Korean Medication Algorithm for Bipolar Disorder 2018: Comparisons with Other Treatment Guidelines

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The objective of this study was to compare recommendations of the Korean Medication Algorithm Project for Bipolar Disorder 2018 (KMAP-BP 2018) with other recently published guidelines for treating bipolar disorder. We reviewed a total of five recently published global treatment guidelines and compared treatment recommendation of the KMAP-BP 2018 with those of other guidelines. For initial treatment of mania, there were no significant differences across treatment guidelines. All guidelines recommended mood stabilizer (MS) or atypical antipsychotic (AAP) monotherapy or a combination of an MS with an AAP as a first-line treatment strategy for mania. However, the KMAP-BP 2018 did not prefer monotherapy with MS or AAP for psychotic mania. Quetiapine, olanzapine and aripiprazole were the first-line AAPs for nearly all phases of bipolar disorder across guidelines. Most guidelines advocated newer AAPs as first-line treatment options for all phases while lamotrigine was recommended for depressive and maintenance phases. Lithium and valproic acid were commonly used as MSs in all phases of bipolar disorder. As research evidence accumulated over time, recommendations of newer AAPs (such as asenapine, cariprazine, paliperidone, lurasidone, long-acting injectable risperidone and aripiprazole once monthly) became prominent. KMAP-BP 2018 guidelines were similar to other guidelines, reflecting current changes in prescription patterns for bipolar disorder based on accumulated research data. Strong preference for combination therapy was characteristic of KMAP-BP 2018, predominantly in the treatment of psychotic mania and severe depression. Further studies were needed to address several issues identified in our review.

KEY WORDS: Bipolar disorder; Pharmacotherapy; Algorithm; Treatment guideline; Korean Medication Algorithm Project for Bipolar Disorder 2018.

INTRODUCTION

Medical practice has shifted from experience-based to more evidence-based approaches from the early 1990s.11 This trend has contributed to the development of treatment algorithms or clinical practice guidelines in psychiatric fields,21 including several treatment algorithms for mood disorder.11-10 However, the medical situation differs across countries. At times, the use of treatment guidelines may be constrained by cultural differences in clinical environments and medical situations, different health insurance policies and economic states, or culture-specific needs of clinicians and patients.

In Korea, a medication algorithm project (Korean Medication Algorithm Project for Bipolar Disorder, KMAP-BP)
was initiated in 2001. KMAP-BP was published in 2002 (KMAP-BP 2002), and its feasibility has been confirmed.\textsuperscript{11,12} Revised versions of KMAP-BP were released in 2006, 2010, and 2014.\textsuperscript{13-15} Due to rapid development of psychopharmacologic fields, newer atypical antipsychotics (AAP), mood stabilizer (MS), and other agents are being introduced for the treatment of bipolar disorder.

To reflect current changes in treatment situations for bipolar disorder, previous algorithm needs to be revised, resulting in publication of KMAP-BP in 2018 (KMAP-BP 2018).\textsuperscript{16} In this review article, we compared recommendations of KMAP-BP 2018\textsuperscript{16} with those of other recently published global treatment guidelines, including British Association for Psychopharmacology Guidelines for Treatment of Bipolar Disorder (BAP 2016),\textsuperscript{17} Canadian Network for Mood and Anxiety Treatments (CANMAT 2018),\textsuperscript{18} The International College of Neuropsychopharmacology Treatment Guidelines for Bipolar Disorder (CINP-BD 2017),\textsuperscript{19-22} National Institute for Health and Clinical Excellence Clinical Guideline for Bipolar Disorder (NICE 2014),\textsuperscript{23} and The World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorder (WFSBP) (Table 1).\textsuperscript{24-26} By identifying similarities and differences across treatment guidelines, our goal was to identify potential deficiencies in KMAP-BP 2018 that would require additional attention or supplementary information to enhance the usefulness of KMAP-BP 2018 guidelines in clinical practice.

### TREATMENT GUIDELINES AS COMPARISON TARGETS

#### British Association for Psychopharmacology

**Guidelines for Treatment of Bipolar Disorder (BAP)**

The British Association for Psychopharmacology constructed a set of guidelines based on the American Psychiatric Association Practice Guidelines for Bipolar Disorder, revised in 2002 and 2009.\textsuperscript{27,28} The BAP adapted the American guidelines with the aim of guiding clinical decision-making in Britain and published these revisions in 2016 as Evidence-based guideline for treating bipolar disorder: revised third edition Recommendations from the British Association for Psychopharmacology (BAP 2016).\textsuperscript{17} BAP 2016 consists of a list of clinical guidelines and their key points and supporting evidence. It provides evaluation for supporting evidence. The evidence is categorized, ranging from Category I (the most powerful evidence) to Category IV (the weakest). In addition, the strength of each recommendation is categorized, ranging Grade High (the strongest recommendation) to Grade Very Low (the weakest). The guidelines\textsuperscript{17} reflected the consensus of experts and a wide range of feedback. This BAP guideline should be read alongside NICE 2014.\textsuperscript{23} The BAP 2016 also provides basic information to patients and caregivers about diagnosis and treatment.

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### Table 1. Summary of recent bipolar disorder treatment guidelines

| Organization | Publication date | Audience | Methodology |
|--------------|-----------------|----------|-------------|
| Korean Medication Algorithm Project for Bipolar Disorder 2018 (KMAP-BP 2018) | 2018\textsuperscript{16} | Psychiatrists | Expert consensus |
| British Association for Psychopharmacology (BAP) | 2016\textsuperscript{17} | Psychiatrists Primary care physicians | Evidence-based |
| Canadian Network for Mood and Anxiety Treatments (CANMAT) | 2018\textsuperscript{18} | Psychiatrists | Evidence-based |
| The International College of Neuropsychopharmacology Treatment Guidelines for Bipolar Disorder (CINP-BD 2017) | 2017\textsuperscript{19-22} | Primary and secondary care physicians | Evidence-based |
| National Institute for Health and Clinical Excellence (NICE) | 2014\textsuperscript{23} | Psychiatrists Primary care physicians | Evidence-based |
| World Federation of Societies of Biological Psychiatry (WFSBP) | 2009 (acute mania, mixed, rapid cycling)\textsuperscript{24} | Psychiatrists | Evidence-based |
| | 2010 (acute depression)\textsuperscript{25} | Primary care physicians |
| | 2013 (maintenance)\textsuperscript{26} | | |
Canadian Network for Mood and Anxiety Treatments
Clinical Guidelines for the Management of Patients with Bipolar Disorder (CANMAT)

The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments collaborated to publish evidence-based clinical guidelines for bipolar disorder in 1997.29) These guidelines were subsequently revised in 2005,30) 2007,31) 2009,32) 2013,33) and 201815) to reflect new evidence. CANMAT is a set of evidence-based treatment guidelines reflecting a comprehensive literature review. The evidence of efficacy, safety/tolerability and risk of treatment-emergent switch with pharmacological agents were categorized, ranging from level 1 (the most powerful evidence, meta-analysis with narrow confidence interval [CI] or replicated double-blind, randomized controlled trial that includes a placebo or active control comparison [n ≥ 30 in each active treatment arm]) to level 4 (the weakest, uncontrolled trial, anecdotal reports, or expert opinion). Treatment recommendations were categorized into four levels based on the strength of supporting evidence.

The International College of Neuropsychopharmacology
Treatment Guidelines for Bipolar Disorder (CINP-BD)

CINP-BD guideline has been commissioned by the College of Neuropsychopharmacology. The workgroup consisted of experts with extensive research and clinical experience in the field of bipolar disorders. It included a systematic literature review and a detailed presentation of results for bipolar disorder.19-22) Treatment efficacy was graded from level 1 (the most powerful evidence) to level 5 (negative data). Grading for safety/tolerability ranged from level 1 (very good tolerability) to level 3 (poor tolerability). Based on grading of efficacy and safety/tolerability, treatment recommendations are offered at five levels.

National Institute for Health and Clinical Excellence
Clinical Guideline for Bipolar Disorder (NICE Clinical Guideline 185)

NICE guideline has published numerous treatment guidelines. Among them, a set of guidelines for bipolar disorder were based on comprehensive literature review. The first edition of the NICE guidelines for bipolar disorder was published in 2006.14) It was subsequently revised in 2014.23) Because NICE guidelines intended to serve a group of professionals working in various psychiatrics fields, they provided relatively simple recommendations pertaining to the level of diagnosis and treatment without clearly defining the strength of evidence or clearly differentiating among treatment recommendations.

The World Federation Society of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorder (WFSBP)

The World Federation of Societies of Biological Psychiatry developed guidelines for bipolar disorder based on a comprehensive literature review. Guidelines addressing depressive episode were published in 2002,35) followed by guidelines for manic episode in 2003,36) and maintenance therapy in 2004.37) Revisions were released in 2009 (manic episode),24) 2010 (depressive episode)25) and 2013 (maintenance therapy)26) to reflect new evidence. Treatment recommendations are categorized into five levels depending on the strength of the supporting evidence.

Development of KMAP-BP 2018

The KMAP-BP 201815) guidelines reflected expert consensus. This revised edition of the KMAP-BP used the same framework as KMAP-BP 2014 (the third revision of the algorithm).15) The survey questionnaire used for the KMAP-BP 2018 included many of the same questions used in KMAP-BP 2014.15) However, it also contained several modifications.

The 2018 edition featured newly added questions regarding treatment strategies for manic/hypomanic episodes, depressive episodes, mixed features, rapid cycling, and maintenance based on changes in the Diagnostic and Statistical Manual of Mental Disorders 5th edition. We added new questions to the choice of available medications such as monotherapy and combination therapy with MIs in the questionnaire for the initial treatment strategy. It also has questions pertaining to safety and compliance issues as well as strategies for special situations.

The final 50-item questionnaire consisted of 184 sub-item and 1,326 response options. The 9-point scale from RAND Corporation5) was used to evaluate the adequacy of each treatment option. The survey was sent to a review panel of 84 Korean psychiatrists with extensive clinical experience and academic achievements in bipolar dis-
order. Reflecting a variety of medical contexts, reviewers’ affiliations included university hospitals, general hospitals, mental hospitals, and private psychiatric clinics. Fifty-seven of these 84 reviewers worked at university hospitals, 21 at general hospitals/mental hospitals, and 6 in private clinics. Sixty-one (72.6%) of these 84 responded to the survey questionnaire.

By estimating means and 95% CI for each question item, we classified each treatment opinion into one of three categories based on the lowest CI category: 6.5 or greater for first-line treatment, 3.5 to 6.5 for second-line treatment, and lower than 3.5 for third-line treatment. If a first-line option was recommended by 50% or more of these experts, it was labeled as a "treatment of choice (TOC)."

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board (IRB) at each respective study site. The IRB waived the requirement for informed consent for this survey. All respondents received predetermined fee for their participation.

COMPARISONS OF RECOMMENDATIONS ACROSS TREATMENT GUIDELINES

Acute Mania/Hypomania

Initial treatment

For acute mania, combination of MS and AAP were the most preferred first-line treatments (TOC) in KMAP-BP 2018.16) MS monotherapy (lithium [Li] or valproic acid [Val]) was a first-line treatment strategy for non-psychotic mania while AAP monotherapy was a first-line treatment strategy for non-psychotic and psychotic mania. Treatment strategy for hypomanic episodes was monotherapy of MS or AAP. In KMAP-BP 2018,16) the preferred medication for the monotherapy of non-psychotic mania, Val, Li, olanzapine (OLZ) and quetiapine (QTP) were recommended as the first-line, aripiprazole (ARP) and risperidone (RIS) were the second-line. For psychotic mania, OLZ, QTP, Li, ARP and OLZ were recommended as the first-line, and QTP or ARP as second-line. For non-psychotic and psychotic mania, treatment strategy was monotherapy of MS or AAP. The preferred medication for the monotherapy of non-psychotic mania, Val, Li, olanzapine (OLZ) and quetiapine (QTP) were recommended as the first-line, aripiprazole (ARP) and risperidone (RIS) were the second-line. For psychotic mania, OLZ, QTP, Li, olanzapine (OLZ) and quetiapine (QTP) were recommended as the first-line, aripiprazole (ARP) and risperidone (RIS) were the second-line.

Next-step strategy

In cases of non-response or incomplete response to first-line strategies, guidelines recommended switching or adding another first-line agent. In KMAP-BP 2018,16) the preferred medication for non-psychotic mania was monotherapy of MS or AAP. The preferred medication for non-psychotic mania was monotherapy of MS or AAP. The preferred medication for non-psychotic mania, Val, Li, olanzapine (OLZ) and quetiapine (QTP) were recommended as the first-line, aripiprazole (ARP) and risperidone (RIS) were the second-line.

Second-line treatment was recommended in the WFSBP guideline, Val, ARP, ziprasidone (ZIP) and RIS was recommended as first-line treatment for manic patients.19) But in the WFSBP guideline, Val, ARP, ziprasidone (ZIP) and RIS was recommended as first-line treatment for manic patients.24)
Table 2. Treatment for acute mania across practice guidelines

| Guidelines       | First-line treatment                                                                 | Next-step intervention                                                                 | Later intervention       |
|------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------|
| KMAP-BP 2018     | Non-psychotic: Val, Li, OLZ, QTP, MS + OLZ (or QTP or RIS or ARP)                      | 2 MSs + AAP, MS + 2 AAPs                                                             | Replace MS or AAP, TAP   |
|                  | Psychotic: OLZ, QTP, RIS, ARP, MS + OLZ (or QTP or RIS or ARP)                         | Psychotic: 2 MSs + AAP, MS + 2 AAPs                                                  |                          |
|                  | Hypomania: Val, QTP, Li, ARP, OLZ                                                     | Hypomania: MS + AAP                                                                  |                          |
| BAP 2016         | Without AM: HP, OLZ, QTP, RIS, QTP, Val                                              | Without AM: ARP, CBZ, Li                                                              | ECT or CLZ               |
|                  | With Li: optimization, Add HP, OLZ, RIS, QTP, Val, ARP                               | With Li: MS + AAP                                                                    |                          |
| CANMAT 2018      | Li, QTP, Val, ASP, ARP, PAL, RIS, cariprazine                                          | OLZ, CBZ, OLZ + Li (or Val), Li + Val, ZIP, HP, ECT                                | CBZ + Li (or Val), CPZ, CNZP, CLZ, HP + Li (or Val), rTMS, tamoxifen, tamoxifen + Li (or Val) |
| CINP-BD-2017     | Combination with MS: QTP, ARP, RIS, ASP, cariprazine                                   | Li (or Val) + ARP (or HP or OLZ or QTP or RIS)                                       | ECT, OXC                 |
|                  | Switch to other first-step monotherapy                                               | Li + allopurinol, Val + TAP, MS + medroxyprogesterone, Val + celcoxib                  |                          |
| NICE 2014        | Without AM: HP, OLZ, QTP, RIS                                                         | Alternative AP or adding Li or Val                                                   | ECT                      |
|                  | With Li: optimization, adding HP, OLZ, RIS, QTP, RIS                                   |                                                                                       |                          |
| WFSBP 2009       | Monotherapy of CE 1 and RG A such as Val, ARP, ZIP, and RIS                           | Optimize dosage; switch to another first-line agent; in severe mania, consider combination | Add-on with first-line agent; combination of two first-line choices |

KMAP-BP, Korean Medication Algorithms for Bipolar Disorder; BAP, The British Association for Psychopharmacology Guidelines for Treatment for Bipolar Disorder; CANMAT, Canadian Network for Mood and Anxiety Treatments; CINP-BD, International College of Neuro- Psychopharmacology Treatment Guidelines for Bipolar Disorder; NICE, National Institute for Health and Clinical Excellence Treatment for Bipolar Disorder; WFSBP, World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorder; Treatment for acute mania; Val, various kinds of valproic acid; Li, lithium; OLZ, olanzapine; QTP, quetiapine; MS, mood stabilizer; RIS, risperidone; ARP, aripiprazole; AAP, atypical antipsychotic; TAP, typical antipsychotics; AM, anti-manic agents; HP, haloperidol; CBZ, carbamazepine; ECT, electroconvulsive therapy; CLZ, clozapine; ASP, asenapine; PAL, paliperidone; ZIP, ziprasidone; ECT, electroconvulsive therapy; CPZ, chlorpromazine; CNZP, clonazepam; rTMS, repetitive transcranial magnetic stimulation; OXC, oxcarbazepine; CE, categories of evidence; RG, recommendation of grade.

mization of dosage and switching to another first-line agent. In case of severe manic states, combination therapy could be considered as second-line treatment. Adding with first-line agent and combination of 2 first-line choices were listed for later intervention (Table 2).

**Bipolar Depression**

**Initial treatment**

KMAP 2018 divided bipolar depression into categories of mild to moderate, nonpsychotic severe, and psychotic severe. As the first-line treatment strategy for mild to moderate depression, monotherapy with MS, AAP and lamotrigine (LTG), and MS + AAP, MS + LTG and AAP + LTG were recommended as first-line. The 1st-line recommendation for non-psychotic severe depression was MS + AAP, MS + LTG and AAP + LTG. For psychotic depression, MS + AAP was the TOC, and AAP + antidepressant (AD) and AAP + LTG were also recommended as first-line.

First-line medications included Li, Val, LTG, ARP and QTP for monotherapy, and Li, Val, LTG, ARP, OLZ and QTP for combination therapy in non-psychotic severe depression. Li, Val, LTG, QTP, OLZ and ARP were firstly preferred for monotherapy and Li, Val, LTG, QTP, OLZ and ARP for combination therapy in psychotic severe depression. If AD was needed, escitalopram, bupropion and sertraline were primarily preferred (Table 3).

Monotherapy of QTP, olanzapine fluoxetine complex (OFC) and lurasidone was firstly recommended in BAP 2016, while OFC, QTP, OLZ and LTG were in NICE guideline. LTG combination, AD combination, MS + QTP, MS + OFC, MS + lurasidone, MS + LTG and MS + AD were first-line combination strategies for bipolar depression in BAP 2016, while adjunctive OFC or QTP or OLZ or LTG strategies were in NICE.
Table 3. Treatment of bipolar depression across practice guidelines

| Guidelines | First-line treatment | Next-step intervention | Later intervention |
|------------|----------------------|------------------------|--------------------|
| KMAP-BP 2018 | Mild to moderate: Li, Val, LTG, ARP, QTP, MS+ (ARP or OLZ or QTP) | Mild to moderate: Add LTG or AAP or MS | Add (or change to) CLZ, Add buspirone or stimulant or thyroid hormone, ECT, rTMS |
| BAP 2016 | Non-psychotic severe: Li, Val, LTG, ARP, QTP, MS+ (ARP or OLZ or QTP) | Non-psychotic severe: Add MS or AAP or LTG or AD, Change MS or AAP, ECT |  |
| CANMAT 2018 | Psychotic: Li, Val, LTG, QTP, OLZ, ARP, MS+ (QTP or OLZ or ARP) | Psychotic: Add MS or AAP or LTG or AD, Change MS or AAP |  |
| CINP-BD 2017 | Mild to moderate: Add LTG or AAP or MS |  |  |
| NICE 2014 | Non-psychotic severe: Add MS or AAP or LTG or AD, Change MS or AAP |  |  |
| WFSBP 2010 | Optimize if no response |  |  |

KMAP-BP, Korean Medication Algorithms for Bipolar Disorder; BAP, The British Association for Psychopharmacology Guidelines for Treatment for Bipolar Disorder; CANMAT, Canadian Network for Mood and Anxiety Treatments; CINP-BD, International College of Neuro-Psychopharmacology Treatment Guidelines for Bipolar Disorder; NICE, National Institute for Health and Clinical Excellence Treatment for Bipolar Disorder; WFSBP, World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorder on the treatment of acute bipolar depression; Li, lithium; Val, various kinds of valproic acid; LTG, lamotrigine, ARP, aripiprazole; QTP, quetiapine; MS, mood stabilizer; OLZ, olanzapine; AAP, atypical antipsychotic; AD, antidepressant; ECT, electroconvulsive therapy; CLZ, clozapine; rTMS, repetitive transcranial magnetic stimulation; AM, antimanic agents; OFC, olanzapine-fluoxetine complex; SSRI, selective serotonin reuptake inhibitor; BUP, bupropion; adj, adjunctive; CBZ, carbamazepine; SNRI, serotonin norepinephrine reuptake inhibitor; MAOI, monoamine oxidase inhibitor; ASP, asenapine; FX, fluoxetine; OXC, oxcarbazepine; MDF, modafinil.

CANMAT recommended monotherapy of QTP, LTG and lurasidone, and MS+lurasidone or adjunctive LTG as first-line treatment strategies for treating depression. 18

In CINP-BD 2017, monotherapy of QTP, lurasidone and OFC was the first-line treatment for depressive patients. 19

However, WFSBP guideline recommended QTP, adjunctive QTP, OFC, OLZ, LTG, LTG+Li and Val as first-line treatment for bipolar depression (Table 3). 25

Next-step strategy

KMAP-BP 2018 prefers adjunctive use of another medication for all clinical situations while medication switching strategies are preferred for severe depression. When response was insufficient to initial treatment strategy, adding an AAP or LTG or MS was the next-step intervention for mild to moderate, non-psychotic and psychotic severe depressive patients. Adding AD strategy and switching MS or AAP could be considered for non-psychotic and psychotic severe depression. ECT, CLZ, buspirone, stimulant, thyroid hormone and rTMS were recommended as later intervention.

BAP 2016 recommends adding antimanic agents and ECT as a second-line strategy, and NICE guideline recommends adding LTG as the second-line.

Next-step strategies in CANMAT 2018 were mono-
therapy of Val, cariprazine and OFC, and adjunctive SSRI or bupropion. ECT was also preferred as second-line in CANMMA(T (Table 3).

Second-line treatment in CINP-BD 2017 guideline was Val or Li monotherapy, MS + lurasidone (or modafinil or pramipexole), Li + pioglitazone, and adding escitalopram or fluoxetine (FX).

For next-step treatments, WFSBP 2010 recommended optimization of first-line medications, QTP + CBZ (or Li), modafinil + Li (or Val or ADs), and ECT (Table 3).

**Mixed Features**

**Initial treatment**

KMAP 2018 divided mixed features into the following categories: mixed features with predominant manic symptoms (mixed mania/mania with mixed features), mixed features with predominant depressive symptoms (mixed depression/depression with mixed features) and mixed features without predominance.16) First-line treatment strategies for mixed mania and mixed features without predominance were MS + AAP combination therapy (TOC) and AAP monotherapy. For mixed depression, MS + LTG, MA + AAP and AAP + LTG were also recommended as first-line. First-line medications included Val, Li, ARP, OLZ and QTP for mixed mania and mixed features without predominance. Li, Val, LTG, ARP, OLZ, and QTP were firstly preferred for mixed depression.16

BAP 2016 recommended HP, OLZ, RIS, QTP and Val as first-line monotherapeutic agents, and HP, OLZ, RIS, QTP, Val and ARP with Li were first-line combination agents. Otherwise, monotherapy of HP, OLZ, QTP and RIS was recommended as first-line in NICE guideline,23 first-line combination was Li + HP, Li + OLZ, Li + QTP and Li + RIS.

In CINP-BD 2017, OLZ + MS (Li or Val) was first-line treatment for patients with mixed features.19 However, WFSBP guideline recommended Val, OLZ, ZIP and ARP as a first-line treatment for mixed states (Table 4).20

**Next-step strategy**

When MS and AAP combination therapy resulted in incomplete efficacy for treating mixed mania, KMAP-BP 2018 recommended 2 MSs and AAP + LTG as second-line strategies, and adding TAP or MS + LTG were suggested for later interventions. However, in case of mixed depression, KMAP-BP 2018 recommended changing specific MS or AAP, or adding another MS or AAP in second-line strategies, and 2 MSs, MS + AS and AAP + AD was recommended for later intervention.16

Second-line treatment in CINP-BD 2017 guideline was OLZ, ARP and CBZ, and Val, OFC and ZIP was recommended for later intervention strategies.

As next-step treatments, WFSBP 2010 has recommended RIS and CBZ for mixed states (Table 4).

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**Table 4. Treatment for mixed features across practice guidelines**

| Guidelines | First-line treatment | Next-step intervention | Later intervention |
|------------|----------------------|------------------------|--------------------|
| KMAP-BP 201816 | Mixed mania: MS + AAP, AAP | Mixed mania: MS, 2 MSs, AAP + LTG | Mixed mania: TAP, LTG, MS + LTG |
| BAP 201617 | Same as for mania | Mixed depression: change (or add) AAP or MS or LTG | Mixed depression: LTG, 2 MSs, MS + AD, AAP + AD |
| CANMMA(T 201818 | No recommendations | Same as for mania | Same as for mania |
| CINP-BD 201719 | OLZ + Val (or Li) | OZP, ARP, CBZ | Val |
| NICE 201420 | Same as for mania | Same as for mania | OFC, ZIP |
| WFSBP 200923 | Val, AAP (OLZ, ZIP, ARP) | Same as for mania | RIS, CBZ |

*KMAP-BP, Korean Medication Algorithms for Bipolar Disorder; BAP, The British Association for Psychopharmacology Guidelines for Treatment for Bipolar Disorder; CANMMA(T, Canadian Network for Mood and Anxiety Treatments; CINP-BD, International College of Neuro-Psychopharmacology Treatment Guidelines for Bipolar Disorder; NICE, National Institute for Health and Clinical Excellence Treatment for Bipolar Disorder; WFSBP, World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorder: Treatment for acute mania; MS, mood stabilizer; AAP, atypical antipsychotics; LTG, lamotrigine; TAP, typical antipsychotics; AD, antidepressant; OLZ, olanzapine; Val, various kinds of valproic acids; Li, lithium; ARP, aripiprazole; CBZ, carbamazepine; OFC, olanzapine fluoxetine complex; ZIP, ziprasidone; RIS, risperidone.*
Table 5. Treatment of rapid cycling across practice guidelines

| Guidelines          | First-line treatment                                                                 | Next-step intervention                                      | Later intervention                                                      |
|---------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------------------|
| KMAP-BP 2018        | Currently manic: MS + AAP Current manic: MS + AAP, AAP + LTG, MS + LTG                | Currently manic: add AAP or MS, change MS                    | Currently manic: MS + TAP (or other AAP), ECT                         |
| BAP 2016            | No recommendation                                                                    | OLZ, Li                                                     | MS + QTP (or RIS)                                                     |
| CANMAT 2018         | No recommendation                                                                    |                                                             |                                                                        |
| CINP-BD-2017        | ARP, QTP, Val                                                                       |                                                             |                                                                        |
| NICE 2014           | Same as with other types of bipolar disorder                                        |                                                             |                                                                        |
| WFSBP 2009          | Not mentioned                                                                       |                                                             |                                                                        |

KMAP-BP, Korean Medication Algorithms for Bipolar Disorder; BAP, The British Association for Psychopharmacology Guidelines for Treatment for Bipolar Disorder; CANMAT, Canadian Network for Mood and Anxiety Treatments; CINP-BD, International College of Neuro-Psychopharmacology Treatment Guidelines for Bipolar Disorder; NICE, National Institute for Health and Clinical Excellence Treatment for Bipolar Disorder; WFSBP, World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorder; Treatment for acute mania; MS, mood stabilizer; AAP, atypical antipsychotics; LTG, lamotrigine; ECT, electroconvulsive therapy; TAP, typical antipsychotics; AD, antidepressant; ARP, aripiprazole; QTP, quetapine; Val, various kinds of valproic acids; OLZ, olanzapine; Li, lithium; RIS, risperidone.

Rapid Cycling

For treating rapid-cycling patients, regardless of their current episodes, a combination of MS and AAP were the first-line treatment strategy, (TOC in currently manic state) in the KMAP-BP 2018. However, a combination of LTG and MS (or AAP) was potentially preferable during episodes of current depression. Adding another MS or AAP was the second-line strategy for any episodes. MS change was a second-line in currently manic; ECT was a second-line in currently depressed.\(^{16}\)

In CINP-BD 2017 guideline, ARP, QTP and Val were the first-line treatment for rapid cycling patients. OLZ and Li were recommended as second-line strategy, and MS + QTP and MS + RIS were later intervention (Table 5).\(^{19}\)

Continuation and Maintenance Treatment

Initial treatment

In KMAP-BP 2018,\(^{16}\) preferred maintenance treatment strategies for preventing manic episode was a combination of MS and AAP, MS monotherapy, or AAP monotherapy. Preferred AAPS for maintenance treatment included ARP, (TOC) QTP and OLZ, for use in monotherapy or in adjunctive use with MS. The preferred maintenance strategy was the same for preventing depressed episode in both bipolar I and II disorder. Recommended first-line strategies were MS + AAP, MS + LTG, MS alone, LTG alone, AAP alone, and MS + AAP + LTG.

Monotherapy of Li was firstly recommended in BAP 2016 and NICE guidelines.\(^{17,23}\) CANMAT recommended monotherapy of Li, QTP, Val, LTG, ASP, ARP and ARP once monthly (ARP OM), and MS + QTP and MS + ARP as first-line strategies for maintenance treatment.\(^{18}\)

In CINP-BD 2017, monotherapy of Li, ARP, OLZ, PAL, QTP, RIS and RIS long-acting injectable (RIS LAI) was a first-line in maintenance therapy.\(^{19}\)

In WFSBP 2013,\(^{26}\) ARP, LTG, Li and QTP were suggested as first-line drugs for preventing episodes of bipolar disorder (Table 6).

Next-step strategy

In KMAP-BP 2018,\(^{16}\) combination therapy of MS + LTG, 2 MSs and AAP + LTG was recommended as second-line treatment for preventing manic episode. Triple combination of MS, AAP and LTG was a later intervention for manic episode prevention.

In the case of preventing depressive episode, 2 MSs or MS + AAP + AD were recommended as second-line strategies. Otherwise, AAP + AD and MS + AD combination therapy were a later intervention. Mostly preferred ADs were bupropion, escitalopram and sertraline.

BAP 2016\(^{17}\) recommended the following. If mania predominates, Val, OZP, QTP, RIS LAI, CBZ and OXC are preferred. If depression predominates, LTG, QTP and lurasidone are preferred. Also, combination therapy, AD, CLZ and maintenance ECT were as later intervention.
Table 6. Maintenance treatment across practice guidelines

| Guidelines       | First-line treatment                                                                 | Next-step intervention                                      | Later intervention                                                                 |
|------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------------------------------|
| KMAP-BP 2018     | Preventing manic: MS + AAP, MS + AAP                                                | Preventing manic: MS + LTG, 2 MSs, AAP + LTG                | Preventing manic: MS + AAP + LTG, LTG                                             |
|                  | Preventing depressive: MS + (AAP or LTG), MS, LTG, AAP, MS + AAP + LTG              | Preventing depressive: 2 MSs, MS + AAP + AD                 | Preventing depressive: AAP + AD, MS + AD                                           |
|                  | Li                                                                                    | If mania predominates: Val, OLZ, QTP, RIS LAI, CBZ, OXC     | Combination therapy, AD, CLZ, Maintenance ECT                                     |
|                  |                                                                                      | If depression predominates: LTG, QTP, lurasidone             |                                                                                  |
| BAP 2016         | Li                                                                                    | OLZ, RIS LAI, RIS LAI (adj), CBZ, PAL, lurasidone + Li (or Val) | AR + LTG, OFC, CLZ (adj), gabapentine (adj)                                      |
|                  |                                                                                      | Add FX or Li, Li + CBZ, QTP + Li (or Val), MS + OLZ (or ARP) | Add RIS LAI or CBZ or LTG or N-acetylcysteine                                   |
| CANMAT 2018      | Li, QTP, Val, LTG, ASP, QTP + Li (or Val), ARP + Li (or Val), ARP, ARP OM            | Add FX or Li, Li + CBZ, QTP + Li (or Val), MS + OLZ (or ARP) |                                                                                  |
|                  |                                                                                      | OLZ (mania and any episode), RIS (mania and any episode), Li (any episode), QTP (any episode) |                                                                                  |
| CINP-BD-2017     | Li, ARP, OLZ, PAL, QTP, RIS, RIS LAI                                                 | OLZ (mania and any episode), RIS (mania and any episode), Li (any episode), QTP (any episode) |                                                                                  |
| NICE 2014        | Li                                                                                    | OLZ (mania and any episode), RIS (mania and any episode), Li (any episode), QTP (any episode) |                                                                                  |
| WFSBP 2013       | ARP (mania and any episode), LTG (depression and any episode), Li (any episode), QTP (any episode) | OLZ (mania and any episode), RIS (mania and any episode), Li (any episode), QTP (any episode) |                                                                                  |

KMAP-BP, Korean Medication Algorithms for Bipolar Disorder; BAP, The British Association for Psychopharmacology Guidelines for Treatment for Bipolar Disorder; CANMAT 2018, Canadian Network for Mood and Anxiety Treatments; CINP-BD, International College of Neuropsychopharmacology Treatment Guidelines for Bipolar Disorder; NICE, National Institute for Health and Clinical Excellence; WFSBP, World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorder: Maintenance treatment; MS, mood stabilizer; AAP, atypical antipsychotic; LTG, lamotrigine; AD, antidepressant; Li, lithium; Val, various kinds of valproic acid; OLZ, olanzapine; QTP, quetiapine; RIS LAI, risperidone long-acting injectable; CBZ, carbamazepine; OXC, oxtcarbazepine; AD, antidepressant; CLZ, clozapine; ECT, electroconvulsive therapy; ASA, asenapine; ARP, aripiprazole; ARP OM, aripiprazole once monthly; adj, adjunctive; PAL, paliperidone; ZIP, ziprasidone; OFC, olanzapine-fluoxetine complex; FX, fluoxetine.

DISCUSSION

Although various guidelines have been offered to improve clinical practice, their enforcement has been difficult, because they have different characteristics in terms of clarity, simplicity of recommendations, reliability and use of evidence-based medicine. In this review, we compared recommendations of KMAP-BP 2018 with those of other widely used treatment guidelines. For initial treatment of mania, there were no substantial differences across treatment guidelines. All guidelines recommend MS alone, AAP alone, or MS + AAP as first-line treatment strategies for mania. However, other guidelines recommend MS or AAP monotherapy and combination therapy as a first-line modality in a same degree while MS + AAP combination therapy was ranked as TOC in KMAP-BP 2018. This might reflect that Korean experts were doubtful for the clinical effectiveness of monotherapy and had laid stress on the superiority of combination therapy over monotherapy in terms of efficacy for mania based on results from the clinical trials and meta-analysis. The WFSBP guidelines, BAP 2016 and CINP-BD-2017 recommend Val as the only first-line MS medication. This result seems to reflect concerns regarding the safety of Li. However, guidelines have advised that Val should not be used for women of child bearing potential.
tial because of its unacceptable risk of teratogenesis and impaired intellectual development of the fetus.17,19,24

NICE guidelines do not recommend Li or Val as first-line treatment strategies in drug-naive manic patients. However, newly published KMAP-BP 201816) and CANMAT 201818) recommended Li and Val as first-line MS agents. This discrepancy was thought to be related to the fact that NICE guidelines targeted a group of professionals working in various psychiatrics fields, hence providing relatively simply recommendations for diagnosis and treatment rather than offering a full range of treatments differentiated in accordance with supporting evidence and recommendation strength.

OLZ, ARP, QTP and RIS were first-line AAPs for manic episodes across guidelines; however, CANMAT 201818) and CINP-BD 2017 guideline19) recommended OLZ as a second-line strategy. It might reflect its safety concern, tolerability and adherence issues.45,46) However, OLZ and RIS showed superior antimanic effect over other AAPs in a meta-analysis,47) and OLZ and QTP monotherapy were known to be reducing overall risk of relapse.18,48) Authors recommend that these diverse opinions should be considered in clinical practice. Otherwise, asenapine and cariprazine were recommended as first-line option in newly published guidelines.18,19)

In cases of non-response or incomplete response to first-line strategies, guidelines recommended switching or adding another first-line agent. KMAP-BP 201816) also recommended switching from a MS or AAP to a different agent of the same type. However, triple combinations such as MS + 2 AAPs or Li + Val + AAP were suggested as next-step interventions in KMAP-BP 2018. ECT and CLZ were recommended in most guidelines, while CPZ, CNZP, tamoxifen and rTMS were only recommended in CANMAT 2018.18)

KMAP-BP 2018 recommended monotherapy with MS or AAP as the first-line strategy for only mild to moderate depression. MS + AAP, MS + LTG and AAP + LTG combinations were preferred from mild to moderate depression, to non-psychotic severe case. AAP + AD combination was a first-line treatment only in psychotic severe depression. However, other guidelines recommended monotherapy and combination therapy at approximately similar degree in the first-line strategy for bipolar depression. Additionally, CINP guideline’s first-line strategy only recommended QTP, lurasidone and OFC. Although MS and AAP monotherapy was supported by higher degrees of evidence for bipolar depression, Korean experts preferred combination treatment over monotherapy for treating bipolar depression as in mania. This might be because a high proportion (66%) of Korean experts who participated in KMAP-BP 2018 worked at university hospitals. Their primary interests might lie in treatment-resistant cases that generally require combination therapies. Moreover, there were methodological differences between KMAP-BP 2018 and other guidelines (e.g., expert consensus vs. evidence-based). However, polypharmaceutical approaches to psychotropic medication appear to be increasingly common in clinical practice,49) suggesting that it is difficult to apply research-based findings to real clinical fields.

ARP, QTP and OLZ were recommended as a first-line monotherapy or adjunctive therapy for bipolar depression in KMAP-BP 2018. However, ARP was labeled as 3rd-line recommendation by CANMAT 2018 and CINP-BD 2017 guidelines. It reflects some results showing that ARP monotherapy is not superior over placebo.50,51) However, another meta-analysis suggested that ARP monotherapy could be effective for treating of acute depression because combined data from two negative studies revealed a significant effect.52,53) Additionally, in Korea, the proportion of patients with bipolar depression prescribed with ARI was increased from 1.4% (2004-2006) to 8.5% (2011-2014), but the mean initial and maximum dose was 15 and 30 mg/day respectively in 2004-2006 and 6.3 and 16.8 mg/day respectively in 2011 to 2014.54) The high preference and use of ARP for treating bipolar depression in Korea could be based on some evidence that supports the efficacy of ARP for bipolar depression. Therapeutic efficacy of ARP on bipolar depression was not conclusive now. Well designed large scale studies are needed.

Strict prohibition of AD monotherapy and increasing preference for LTG were found in all guidelines. This increasing preference for LTG might reflect recent meta-analysis results.

The increase in preference for LTG seems to reflect the finding that LTG is more effective than placebo in LTG monotherapy and in adjunctive therapies.55) However, adjunctive AD use with MS or AAP was more widely recommended.

In KMAP-BP 2018, adjunctive use of CLZ, buspirone, stimulant and thyroid hormone, and ECT and rTMS were the 3rd-line strategy for bipolar depression. Moreover, a
A wide variety of treatments were recommended as 3rd-line strategy in other guidelines, such as CBZ (or OXC), ADs, modafinil, eicosapentaenoic acid, rTMS, ketamine, light therapy/sleep deprivation, levotheroxine, N-acetylcysteine, primapexle, armodafinil, ASP and L-sulpiride. It might reflect the difficulty in treating bipolar depression.

Initial treatment strategy was MS + AAP and AAP monotherapy for mixed mania, and MS + LTG, MA + AAP and AAP + LTG for mixed depression in KMAP-BP 2018. Val, Li, ARP, OLZ, QTP and LTG were the mostly preferred medications in KMAP-BP 2018.16 We found that recommendations for mixed features were similar to those for mania. These recommendation trends are also found with in other treatment guidelines.17,19,23,24

Other guidelines did not recommend specific treatment modality for rapid cycling. Only CINP-BD 2017 recommended ARP, QTP and Val as the first-line treatment while OLZ and Li were recommended as a second-line strategy.19 In KMAP-BP 2018, MS + AAP, and LTG + MS (or AAP) (currently depressed), were the first-line treatment strategy.16 MS change and adding another MS or AAP, and ECT were the second-line strategy for treating rapid-cycling patients. These results are consistent with findings of a previous study indicating that MS monotherapy has limited effect on rapid cycling while a combination of Li and Val has been found to be more effective than Li or Val monotherapy.56 Val, QTP, OLZ and ARP were preferred in any episode, and LTG and Li were additional first-line agents for currently depressed. Since recent accumulation of data showed that AAP treatment was also effective for rapid cycling bipolar disorder,7 the preference for AAP alone or in combination with MS was increased in guidelines. In contrast to KMAP-BP 2018, other guidelines did not discuss strategies for treating rapid cycling bipolar disorder. This might be due to insufficient research dealing with this condition. Direct comparison across guidelines will be possible once more comprehensive understanding of rapid cycling is achieved. We found that, in discussing maintenance treatments for bipolar disorder, numerous results were consistent across various guidelines. In KMAP-BP 2018,16 MS + AAP, MS, AAP, MS or LTG and adjunctive LTG were recommended as the first-line strategy in maintenance treatment, and Val, Li, ARP, QTP, OLZ and LTG were the mostly preferred. However, among MS, Li was only first-line agent in BAP,17 NICE23 and CINP-BD-201719-22 guideline. Despite the relapse preventing effect of Li and Val was widely understood, there were some arguments regarding their safety issue. Clinicians should be aware of these issues in clinical applications.

KMAP-BP 201816 and CINP-BD 2017 guideline19 recommended OLZ as a first-line agent in maintenance treatment while other guidelines17,18,23 placed it as second-line. RIS was the first-line agent only in CINP-BD 201719-22 guideline. It was a second-line in KMAP-BP16 and WFSBP26 guideline. However, it was not included in other guidelines.17,18,23 There were no published randomized controlled trials that evaluated bipolar maintenance treatment with RIS, and there are some controversies about OLZ’s depression-preventing effect.26,60,61 However, RIS LAI was preferred recommendations either as a monotherapy or in combination with MS in recently published guidelines,17-19 and this was based on previous results showing its positive effects in preventing bipolar episodes.62-64 Clinicians might wish to consider this point. ARP OM also showed efficacy and safety during maintenance treatment and it was recommended as first-line in CANMAT guideline.18,65,66

There were no substantial differences between KMAP-BP 2018 and other treatment guidelines. In particular, increased preference for AAP and LTG was similar across all guidelines. However, a strong preference for combination therapy was characteristic of KMAP-BP 2018, predominantly for the treatment of psychotic mania and severe depression.

LIMITATIONS

KMAP-BP 201816 guideline was an expert consensus guideline while other guidelines17-26 were evidence-based ones. Some treatment strategies in KMAP-BP 2018 might not have been rated as first-line options despite evidence demonstrating their effectiveness. Evidence-based treatment evaluation is a systematic process that critically evaluates scientific evidence about a particular treatment. Evidence comes from many sources, including randomized clinical trials, cohort studies, observational case studies, and retrospective studies. These good evidences can help clinicians evaluate the actual effect of a treatment on patient outcomes. However, most of these experimental data in evidence-based guidelines were derived from randomized controlled trials and they might...
not reflect the complexity of real clinical situations. This suggests that there might be some discrepancies between findings of randomized controlled trials and the real-world practice. On the other hand, it has not been compared with expert consensus guidelines, but it is due to a lack of recently published one.

KMAP-BP 2018 has limitations as a set of expert consensus guidelines. Hence, we made efforts to compensate for these limitations by opening public hearing at the Academic Conference of the Korean College of Neuropsychopharmacology and by opening results announcement and panel discussion at the Academic Conference of the Korean Society for Affective Disorders. Despite limits of expert opinion, our current comparison showed that there were no major differences in overall treatment recommendations between KMAP-BP 2018 and other guidelines. Furthermore, recommendations of KMAP-BP 2018 aligned well with current changes in the pharmacotherapy of bipolar disorder based on newer evidence. However, we also found some differences between KMAP-BP 2018 and other guidelines with respect to recommended treatments for psychotic mania and severe depression. This likely reflects the controversial nature of results in these areas. As relevant studies accumulate, they may prompt appropriate modifications to some of these guidelines. This algorithm could not recommend for new drugs such as asenapine, cariparzine or lurasidone highly recommended with strong evidences in other algorithms,18,19) because they were not yet marketed in South Korea.

Finally, we have reason to believe that KMAP-BP 2018 provides useful information to Korean clinicians regarding their clinical decision-making, and that the guideline would be well administered in Korean clinical practice.

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