**Review**
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# 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, lurasidine, 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.[1)] This trend has contributed to the development of treatment algorithms or clinical practice guidelines in psychiatric fields,[2)] including several treatment algorithms for mood disorder.[3-10)]

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)

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was initiated in 2001. KMAP-BP was published in 2002 (KMAP-BP 2002), and its feasibility has been confirmed.[11,12] Revised versions of KMAP-BP were released in 2006, 2010, and 2014.[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).[16] In this review article, we compared recommendations of KMAP-BP 2018[16] with those of other recently published global treatment guidelines, including British Association for Psychopharmacology Guidelines for Treatment of Bipolar Disorder (BAP 2016),[17] Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders 2018 guidelines for the management of patients with bipolar disorder (CANMAT 2018),[18] The International College of Neuro-Psychopharmacology Treatment Guidelines for Bipolar Disorder (CINP-BD 2017),[19-22] National Institute for Health and Clinical Excellence Clinical Guideline for Bipolar Disorder (NICE 2014),[23] and The World Federation Society of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorder (WFSBP) (Table 1).[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.[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).[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[17] reflected the consensus of experts and a wide range of feedback. This BAP guideline should be read alongside NICE 2014.[23] The BAP 2016 also provides basic information to patients and caregivers about diagnosis and treatment.

**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[16] | Psychiatrists | Expert consensus |
| British Association for Psychopharmacology (BAP) | 2016[17] | Psychiatrists<br>Primary care physicians | Evidence-based |
| Canadian Network for Mood and Anxiety Treatments (CANMAT) | 2018[18] | Psychiatrists | Evidence-based |
| The International College of Neuropsychopharmacology Treatment Guideline for Bipolar disorder (CINP-BD 2017) | 2017[19-22] | Primary and secondary care physicians | Evidence-based |
| National Institute for Health and Clinical Excellence (NICE) | 2014[23] | Psychiatrists<br>Primary care physicians | Evidence-based |
| World Federation of Societies of Biological Psychiatry (WFSBP) | 2009 (acute mania, mixed, rapid cycling)[24]<br>2010 (acute depression)[25]<br>2013 (maintenance)[26] | Psychiatrists<br>Primary care physicians | Evidence-based |

### 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 2018[18] 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 Neuropsychopahrmacolgy. 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.[34] 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 2018[16] 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 MSs 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 subitem and 1,326 response options. The 9-point scale from RAND Corporation[5] 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 firs-line, aripiprazole (ARP) and risperidone (RIS) were the second-line. For psychotic mania, OLZ, QTP, RIS and ARP were recommended as first-line treatment strategy. OLZ, QTP, RIS and ARP were also preferred as first-line agents when they were combined with MS for non-psychotic and psychotic mania. Monotherapy of Val, QTP, Li, ARP and OLZ were the most preferred agent for hypomanic episodes.

NICE guideline[23] and BAP 2016 guideline[17] recommended haloperidol (HP), OLZ, RIS and QTP as first-line AAPs for drug naïve manic patients. On the other hand, optimazing Li was the first-step for patient already taking long-term treatment medication, then also adding HP, OLZ, RIS and QTP was the first-line strategy.

CANMAT 2018[18] recommends monotherapy of QTP, asenapine, paliperidone (PAL), RIS and cariprazine, and adjunctive QTP or ARP or RIS or asenapine with MS as first-line treatment strategies for treating mania.

In CINP-BD 2017, monotherapy of ARP, asenapine, cariprazine, PAL, QTP, RIS and Vale was a first-line for manic patients.[19]

But in the WFSBP guideline, Val, ARP, ziprasidone (ZIP) and RIS was recommended as first-line treatment for mania (Table 2).[24]

#### Next-step strategy

In cases of non-response or incomplete response to first-line strategies, guidelines recommended switching or adding another first-line agent. KMAP-BP 2018[16] recommended switching from a MS or AAP to a different agent of the same type. Additionally, triple combinations such as MS+2 AAPs or Li+Val+AAP were suggested as next-step interventions in KMAP-BP 2018.

BAP 2016[17] recommended ARP, carbamazepine (CBZ), Li and MS+AAP as a second-line strategy while switching alternative antipsychotics or adding Li or Val was the second-line in NICE guideline.[23] Electroconvulsive therapy (ECT) and clozapine (CLZ) were later intervention.[17,23]

Next-step strategy in CANMAT 2018[18] included monotherapy of OLZ, CBZ, ZIP and HP, and combination of OLZ and MS and 2 MSs (Li+Val). ECT was preferred as second-line in CANMMAT. This guideline also recommended CBZ+MS, chlorpromazine (CPZ), clonazepam (CNZP), CLZ, HP+MS, repetitive transcranial magnetic stimulation (rTMS), tamoxifen and MS+tamoxifen as later intervention strategies.

Second-line treatment in CINP-BD 2017[19] guideline was OLZ, Li, CBZ and HP monotherapy, and combination of MS (Li or Val) and ARP (or HP or OZP or QTP or RIS). Li+allopurinol, Val+typical antipsychotics (TAP), MS+medroxyprogesterone and Val+celcoxib were recommended as second-line treatment. ECT and oxcarbazepine (OXC) were suggested for later intervention.

As next-step strategies, WFSBP[24] recommended opti-

**Table 2.** Treatment for acute mania across practice guidelines

| Guidelines | First-line treatment | Next-step intervention | Later intervention |
|---|---|---|---|
| KMAP-BP 2018[16] | Non-psychotic: Val, Li, OLZ, QTP, MS+OLZ (or QTP or RIS or ARP)<br>Psychotic: OLZ, QTP, RIS, ARP, MS+OLZ (or QTP or RIS or ARP)<br>Hypomania: Val, QTP, Li, ARP, OLZ | 2 MSs+AAP, MS+2 AAPs<br>Psychotic: 2 MSs+AAP, MS+2 AAPs, 2 AAPs<br>Hypomania: MS+AAP | Replace MS or AAP, TAP |
| BAP 2016[17] | Without AM: HP, OLZ, RIS, QTP, Val<br>With Li: optimization, Add HP, OLZ, RIS, QTP, Val, ARP | Without AM: ARP, CBZ, Li<br>With Li: MS+AAP | ECT or CLZ |
| CANMAT 2018[18] | Li, QTP, Val, ASP, ARP, PAL, RIS, cariprazine<br>Combination with MS: QTP, ARP, RIS, ASP | 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[19] | ARP, ASP, cariprazine, PAL, QTP, RIS, Val<br>Switch to other first-step monotheray | OLZ, Li, CBZ, HP<br>Li (or Val)+ARP (or HP or OLZ or QTP or RIS)<br>Li+allopurinol, Val+TAP, MS+medroxyprogesterone, Val+celcoxib | ECT, OXC |
| NICE 2014[23] | Without AM: HP, OLZ, QTP, RIS<br>With Li: optimization, adding HP, OLZ, QTP, RIS | Alternative AP or adding Li or Val | ECT |
| WFSBP 2009[24] | Monotherapy with 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.[16] 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 recommednded as fist-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,[17] while OFC, QTP, OLZ and LTG were in NICE[23] 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,[17] adjunctive OFC or QTP or OLZ or LTG strategies were in NICE.[23]

**Table 3.** Treatment of bipolar depression across practice guidelines

| Guidelines | First-line treatment | Next-step intervention | Later intervention |
|---|---|---|---|
| KMAP-BP 2018[16] | Mild to moderate: Li, Val, LTG, ARP, QTP, MS+(ARP or OLZ or QTP)<br>Non-psychotic severe: Li, Val, LTG, ARP, QTP, MS+(ARP or OLZ or QTP)<br>Psychotic: Li, Val, LTG, QTP, OLZ, ARP, MS+(QTP or OLZ or ARP) | Mild to moderate: Add LTG or AAP or MS<br>Non-psychotic severe: Add MS or AAP or LTG or AD, Change MS or AAP, ECT<br>Psychotic: Add MS or AAP or LTG or AD, Change MS or AAP | Add (or change to) CLZ, Add buspirone or stimulant or thyroid hormone, ECT, rTMS |
| BAP 2016[17] | Without AM: QTP, OFC, lurasidone, LTG combination, AD combination<br>With AM; optimization, QTP, OFC, lurasidone, LTG, AD<br>Consider ECT in severe depression | Add anti-manic agent, ECT | |
| CANMAT 2018[18] | QTP, lurasidone+Li (or Val), LTG, lurasidone, LTG (adj) | Val, SSRI/BUP (adj), ECT, cariprazine, OFC | CBZ,<br>Adj: OLZ, SNRI/MAOI, modafinil, eicosapentaenoic acid, rTMS, ketamine, light therapy/sleep deprivation, Levothyroxine, N-acetylcysteine, pramipexle, ARP, armodafinil, ASP |
| CINP-BD-2017[19] | QTP, lurasidne, OFC | Val, Li, MS+lurasidone (or modafinil or pramipexole) Li+pioglitazone, Add escitalopram or FX | ARP, imipramine, phenezine, Li+OXC (or L-sulpiride) |
| NICE 2014[23] | Without AM; OLZ+FX, QTP, OLZ, LTG<br>With AM; optimization, adjunctive OLZ+FX, adjunctive QTP, OLZ (adj), LTG (adj) | Adding LTG | |
| WFSBP 2010[25] | QTP, QTP (adj), OFC, OLZ, LTG, LTG+Li, Val | Optimization of first-line treatment, QTP add CBZ, Li, MDF+Li/Val/ADs, ECT | |

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, adjuctive QTP, OFC, OLZ, LTG, LTG+Li and Val as first-line treatment for bipolar depression (Table 3).[25]

### Next-step strategy

KMAP-BP 2018[16] 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 severe 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[17] 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[18] were mono-

therapy of Val, cariprazine and OFC, and adjunctive SSRI or bupropion. ECT was also preferred as second-line in CANMMAT (Table 3).

Second-line treatment in CINP-BD 2017[19] 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[25] 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[17] 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).[25]

### 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[19] guideline was OLZ, ARP and CBZ, and Val, OFC and ZIP was recommended for later intervention strategies.

As next-step treatments, WFSBP 2010[24] has recommended RIS and CBZ for mixed states (Table 4).

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

| Guidelines | First-line treatment | Next-step intervention | Later intervention |
|---|---|---|---|
| KMAP-BP 2018[16] | Mixed mania: MS+AAP, AAP<br>Mixed depression: MS+LTG, MS+AAP, AAP+LTG | Mixed mania: MS, 2 MSs, AAP+LTG<br>Mixed depression: change (or add) AAP or MS or LTG | Mixed mania: TAP, LTG, MS+LTG<br>Mixed depression: LTG, 2 MSs, MS+AD, AAP+AD |
| BAP 2016[17] | Same as for mania | Same as for mania | Same as for mania |
| CANMAT 2018[18] | No recommendations | | |
| CINP-BD-2017[19] | OLZ+Val (or Li) | OZP, ARP, CBZ | Val<br>OFC, ZIP |
| NICE 2014[23] | Same as for mania | Same as for mania | Same as for mania |
| WFSBP 2009[24] | Val, AAP (OLZ, ZIP, ARP) | RIS, CBZ | |

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; 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[16] | Currently manic: MS+AAP<br>Currently depressed: MS+AAP, AAP+LTG, MS+LTG | Currently manic: add AAP or MS, change MS<br>Currently depressed: add AAP or LTG or MS, ECT | Currently manic: MS+TAP (or other AAP), ECT<br>Currently depressed: MS+AAP+AD, MS+TAP (or other AAP), change AAP (or MS or AD), ECT |
| BAP 2016[17] | No recommendation | | |
| CANMAT 2018[18] | No recommendation | | |
| CINP-BD-2017[19] | ARP, QTP, Val | OLZ, Li | MS+QTP (or RIS) |
| NICE 2014[23] | Same as with other types of bipolar disorder | | |
| WFSBP 2009[24] | 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 were 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 sertaline.

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 in

**Table 6.** Maintenance treatment across practice guidelines

| Guidelines | First-line treatment | Next-step intervention | Later intervention |
|---|---|---|---|
| KMAP-BP 2018[16] | Preventing manic: MS+AAP, MS, AAP<br>Preventing depressive: MS+(AAP or LTG), MS, LTG, AAP, MS+AAP+LTG | Preventing manic: MS+LTG, 2 MSs, AAP+LTG<br>Preventing depressive: 2 MSs, MS+AAP+AD | Preventing manic: MS+AAP+LTG, LTG<br>Preventing depressive: AAP+AD, MS+AD |
| BAP 2016[17] | Li | If mania predominates; Val , OLZ, QTP, RIS LAI, CBZ, OXC<br>If depression predominates; LTG, QTP, lurasidone | Combination therapy, AD, CLZ, Maintenance ECT |
| CANMAT 2018[18] | Li, QTP, Val, LTG, ASP, QTP+Li (or Val), ARP+Li (or Val), ARP, ARP OM | OLZ, RIS LAI, RIS LAI (adj), CBZ, PAL, lurasidone+Li (or Val), ZIP+Li (or Val) | ARP+LTG, OFC, CLZ (adj), gabapentine (adj) |
| CINP-BD-2017[19] | Li, ARP, OLZ, PAL, QTP, RIS, RIS LAI | Add FX or Li, Li+CBZ, QTP+Li (or Val), MS+OLZ (or ARP) | Add RIS LAI or CBZ or LTG or N-acetylcysteine |
| NICE 2014[23] | Li | Val, OLZ, QTP | |
| WFSBP 2013[26] | 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) | AD (depression), PAL (mania and any episode), Val (depression), adjunctive ZIP (mania and 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 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: 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, oxcarbazepine; 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.

maintenance treatment.

NICE guideline recommended Val, OLZ and QTP as second-line strategy.[23]

Next-step strategies in CANMAT 2018[18] included monotherapy of OLZ, RIS LAI, CBZ and PAL, and adjunctive RIS LAI, and combination of MS+lurasidone and MS+ZIP. ARP+LTG, OFC, adjunctive CLZ and adjunctive gabapentine were recommended for later intervention in maintenance treatment.

Second-line treatment in CINP-BD 2017[19] guideline was adding FX or Li, and Li+CBZ, MS+QTP, MS+OLZ and MS+ARP combinations. Adding RIS LAI, CBZ, LTG and N-acetylcyteine was later intervention in CINP guideline.

WFSBP 2010[26] recommended OLZ and RIS as the next-step strategy. When used in context, AD, PAL, Val and adjunctive ZIP could be recommended for a later intervention (Table 6).

## 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.[8,22,38] 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.[39-44]

The WFSBP guidelines,[24] BAP 2016[17] and CINP-BD-2017[24] 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 poten-

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-naïve manic patients. However, newly published KMAP-BP 2018[16)] and CANMAT 2018[18)] 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 2018[18)] and CINP-BD 2017 guideline[19)] 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 2018[16)] 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 thar 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

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, levothyroxine, N-acetylcysteine, pramipexle, 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,[57-59] 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] NICE[23] and CINP-BD-2017[19-22] guidelines. 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 2018[16] and CINP-BD 2017 guideline[19] recommended OLZ as a first-line agent in maintenance treatment while other guidelines[17,18,23] placed it as second-line. RIS was the first-line agent only in CINP-BD 2017[19-22] guideline. It was a second-line in KMAP-BP[16] and WFSBP[26] 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 2018[16] guideline was an expert consensus guideline while other guidelines[17-26] 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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## REFERENCES

1. Evidence-Based Medicine Working Group. *Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA 1992;268:2420-2425.*
2. American Psychiatric Association. *Practice guideline for major depressive disorder in adults. American Psychiatric Association. Am J Psychiatry 1993;150(4 Suppl):1-26.*
3. American Psychiatric Association. *Practice guideline for the treatment of patients with bipolar disorder. American Psychiatric Association. Am J Psychiatry 1994;151(12 Suppl): 1-36.*
4. Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP. *The expert consensus guideline series: medication treatment of bipolar disorder 2000. Postgrad Med 2000;Spec No:1-104.*
5. Kahn DA, Sachs GS, Printz DJ, Carpenter D, Docherty JP, Ross R. *Medication treatment of bipolar disorder 2000: a summary of the expert consensus guidelines. J Psychiatr Pract 2000; 6:197-211.*
6. Suppes T, Dennehy EB, Hirschfeld RM, Altshuler LL, Bowden CL, Calabrese JR, *et al. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. J Clin Psychiatry 2005;66:870-886.*
7. Goodwin GM. *Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2003;17:149-173; discussion 147.*
8. Parker GB, Graham RK, Tavella G. *Is there consensus across international evidence-based guidelines for the management of bipolar disorder? Acta Psychiatr Scand 2017;135:515-526.*
9. Wang HR, Bahk WM, Seo JS, Woo YS, Park YM, Jeong JH, *et al. Korean medication algorithm for depressive disorder: comparisons with other treatment guidelines. Clin Psychopharmacol Neurosci 2017;15:199-209.*
10. Seo JS, Bahk WM, Woo YS, Park YM, Jeong JH, Kim W, *et al. Korean Medication Algorithm for Depressive Disorders 2017:* third revision. *Clin Psychopharmacol Neurosci 2018;16: 67-87.*
11. The Executive Committee of Korean Bipolar Medication Algorithm Project for Bipolar Disorder. *The Korean medication guideline for bipolar disorder. Seoul:Jungang Moonwhasa;2002.*
12. Jon DI, Bahk WM, Yoon BH, Min KJ, Shin YC, Cho HS, *et al. Algorithm-driven treatment for bipolar disorder in Korea: Clinical feasibility, efficacy, and safety. Int J Psychiatry Clin Pract 2009;13:122-129.*
13. Jon DI, Bahk WM, Yoon BH, Shin YC, Cho HS, Lee E, *et al. Revised Korean medication algorithm for bipolar disorder. World J Biol Psychiatry 2009;10:846-855.*
14. Shin YC, Min KJ, Yoon BH, Kim W, Jon DI, Seo JS, *et al. Korean medication algorithm for bipolar disorder: second revision. Asia Pac Psychiatry 2013;5:301-308.*
15. Woo YS, Lee JG, Jeong JH, Kim MD, Sohn I, Shim SH, *et al. Korean Medication Algorithm Project for Bipolar Disorder: third revision. Neuropsychiatr Dis Treat 2015;11:493-506.*
16. Woo YS, Bahk WM, Lee JG, Jeong JH, Kim MD, Sohn IK, *et al. Korean Medication Algorithm Project for Bipolar Disorder*

*2018 (KMAP-BP 2018): fourth revision. Clin Psychopharmacol Neurosci 2018;16:434-448.*

17. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, *et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2016;30:495-553.*
18. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, *et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018;20:97-170.*
19. Fountoulakis KN, Grunze H, Vieta E, Young A, Yatham L, Blier P, *et al. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 3: the clinical guidelines. Int J Neuropsychopharmacol 2017;20:180-195.*
20. Fountoulakis KN, Yatham L, Grunze H, Vieta E, Young A, Blier P, *et al. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 2: review, grading of the evidence, and a precise algorithm. Int J Neuropsychopharmacol 2017;20:121-179.*
21. Fountoulakis KN, Young A, Yatham L, Grunze H, Vieta E, Blier P, *et al. The International College of Neuropsychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 1: background and methods of the development of guidelines. Int J Neuropsychopharmacol 2017; 20:98-120.*
22. Fountoulakis KN, Vieta E, Young A, Yatham L, Grunze H, Blier P, *et al. The International College of Neuropsychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 4: unmet needs in the treatment of bipolar disorder and recommendations for future research. Int J Neuropsychopharmacol 2017;20:196-205.*
23. National Collaborating Centre for Mental Health (UK). *Bipolar disorder: The NICE guideline on the assessment and management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Leicester, UK:British Psychological Society;2014.*
24. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, *et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World J Biol Psychiatry 2009;10:85-116.*
25. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, *et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry 2010;11:81-109.*
26. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, *et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry 2013;14:154-219.*
27. American Psychiatric Association. *Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 2002;159(4 Suppl):1-50.*
28. Goodwin GM. *Evidence-based guidelines for treating bipolar disorder: revised second edition--recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2009;23:346-388.*
29. Sharma V, Yatham LN, Haslam DR, Silverstone PH, Parikh SV, Matte R, *et al. Continuation and prophylactic treatment of bipolar disorder. Can J Psychiatry 1997;42 Suppl 2:92S-100S.*
30. Yatham LN, Kennedy SH, O'Donovan C, Parikh S, MacQueen G, McIntyre R, *et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar Disord 2005;7 Suppl 3:5-69.*
31. Yatham LN, Kennedy SH, O'Donovan C, Parikh SV, MacQueen G, McIntyre RS, *et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. Bipolar Disord 2006;8:721-739.*
32. Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, *et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord 2009;11:225-255.*
33. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, *et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord 2013;15:1-44.*
34. National Collaborating Centre for Mental Health (UK). *Bipolar disorder: the management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Leicester, UK:British Psychological Society;2006.*
35. Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht R, *et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders. Part I: treatment of bipolar depression. World J Biol Psychiatry 2002;3:115-124.*
36. Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht RW, *et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part II: treatment of mania. World J Biol Psychiatry 2003;4:5-13.*
37. Grunze H, Kasper S, Goodwin G, Bowden C, Moller HJ. *The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar dis-*

*orders, part III: maintenance treatment. World J Biol Psychiatry 2004;5:120-135.*
38. Davis DA, Taylor-Vaisey A. *Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. CMAJ 1997;157:408-416.*
39. Lin D, Mok H, Yatham LN. *Polytherapy in bipolar disorder. CNS Drugs 2006;20:29-42.*
40. Ketter TA. *Monotherapy versus combined treatment with second-generation antipsychotics in bipolar disorder. J Clin Psychiatry 2008;69 Suppl 5:9-15.*
41. Bourin MS, Severus E, Schronen JP, Gass P, Szamosi J, Eriksson H, *et al. Lithium as add-on to quetiapine XR in adult patients with acute mania: a 6-week, multicenter, double-blind, randomized, placebo-controlled study. Int J Bipolar Disord 2014;2:14.*
42. Xu L, Lu Y, Yang Y, Zheng Y, Chen F, Lin Z. *Olanzapine-valproate combination versus olanzapine or valproate monotherapy in the treatment of bipolar I mania: a randomized controlled study in a Chinese population group. Neuropsychiatr Dis Treat 2015;11:1265-1271.*
43. Ogawa Y, Tajika A, Takeshima N, Hayasaka Y, Furukawa TA. *Mood stabilizers and antipsychotics for acute mania: a systematic review and meta-analysis of combination/augmentation therapy versus monotherapy. CNS Drugs 2014;28:989-1003.*
44. Shim IH, Woo YS, Wang HR, Bahk WM. *Predictors of a shorter time to hospitalization in patients with bipolar disorder: medication during the acute and maintenance phases and other clinical factors. Clin Psychopharmacol Neurosci 2017; 15:248-255.*
45. Hu C, Torres IJ, Qian H, Wong H, Halli P, Dhanoa T, *et al. Trajectories of body mass index change in first episode of mania: 3-year data from the systematic treatment optimization program for early mania (STOP-EM). J Affect Disord 2017; 208:291-297.*
46. Baldessarini RJ, Perry R, Pike J. *Factors associated with treatment nonadherence among US bipolar disorder patients. Hum Psychopharmacol 2008;23:95-105.*
47. Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, *et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 2011;378:1306-1315.*
48. Lindström L, Lindström E, Nilsson M, Höistad M. *Maintenance therapy with second generation antipsychotics for bipolar disorder - a systematic review and meta-analysis. J Affect Disord 2017;213:138-150.*
49. Mojtabai R, Olfson M. *National trends in psychotropic medication polypharmacy in office-based psychiatry. Arch Gen Psychiatry 2010;67:26-36.*
50. Cruz N, Sanchez-Moreno J, Torres F, Goikolea JM, Valenti M, Vieta E. *Efficacy of modern antipsychotics in placebo-controlled trials in bipolar depression: a meta-analysis. Int J Neuropsychopharmacol 2010;13:5-14.*
51. Selle V, Schalkwijk S, Vazquez GH, Baldessarini RJ. *Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. Pharmacopsychiatry 2014;47:43-52.*
52. Fountoulakis KN, Kontis D, Gonda X, Yatham LN. *A systematic review of the evidence on the treatment of rapid cycling bipolar disorder. Bipolar Disord 2013;15:115-137.*
53. Vieta E, Valenti M. *Pharmacological management of bipolar depression: acute treatment, maintenance, and prophylaxis. CNS Drugs 2013;27:515-529.*
54. Woo YS, Shim IH, Lee SY, Lee DB, Kim MD, Jung YE, *et al. Dose trends of aripiprazole from 2004 to 2014 in psychiatric inpatients in Korea. Clin Psychopharmacol Neurosci 2017; 15:177-180.*
55. Solmi M, Veronese N, Zaninotto L, van der Loos ML, Gao K, Schaffer A, *et al. Lamotrigine compared to placebo and other agents with antidepressant activity in patients with unipolar and bipolar depression: a comprehensive meta-analysis of efficacy and safety outcomes in short-term trials. CNS Spectr 2016;21:403-418.*
56. Calabrese JR, Shelton MD, Bowden CL, Rapport DJ, Suppes T, Shirley ER, *et al. Bipolar rapid cycling: focus on depression as its hallmark. J Clin Psychiatry 2001;62 Suppl 14:34-41.*
57. Zupancic ML. *Role of atypical antipsychotics in rapid cycling bipolar disorder: a review of the literature. Ann Clin Psychiatry 2011;23:141-149.*
58. Poo SX, Agius M. *Atypical anti-psychotics in adult bipolar disorder: current evidence and updates in the NICE guidelines. Psychiatr Danub 2014;26 Suppl 1:322-329.*
59. Goldberg JF, Freeman MP, Balon R, Citrome L, Thase ME, Kane JM, *et al. The American Society of Clinical Psychopharmacology survey of psychopharmacologists' pratice patterns for the treatment of mood disorders. Depress Anxiety 2015; 32:605-613.*
60. Tohen M, Calabrese JR, Sachs GS, Banov MD, Detke HC, Risser R, *et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry 2006;163:247-256.*
61. Tohen M, Greil W, Calabrese JR, Sachs GS, Yatham LN, Oerlinghausen BM, *et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 2005;162:1281-1290.*
62. Quiroz JA, Yatham LN, Palumbo JM, Karcher K, Kushner S, Kusumakar V. *Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. Biol Psychiatry 2010;68:156-162.*
63. Vieta E, Montgomery S, Sulaiman AH, Cordoba R, Huberlant B, Martinez L, *et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I*

*disorder. Eur Neuropsychopharmacol 2012;22:825-835.*

64. Chan HW, Huang CY, Feng WJ, Yen YC. *Clinical outcomes of long-acting injectable risperidone in patients with bipolar I disorder: a 1-year retrospective cohort study. J Affect Disord 2016;205:360-364.*
65. Calabrese JR, Sanchez R, Jin N, Amatniek J, Cox K, Johnson B, *et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. J Clin Psychiatry 2017;78:324-331.*
66. Calabrese JR, Sanchez R, Jin N, Amatniek J, Cox K, Johnson B, *et al. Symptoms and functioning with aripiprazole once-monthly injection as maintenance treatment for bipolar I disorder. J Affect Disord 2018;227:649-656.*