternative medicine treatments for treatment-resistant depression

Complementary and alternative treatments for depression, such as light therapy, nutritional therapy, vagus nerve stimulation (VNS), deep brain stimulation or sleep deprivation were not recommended as the first-line treatment in the KMAP-DD 2017. In the APA,[15] TMAP[23] and WFSBP[17] guidelines, it was mentioned that VNS could be considered for treatment resistant depression. Light therapy was mentioned as an optional strategy for seasonal affective disorder in the WFSBP.[17] Omega-3 polyunsaturated fatty acids were mentioned as an adjunctive treatment in the Australia and New Zealand guideline.[20]

CONCLUSION

We compared the recommendations of the KMAP-DD 2017 with those of other global guidelines. Among the six guidelines compared with the KMAP-DD 2017, four were evidence-based guidelines,[14-17] one was an expert consensus-based guideline,[23] and one[20] integrated both evidence-based and clinical CBRs. The recommendations for initial treatment, next step treatment in cases of inadequate response to initial treatment, maintenance treatment, persistent depressive disorder, various depression subtypes, special populations, and specific situations were broadly similar across the guidelines, even though there were some differences in the details. In addition, we found that the expert CBRs in the KMAP-DD 2017 and the Australian and New Zealand guidelines seemed to be mutually complementary to those in the evidence-based guidelines. Although the KMAP-DD 2017 has some limitations in that it was based on expert consensus only, clinical evidence cannot be drawn from designed clinical trials in various situations. Considering this, the KMAP-DD 2017 will provide valuable information to Korean clinicians for making decisions in various clinical situations, by complementing other evidence-based guidelines.

REFERENCES

1. Song HR, Bahk WM, Woo YS, Jeong JH, Kwon YJ, Seo JS, et *al*. *Efficacy and tolerability of generic mirtazapine (Mirtax) for major depressive disorder: multicenter, open-label, uncontrolled, prospective study. Clin Psychopharmacol Neurosci 2015;13:144-149.*
2. Citrome L. *Vortioxetine for major depressive disorder: an indirect comparison with duloxetine, escitalopram, levomilnacipran, sertraline, venlafaxine, and vilazodone, using number needed to treat, number needed to harm, and likelihood to be helped or harmed. J Affect Disord 2016; 196:225-233.*
3. McCormack PL. *Vilazodone: a review in major depressive*

disorder in adults. Drugs 2015;75:1915-1923.
4. Laoutidis ZG, Kioulos KT. *Desvenlafaxine for the acute treatment of depression: a systematic review and meta-analysis. Pharmacopsychiatry 2015;48:187-199.*
5. Zadka Ł, Dziwota E, Olajossy M. *Levomilnacipran—a successor of milnacipran with a higher noradrenergic selectivity. Acta Pol Pharm 2016;73:285-289.*
6. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, *et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163:1905-1917.*
7. Vieta E, Colom F. *Therapeutic options in treatment-resistant depression. Ann Med 2011;43:512-530.*
8. Sueki A, Suzuki E, Takahashi H, Ishigooka J. *Does early improvement in depressive symptoms predict subsequent remission in patients with depression who are treated with duloxetine? Neuropsychiatr Dis Treat 2016;12:1269-1273.*
9. Shim IH, Woo YS, Bahk WM. *Prevalence rates and clinical implications of bipolar disorder "with mixed features" as defined by DSM-5. J Affect Disord 2015;173:120-125.*
10. Wang HR, Woo YS, Ahn HS, Ahn IM, Kim HJ, Bahk WM. *Can atypical antipsychotic augmentation reduce subsequent treatment failure more effectively among depressed patients with a higher degree of treatment resistance? A meta-analysis of randomized controlled trials. Int J Neuropsychopharmacol 2015;18:pyv023.*
11. Woo YS, Rosenblat JD, Kakar R, Bahk WM, McIntyre RS. *Cognitive deficits as a mediator of poor occupational function in remitted major depressive disorder patients. Clin Psychopharmacol Neurosci 2016;14:1-16.*
12. 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.*
13. 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.*
14. National Collaborating Centre for Mental Health (UK). *Depression: the treatment and management of depression in adults. London:British Psychological Society;2010.*
15. American Psychiatric Association. *Treatment of patients with major depression and practical guideline. American Psychiatric Association; 2010 [cited 2016 Nov 10]. Available from: http://psychiatryonline.org/guidelines.aspx.*
16. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, *et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. pharmacological treatments. Can J Psychiatry 2016;61:540-560.*
17. Bauer M, Pfennig A, Severus E, Whybrow PC, Angst J, Möller HJ, *et al. Task force on unipolar depressive disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry 2013;14:334-385.*
18. Wang HR, Bahk WM, Park YM, Lee HB, Song HR, Jeong JH, *et al. Korean medication algorithm for depressive disorder: comparisons with other treatment guidelines. Psychiatry Investig 2014;11:1-11.*
19. Bauer M, Severus E, Köhler S, Whybrow PC, Angst J, Möller HJ, *et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. part 2: maintenance treatment of major depressive disorder-update 2015. World J Biol Psychiatry 2015;16:76-95.*
20. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, *et al. Royal australian and New Zealand college of psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2015;49:1087-1206.*
21. Kennedy SH, Lam RW, Parikh SV, Patten SB, Ravindran AV. *Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. Introduction. J Affect Disord 2009;117 Suppl 1:S1-S2.*
22. MacQueen GM, Frey BN, Ismail Z, Jaworska N, Steiner M, Lieshout RJ, *et al. 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.*
23. Suehs B, Argo TR, Bendele SD, Crimson ML, Trivedi MH, Kurian B. *Texas medication algorithm project procedural manual major depressive disorder algorithms. Austin, TX:Texas Department of State Health Services;2008.*
24. Bauer M, Bschor T, Pfennig A, Whybrow PC, Angst J, Versiani M, *et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care. World J Biol Psychiatry 2007;8:67-104.*
25. Wang HR, Seo JS, Woo YS, Park YM, Jeon JH, Kim W, *et al. Korean medication algorithm for depressive disorder 2017. Seoul:ML Communication;2017.*
26. Edwards SJ, Hamilton V, Nherera L, Trevor N. *Lithium or an atypical antipsychotic drug in the management of treatment-resistant depression: a systematic review and economic evaluation. Health Technol Assess 2013;17:1-190.*
27. Dickstein DP, Towbin KE, Van Der Veen JW, Rich BA, Brotman MA, Knopf L, *et al. Randomized double-blind placebo-controlled trial of lithium in youths with severe mood dysregulation. J Child Adolesc Psychopharmacol 2009;19:61-73.*