Review
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Korean Medication Algorithm Project for Bipolar Disorder 2022: 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 2022 (KMAP-BP 2022) with other recently published guidelines for treating bipolar disorder. We reviewed a total of six recently published global treatment guidelines and compared treatment recommendation of the KMAP-BP 2022 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 in a same degree for mania. However, the KMAP-BP 2022 recommended MS + AAP combination therapy for psychotic mania, mixed mania and psychotic depression as treatment of choice. Aripiprazole, quetiapine and olanzapine were the first-line AAPs for nearly all phases of bipolar disorder across guidelines. Some guideline suggested olanzapine is a second-line options during maintenance treatment, related to concern about long-term tolerability. Most guidelines advocated newer AAPs (asenapine, cariprazine, long-acting injectable risperidone, and aripiprazole once monthly) 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. KMAP-BP 2022 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 2022, predominantly in the treatment of psychotic mania, mixed mania and psychotic depression.

KEY WORDS: Bipolar disorder; Pharmacotherapy; Algorithm; Guideline; KMAP-BP 2022.

INTRODUCTION

Bipolar disorder is characterized by diverse symptoms including manic, hypomanic, depressive, mixed and psychotic features, and by chronically debilitating patterns that create challenges for treatment.

Medical practice has shifted from individual 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 [2], including several treatment algorithms for mood disorder [3-10]. However, the medical landscape varies between countries. Often, the use of treatment guidelines may be dictated by cultural differences in clinical environments and medical situations,

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different health insurance policies and economic states, or the culture-specific imperatives of clinicians and patients.

In Korea, a medication algorithm project called the Korean Medication Algorithm Project for Bipolar Disorder (KMAP-BP) was initiated in 2001. KMAP-BP was published in 2002 (KMAP-BP 2002) and its reliability has been confirmed [11,12], Revised versions of KMAP-BP were released in 2006, 2010, 2014 and 2018 [13-16]. Due to rapid developments in the psychopharmacologic field, newer atypical antipsychotics (AAP), mood stabilizers (MS), and other agents have been introduced for the treatment of bipolar disorder.

To reflect current changes in treatment options for bipolar disorder, it was felt the earlier algorithm needed to be revised, resulting in publication of this Korean Medication Algorithm Project for Bipolar Disorder in 2022 (KMAP-BP 2022) [17].

By identifying similarities and differences across treatment guidelines, our goal was to identify potential deficiencies in KMAP-BP 2022 that may require additional attention or supplementary information to enhance its usefulness in clinical practice. In this review article, we compared recommendations of KMAP-BP 2022 [17] with those of other recently published global treatment guidelines (Table 1) [18-28].

TREATMENT GUIDELINES AS COMPARISON TARGETS

British Association for Psychopharmacology Guidelines for Treatment of Bipolar Disorder (BAP)

BAP constructed a set of guidelines based on the American Psychiatric Association Practice Guidelines for Bipolar Disorder, revised in 2002 and 2009 [29,30]. 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)" [18]. BAP 2016 consists of a list of clinical guidelines and their key points and supporting evidence. It provides an evaluation method 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 from Grade High (the strongest recommendation) to Grade Very Low (the weakest). The guidelines [18] reflected the consensus of experts and a wide range of feedback. This BAP guideline should be read alongside National Institute for Health and Clinical Excellence Clinical Guideline for Bipolar Disorder (NICE) 2014 [22]. 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 2022 (KMAP-BP 2022)	2022 [17]	Psychiatrists	Expert consensus
British Association for Psychopharmacology (BAP)	2016 [18]	Psychiatrists Primary care physicians	Evidence-based
Canadian Network for Mood and Anxiety Treatments (CANMAT)	2018 [19] 2021 (mixed) [20]	Psychiatrists	Evidence-based
The International College of Neuropsychopharmacology Treatment Guideline for Bipolar disorder (CINP-BD-2017)	2017 [21]	Primary and secondary care physicians	Evidence-based
National Institute for Health and Clinical Excellence (NICE)	2014 [22] 2018 [23]	Psychiatrists Primary care physicians	Evidence-based
Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders (RANZCP)	2020 [24]	Psychiatrists General practitioners	Evidence-based
World Federation of Societies of Biological Psychiatry (WFSBP)	2009 (acute mania, rapid cycling) [25] 2010 (acute depression) [26] 2018 (mixed) [28] 2012 (maintenance) [27]	Psychiatrists 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 CANMAT collaborated to publish evidence-based clinical guidelines for bipolar disorder in 1997 [31]. These guidelines were subsequently revised in 2005 [32], 2007 [33], 2009 [34], 2013 [35], and 2018 [19] to reflect new evidence. These were then further updated to include the management of patients with bipolar disorder with mixed presentation in 2021 [20]. 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 switches with pharmacological agents, were categorized, ranging from level 1 (the most powerful evidence, meta-analysis with narrow confidence interval or replicated double-blind, randomized controlled trial that includes a placebo or active control comparison [n $\geq$ 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)

The CINP-BD guideline was commissioned by the College of Neuropsychopharmacolgy. 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 [21]. 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 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 [36]. It was subsequently revised in 2014 (NICE clinical guideline 185) [22]. In 2018, a modestly updated edition was published to reflect rapidly expanding evidence [23]. Because the NICE guidelines were 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 2020 Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines for Mood Disorders (RANZCP 2020)

The RANZCP 2020 guidelines for mood disorders published in 2020, provided accessible and summarized reviews of current recommendations for diagnosis and management [24]. This replaced the 2015 version [37], and included some differences in terminology. Treatment steps are listed as 'actions', 'choices' and 'alternatives', replacing (but not directly corresponding to) steps 0−4 in previous versions. The RANZCP 2020 treatment steps are based on a combination of evidence-based and consensus-based recommendations, in line with other mood disorder treatment guidelines.

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

The World Federation of Societies of Biological Psychiatry developed guidelines for bipolar disorders based on a comprehensive literature review. Guidelines addressing depressive episode were published in 2002 [38], followed by guidelines for manic episode in 2003 [39], and maintenance therapy in 2004 [40]. Revisions were released in 2009 (manic episode) [25], 2010 (depressive episode) [26], 2013 (maintenance therapy) [27] and 2018 (mixed features) [28] to reflect new evidence. Treatment recommendations are categorized into five levels depending on the strength of the supporting evidence.

DEVELOPMENT OF KMAP-BP 2022

The KMAP-BP 2022 [17] guidelines reflected expert consensus. This revised edition of the Korean Medication Algorithm for Bipolar Disorder used the same framework as KMAP-BP 2018 (the fourth revision of the algorithm)

[16]. The survey questionnaire used for the KMAP-BP 2022 included many of the same questions used in KMAP-BP 2018 [16]. However, it also contained several modifications. Agomelatine which had been withdrawn from Korean market and was then reintroduced in 2019, and esketamine, which was introduced to Korea in 2020, were included as antidepressants (ADs).

The 2022 edition also 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 (DSM-5). We applied questions to the choice of available medications such as monotherapy and combination therapy with mood stabilizers, in the questionnaire for decision-making on initial treatment strategy. It also has questions pertaining to safety and compliance issues as well as strategies for special situations.

The final 56-item questionnaire consisted of 189 sub-items for adult bipolar disorder, and 7-item including 23 sub-items for pediatric bipolar disorder. The 9-point scale from RAND Corporation [4] was used to evaluate the adequacy of each treatment option. The questionnaire includes 24 multiple-choice questions that ask the responder to select one or more treatment options, and 40 open-ended questions.

The survey was sent to a review panel of 93 Korean psychiatrists who were either life-long members of the Korean College of Neuropsychopharmacology, or the Korean Society for Affective Disorders. All had extensive clinical experience and academic achievements in bipolar disorder. As well, 60 experts in child and adolescent psychiatry were included in the review committee for the development of the child and adolescent section. Reflecting a variety of medical contexts, the reviewers' affiliations included university hospitals, general hospitals, mental hospitals, and private psychiatric clinics. Among the 93 psychiatrists initially selected, 87 (93.5%) of the total responded to our survey. Sixty-one of these 87 responders worked at university hospitals, 19 at general hospitals/mental hospitals, and 7 in private clinics. Forty of the 60 child and adolescent psychiatrists (66.7%) responded, of whom 31 worked at university hospital, 1 at general hospitals/mental hospitals, and 8 in private clinics.

By estimating means and 95% confidence intervals (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, 3.5−6.5 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 a predetermined fee for their participation.

COMPARISONS OF RECOMMENDATIONS ACROSS TREATMENT GUIDELINES

Acute Mania/Hypomania

Initial treatment

For acute mania, a combination of MS and AAP were the preferred first-line treatments (TOC) for manic episodes with psychotic features, and the first-line strategy for manic without psychotic features in KMAP-BP 2022 [17]. MS monotherapy (lithium [Li] or valproic acid [Val]) were first-line treatment strategies for non-psychotic mania while AAP monotherapy was a first-line treatment strategy for non-psychotic and psychotic mania. First-line treatment strategies for hypomanic episodes were monotherapies of MS or AAP, or a combination of MS and AAP. The preferred medications for monotherapies of non-psychotic mania, were aripiprazole (ARP), Li, olanzapine (OLZ), quetiapine (QTP) and Val. Risperidone (RIS) was a second-line medication. For psychotic mania, ARP, OLZ, QTP and RIS were recommended as first-line treatment strategies. OLZ, ARP, QTP and RIS were also preferred as first-line agents when combined with MS for non-psychotic and psychotic mania. Monotherapy with ARP, Li, QTP or Val were most preferred for hypomanic episodes.

NICE [22] and BAP 2016 guidelines [18] recommended haloperidol (HAL), OLZ, RIS and QTP as first-line AAPs for drug naïve manic patients. On the other hand, optimization was the first-step for patients already taking long-term medications, thereby also adding HAL, OLZ, RIS and QTP as first-line strategy medications. CANMAT 2018 [19] recommends monotherapy of QTP, asenapine (ASP), paliperidone (PAL), RIS and cariprazine (CAR), and one of QTP or ARP or RIS or ASP with MS, as adjunctive

first-line treatment strategies for treating mania. In CINP-BD 2017 and RANZCP 2020, monotherapy of ARP, ASP, CAR, QTP, RIS, or Val, were first-line choices for manic patients [21,24]. Monotherapy with PAL was also recommended as a first-line strategy in the CINP-BD 2017, while monotherapy of Li and combined AAP and MS, were first-line in RANZCP 2020. In contrast, the WFSBP guidelines list Val, ARP, ziprasidone (ZIP) and RIS as recommended as first-line treatments for mania (Table 2) [25].

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 2022 [17] recommended switching from a MS or AAP to a different agent of the same type. Additionally, triple combinations such as MS + 2AAPs or 2MSs + AAP were suggested as next-step interventions in KMAP-BP 2022.

BAP 2016 [18] recommended ARP, carbamazepine (CBZ), Li and MS + AAP as next-step interventions while switching to alternative antipsychotics or adding Li or Val was a next-step in the NICE guideline [22]. Electroconvulsive therapy (ECT) and clozapine (CLZ) were later interventions [18,22]. A next-step strategy in CANMAT 2018 [19] included monotherapy of OLZ, CBZ, ZIP and HAL, 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, HAL + MS, repetitive transcranial magnetic stimulation (rTMS), tamoxifen and MS + tamoxifen as later intervention strategies. Second-line treatment in the CINP-BD 2017 [21] guideline was OLZ, Li, CBZ and HAL monotherapy, and combinations of MS (Li or Val) and ARP (or HAL or OLZ or QTP or RIS).

Table 2. Treatment for acute mania across practice guidelines

Guidelines	First-line treatment	Next-step intervention	Later intervention
KMAP-BP 2022 [17]	Non-psychotic: ARP, Li, OLZ, QTP, Val, MS + AAP (ARP/OLZ/QTP/RIS) Psychotic: ARP, OLZ, QTP, RIS, MS + AAP (OLZ/QTP/ARP/RIS) Hypomania: ARP, Li, QTP, Val, MS + AAP (ARP/QTP)	Non-psychotic: adding or replace MS or AAP, MS + AAP, 2MSs Psychotic: adding or replace MS or AAP, MS + AAP, 2AAPs, 2MSs + AAP Hypomania: adding or replace MS or AAP (OLZ, RIS), MS + AAP	Non-psychotic: 2MSs + AAP, MS + 2AAPs, 2MSs + 2AAPs, CLZ, ECT Psychotic: MS + 2AAPs, 2MSs + 2AAPs, CLZ, ECT Hypomania: 2MSs, 2AAPs, 2MSs + AAP, MS + 2AAPs, TAP
BAP 2016 [18]	Without AM: HAL, OLZ, RIS, QTP, Val With AM: optimization, Add HAL, OLZ, RIS, QTP, another MS	Without AM: alternative AM (ARP, other AP, CBZ, Li) With AM: MS + AAP	CLZ or CLZ
CANMAT 2018 [19]	Li, QTP, Val, ASP, ARP, PAL, RIS, CAR Combination with MS: QTP, ARP, RIS, ASP	OLZ, CBZ, OLZ + Li (or Val), Li + Val, ZIP, HAL, ECT	CBZ + Li (or Val), CPZ, CNZP, CLZ, HAL + Li (or Val), rTMS, tamoxifen, tamoxifen + Li (or Val)
CINP-BD-2017 [21]	ARP, ASP, CAR, PAL, QTP, RIS, Val, Switch to other first-step monotheray	OLZ, Li, CBZ, HAL, Li (or Val) + ARP (or HAL or OLZ or QTP or RIS), Li + allopurinol, Val + TAP, MS + medroxyprogesterone, Val + celcoxib	ECT, OXC
NICE 2014 [22]	Without AM: HAL, OLZ, QTP, RIS With AM: optimization, adding HAL, OLZ, QTP, RIS	Alternative AP or adding Li or Val	ECT
RANZCP 2020 [24]	ARP, ASP, RIS, QTP, CAR, Li, Val, MS + AAP	CBZ, ZIP, HAL, OLZ	ECT
WFSBP 2009 [25]	Monotherapy with CE 1 and RG A such as Val, ARP, ZIP, 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 2022, Korean Medication Algorithms for Bipolar Disorder 2022; BAP 2016, The British Association for Psychopharmacology Guidelines for Treatment for Bipolar Disorder 2016; CANMAT 2018, Canadian Network for Mood and Anxiety Treatments 2018; NICE 2014, National Institute for Health and Clinical Excellence Treatment for Bipolar Disorder; RANZCP 2020, The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders; WFSBP 2009, World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorders 2009: 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; HAL, haloperidol; CBZ, carbamazepine; ECT, electroconvulsive therapy; CLZ, clozapine; ASP, asenapine; PAL, paliperidone; ZIP, ziprasidone; CPZ, chlorpromazine; CNZP, clonazepam; rTMS, repetitive transcranial magnetic stimulation; OXC, oxcarbazepine; CE, categories of evidence; RG, recommendation of grade.

Li + allopurinol, Val + typical antipsychotics (TAP), MS + medroxyprogesterone and Val + celcoxib were recommended as second-line treatments. ECT and oxcarbazepine (OXC) were suggested for later intervention. In RANZCP 2020, CBZ, ZIP, HAL and OLZ were the second-line treatment strategies and ECT was recommended as a tertiary intervention [24]. As next-step strategies, WFSBP [25] recommended optimization 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 first-line agents and combinations of two first-line choices were listed for later intervention (Table 2).

Bipolar Depression

Initial treatment

KMAP-BP 2022 divided bipolar depression into categories of mild to moderate, nonpsychotic severe, and psychotic severe [17]. As the first-line treatment strategy for mild to moderate depression, monotherapy with Li, Val, LTG, ARP, QTP and OLZ, and combinations of MS + AAP, and LTG + AAP were recommended. The 1st-line recommendations for non-psychotic severe depression were MS + AAP (TOC), MS + LTG and AAP + LTG. For psychotic depression, MS + AAP was the TOC, and LTG + AAP was also recommended as first-line.

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

Monotherapy with QTP, OLZ or lurasidone (LUR) were first recommendations in BAP 2016 [18], OFC, QTP, OLZ and LTG were first in the NICE 2014 guideline [22], while Li, LTG, Val, QTP, LUR and CAR were first in RANZCP 2020 [24]. LTG combination and MS + QTP (or OFC or LUR) were first-line combination strategies for bipolar depression in BAP 2016 [18], while adjunctive OFC, QTP, OLZ or LTG strategies were in NICE 2014 [22]. CANMAT 2018 recommended monotherapy of QTP, LTG or LUR, and MS + LUR or adjunctive LTG as first-line treatment strategies for treating depression [19]. In CINP-BD 2017, monotherapy of QTP, LUR and OFC were the first-line treatments for depressive patients [21]. However, the WFSBP 2010 guideline recommended QTP, adjunctive QTP, OFC, OLZ, LTG, LTG + Li and Val as first-line treatments for bipolar depression [26] (Table 3).

Next-step strategy

KMAP-BP 2022 [17] prefers adjunctive use of another medication for all clinical situations while medication switching strategies are preferred for severe depression. When a response is insufficient to the initial treatment strategy, adding an AAP or LTG or MS was the next-step intervention for mild to moderate (MS + LTG and 2AAPs), non-psychotic severe (MS + LTG + AAP, MS + 2AAPs, 2MSs + AAP, LTG + 2AAPs), and psychotic severe (MS + LTG, MS + LTG + AAP, MS + 2AAPs, 2MSs + AAP, LTG + 2AAPs) depressive patients. Adding an AD strategy and switching to 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 interventions.

RANZCP 2020, was the most recently published guideline, and had similar recommendations to KMAP BP as second-step interventions (MS + AAP, 2MSs, MS + AD, AAP + AD, 2MSs + AAP, 2MSs + AD, MS + AAP + AD, 2MSs + AAPs + AD, ECT) [24]. Their later interventions were monotherapy of CBZ and OLZ, and adjunctive treatment with ASP, armodafinil and levothyroxine. BAP 2016 [18] recommends adding AD, and ECT as a second-line strategy, and the NICE 2014 guideline recommends adding LTG as the second-line but with no recommendation for ECT [22]. And next-step strategies in CANMAT 2018 [19] were monotherapy of Val, CAR and OFC, and adjunctive SSRI or bupropion. ECT was also preferred as second-line in CANMMAT (Table 3). Second-line treatment in the CINP-BD 2017 [21] guideline was Val or Li monotherapy, MS + LUR (or modafinil or pramipexole), Li + pioglitazone, and adding escitalopram or fluoxetine. For next-step treatments, WFSBP 2010 [26] 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 2022 divided mixed features into the following

Table 3. Treatment of bipolar depression across practice guidelines

Guidelines	First-line treatment	Next-step intervention	Later intervention
KMAP-BP 2022 [17]	Mild to moderate: Li, Val, LTG, ARP, QTP, OLZ, MS + AAP (ARP/QTP/OLZ) LTG + AAP (ARP/QTP/OLZ) Non-psychotic severe: MS + AAP (ARP/QTP/OLZ), AAP + LTG, MS + LTG Psychotic: MS + AAP (ARP/QTP/OLZ/RIS) LTG + AAP	Mild to moderate: adding or change AAP/LTG/MS, MS + LTG, 2AAPs Non-psychotic severe: Change MS or AAP, MS + LTG + AAP, MS + 2AAPs, 2MSs + AAP, LTG + 2AAPs MS + AD, AAP + AD Psychotic: Change MS or AAP, MS + LTG, MS + LTG + AAP, MS + 2AAPs, 2MSs + AAP, LTG + 2AAPs AAP + AD, MS + AD	Add (or change to) CLZ, Add buspirone or stimulant or thyroid hormone, ECT, rTMS
BAP 2016 [18]	Without AM: QTP, OLZ, LTG, LUR, LTG combination With AM optimization, QTP, OLZ, LUR, LTG Consider ECT in severe depression	AD combination, ECT	
CANMAT 2018 [19]	QTP, LUR + Li (or Val), LTG, LTG (adj)	Val, SSRI/bupropion (adj), ECT, CAR, OFC	CBZ Adj: OLZ, SNRI/MAOI, modafinil, eicosapentaenoic acid, rTMS, ketamine, light therapy/sleep deprivation, Levothyroxine, N-acetylcysteine, pramipexle, ARP, armodafinil, ASP
CINP-BD-2017 [21]	QTP, LUR, OFC	Val, Li, MS + (or modafinil or pramipexole), Li + pioglitazone, Add escitalopram or FX	ARP, imipramine, phenezine, Li + OXC (or L-sulpiride)
NICE 2014 [22]	Without AM: OFC, QTP, OLZ, LTG With AM: optimization, OFC (adj), QTP (adj), OLZ (adj), LTG (adj)	Adding LTG	
RANZCP 2020 [24]	Li, LTG, Val, QTP, LUR, CAR	MS + AAP, 2MSs, MS + AD, AAP + AD, 2MSs + AAP, 2MSs + AD, MS + AAP + AD, 2MSs + AAPs + AD, ECT	CBZ, OLZ, ASP (adj), Armodafinil (adj), Levothyroxine (adj)
WFSBP 2010 [26]	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 2022, Korean Medication Algorithms for Bipolar Disorder 2022; BAP 2016, The British Association for Psychopharmacology Guidelines for Treatment for Bipolar Disorder 2016; CANMAT 2018, Canadian Network for Mood and Anxiety Treatments 2018; NICE 2014, National Institute for Health and Clinical Excellence Treatment for Bipolar Disorder; RANZCP 2020, The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders; WFSBP 2010, World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorders 2010 on the treatment of acute bipolar depression; Li, lithium; Val, various kinds of valproic acid; LTG, lamotrigine; ARP, aripiprazole; QTP, quetiapine; OLZ, olanzapine; MS, mood stabilizer; AAP, atypical antipsychotic; RIS, risperidone; AD, antidepressant; CLZ, clozapine; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; AM, antimanic agents; LUR, lurasidone; OFC, olanzapine-fluoxetine complex; adj, adjunctive; SSRI, selective serotonin reuptake inhibitor; CBZ, carbamazepine; SNRI, serotonin norepinephrine reuptake inhibitor; MAOI, monoamine oxidase inhibitor; ASP, asenapine; FX, fluoxetine; OXC, oxcarbazepine; MDF, modafinil.

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 [17]. First-line treatment strategies for bipolar disorder with mixed features was MS + AAP combination therapy (TOC for mixed mania), AAP monotherapy and MS monotherapy. For mixed depression, MS + LTG and AAP + LTG were also recommended as first-line. First-line medications included Val, Li, ARP, OLZ, QTP and RIS for mixed mania, and Li, Val, ARP, OLZ and QTP for mixed features without predominance. Li, Val, LTG, ARP, OLZ, and QTP were preferred first for mixed depression [17].

The CANMAT 2021 guideline for patients with mixed presentation insisted 'none determined' as first-line treatment in mixed mania and mixed depression. However, ASP or ARP could be used as first-line agents in mixed features without predominance [20]. In contrast, RANZCP 2020 recommended Li, Val and QTP as first-line treatment [24]. And also BAP 2016 [18] recommended HAL, OLZ, RIS, QTP and Val as first-line monotherapeutic agents, and HAL, OLZ, RIS, QTP, Val and ARP with Li were first-line combination agents. Otherwise, monotherapy of HAL,

OLZ, QTP and RIS was recommended as first-line in the NICE 2014 guideline [22], and first-line combination was Li + HAL, 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 [21]. However, WFSBP 2018 guideline recommended monotherapy of OLZ and combination therapy of OLZ and Val as a first-line treatment for mixed states (Table 4) [28].

Next-step strategy

When MS and AAP combination therapy results in incomplete efficacy for treating mixed mania, KMAP-BP 2022 recommends 2MSs, AAP + LTG, LTG, MS + LTG, 2MSs + AAP, MS + 2AAPs, MS + LTG + AAP and 2AAPs as second-line strategies, and TAP, CBZ or ZIP were suggested for later interventions. However, in case of mixed depression, KMAP-BP 2022 recommended changing specific MS or AAP, or adding another MS or AAP in second-line strategies. 2MSs, 2MS + AAP, MS + 2AAPs, MS + LTG + AAP, 2AAPs, MS + AD, AAP + AD and TAP were recommended for later intervention [17]. In addition, MS + LTG, 2MSs, AAP + LTG, LTG and TAP were recommended as second-line strategies in in patients with mixed features without predominance.

CANMAT 2021 recommended ASP, CAR, Val and ARP as second-line treatment for mixed mania, and CAR and LUR for mixed depression, and OLZ + MS, CBZ, OLZ and Val in mixed features without predominance [20]. RANZCP

Table 4. Treatment for mixed features across practice guidelines

Guidelines	First-line treatment	Next-step intervention	Later intervention
KMAP-BP 2022 [17]	Mixed mania: MS + AAP, Val, Li, ARP, OLZ, QTP, RIS Mixed depression: MS + AAP, LTG + AAP, LTG + MS, Li, Val, LTG, ARP, OLZ, QTP Mixed bipolar: MS + AAP, Li, Val, LTG, ARP, OLZ, QTP	Mixed mania: 2MSs, AAP + LTG, LTG, MS + LTG, TAP, CBZ, ZIP 2MSs + AAP, MS + 2AAPs, MS + LTG + AAP, 2AAPs Mixed depression: 2MSs, 2MSs + AAP, MS + 2AAPs, MS + LTG + AAP, 2AAPs, MS + AD, AAP + AD, TAP Mixed bipolar: MS + LTG, 2MSs, AAP + LTG, LTG, TAP	Mixed mania: adding AD Mixed depression: Switching AD Mixed bipolar: MS + AD, AAP + AD
BAP 2016 [18]	Same as for mania	Same as for mania	Same as for mania
CANMAT 2021 [20]	Mixed mania: None determined Mixed depression: None determined Mixed bipolar: ASP, ARP	Mixed mania: ASP, CAR, Val, ARP Mixed depression: CAR, LUR Mixed bipolar: OLZ + MS, CBZ, OLZ, Val	Mixed mania: ZIP, OLZ, OLZ + MS, QTP, CBZ, ECT Mixed depression: OLZ, OFC, QTP, Val, LTG, ZIP, ECT Mixed bipolar: ZIP, Val + CBZ, CAR, Li + Val, ECT
CINP-BD-2017 [21]	OLZ + Val (or Li)	OLZ, ARP, CBZ	Val OFC, ZIP
NICE 2014 [22]	Same as for mania	Same as for mania	Same as for mania
RANZCP 2020 [24]	Li, Val, QTP	Mixed mania: adding ARP or ASP Mixed depression: adding LUR Mixed bipolar: CAR, ZIP	Mixed mania: MS + OLZ Mixed depression: OLZ, OFC Mixed bipolar: CBZ ECT
WFSBP 2018 [28]	Mixed mania: OLZ, OLZ + Val	Mixed mania: ARP, PAL, QTP + MS Mixed depression: ZIP	Mixed mania: ASP, CBZ, CAR, CLZ, MS + gabapentine, Li + CBZ, RIS, TAP, Val, ZIP, ECT Mixed depression: OLZ, CBZ, LUR, ECT

KMAP-BP 2022, Korean Medication Algorithms for Bipolar Disorder 2022; BAP 2016, The British Association for Psychopharmacology Guidelines for Treatment for Bipolar Disorder 2016; CANMAT 2021, Canadian Network for Mood and Anxiety Treatments recommendations for the management of patients with bipolar disorder with mixed presentations; NICE 2014, National Institute for Health and Clinical Excellence Treatment for Bipolar Disorder; RANZCP 2020, The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders; WFSBP 2018, The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term treatment of mixed states in bipolar disorder; MS, mood stabilizer; AAP, atypical antipsychotics; Val, various kinds of valproic acids; Li, lithium; ARP, aripiprazole; OLZ, olanzapine; QTP, quetiapine; RIS, risperidone; LTG, lamotrigine; TAP, typical antipsychotics; CAR, cariprazine; LUR, lurasidone; CBZ, carbamazepine; ZIP, ziprasidone; AD, antidepressant; ASP, asenapine; ECT, electroconvulsive therapy; OFC, olanzapine fluoxetine complex; CLZ, clozapine.

2020 suggested adjunctive ARP and ASP as next-step intervention for mixed depression, and adjunctive LUR for mixed depression, and CAR and ZIP for mixed features without predominance [24]. Second-line treatment in the CINP-BD 2017 [21] guideline was OLZ, ARP and CBZ, and Val, with OFC and ZIP recommended for later intervention strategies. As next-step treatments, WFSBP 2018 [28] recommended ARP, PAL and QTP + MS for mixed mania and ZIP for mixed depression (Table 4).

Rapid Cycling

For treating rapid-cycling patients, regardless of their current episodes, a combination of MS and AAP, or monotherapy of Val, Li, QTP, ARP and OLZ were the first-line treatment strategy in the KMAP-BP 2022. However, a combination of LTG and MS (or AAP) was potentially preferable during episodes of current depression, and monotherapy of RIS was preferred during currently manic states. Adding or change another MS or AAP or adding TAP, and ECT were the second-line strategy for any episodes. Adding AD was a second-line in current manic episodes [17]. 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 for later intervention (Table 5) [21].

Maintenance Treatment

Initial treatment

In KMAP-BP 2022 [17], the preferred maintenance treatment strategies for preventing manic episodes were a MS monotherapy, combination of MS and AAP and AAP monotherapy. Preferred AAPs for maintenance treatment included ARP, QTP and OLZ, for use in monotherapy or in adjunctive use with MS. The preferred maintenance strategy was the same for preventing depressed episodes in both bipolar I and II disorder. Monotherapy with an MS, an AAP, or LMT, a combination of two of these three medications, or a combination of two MSs were all recommended as first-line treatment strategy to prevent a depressive episode.

Monotherapy of Li was recommended first for maintenance treatment in BAP 2016 and NICE guidelines [18,22].

The RANZCP 2020 guideline recommended Li, Val, QTP, ASP, Li + QTP, Val + QTP and Li + ARP as first-line treatment for preventing episodes. However, ARP was a first-line treatment for preventing manic episodes and LTG for preventing depressive episodes [24]. CANMAT 2021 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 [19]. In the CINP-BD 2017, monotherapy of Li, ARP, OLZ, PAL, QTP, RIS and RIS long acting injectable (RIS LAI) were first-line for maintenance therapy [21]. In

Table 5. Treatment of rapid cycling across practice guidelines

Guidelines	First-line treatment	Next-step intervention	Later intervention
KMAP-BP 2022 [17]	Currently manic: MS + AAP, Val, Li, QTP, ARP, OLZ, RIS Currently depressed: MS + AAP, QTP, ARP, Li, Val, OLZ, AAP + LTG, MS + LTG	Currently manic: 2MSs. MS + LTG, AAP + LTG, MS + TAP, ECT Currently depressed: LTG, 2MSs, MS + AAP + AD, MS + AD, MS + TAP, ECT	Currently manic: MS + AD Currently depressed: AD
BAP 2016 [18]	No recommendation		
CANMAT 2018 [19]	No recommendation		
CINP-BD-2017 [21]	ARP, QTP, Val	OLZ, Li	MS + QTP (or RIS)
NICE 2014 [22]	Same as with other types of bipolar disorder		
RANZCP 2020 [24]	No recommendation		
WFSBP 2009 [25]	Not mentioned		

KMAP-BP 2022, Korean Medication Algorithms for Bipolar Disorder 2022; BAP 2016, The British Association for Psychopharmacology Guidelines for Treatment for Bipolar Disorder 2016; CANMAT 2018, Canadian Network for Mood and Anxiety Treatments 2018; NICE 2014, National Institute for Health and Clinical Excellence Treatment for Bipolar Disorder; RANZCP 2020, The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders; WFSBP 2009, World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Bipolar Disorders 2009: the treatment of acute mania; MS, mood stabilizer; AAP, atypical antipsychotics; Val, various kinds of valproic acids; Li, lithium; QTP, quetiapine; ARP, aripiprazole; OLZ, olanzapine; RIS, risperidone; LTG, lamotrigine; TAP, typical antipsychotics; ECT, electroconvulsive therapy; AD, antidepressant.

WFSBP 2013 [27], 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 2022 [17], combination therapy with MS + LTG, 2MSs, AAP + LTG, or MS + AAP + LTG, or alternatively LTG monotherapy, were recommended as second-line treatments for preventing manic episode. Adding an AD was a later intervention for manic episode prevention. For preventing depressive episodes, use of a triple combination of MS, AAP and LTG was recommended as a second-line strategy. Otherwise, AAP + AD, MS + AD or MS + AAP + AD combination therapy was a later intervention. The most preferred AD was bupropion.

RANZCP 2020 [24] recommended PAL, RIS, OLZ, CBZ, 2MSs and MS + OLZ (or RIS or ZIP) as second-line treatments for preventing manic episodes, and 2MSs, MS + OLZ, MS + LTG, LTG + ARP (or OLZ, QTP, fluoxetine [FX] or LUR) for preventing depressive episodes. OFC was suggested as being useful for later intervention because of the possibility of poor long-term tolerability. Next-step strategies in CANMAT 2018 [19] included monotherapy with OLZ, RIS LAI, CBZ and PAL, and adjunctive RIS LAI, and combinations of MS + LUR and MS + ZIP. ARP + LTG, OFC, adjunctive CLZ and adjunctive gabapentine were recommended for later intervention in maintenance treatment. BAP 2016 [18] recommended the following. If mania predominates, Val, OLZ, QTP, RIS LAI, CBZ and OXC are preferred. If depression predominates, LTG, QTP and LUR are preferred. Also, combination therapy, AD, CLZ and maintenance ECT were to be used as later interventions in maintenance treatment. The NICE guideline recommended Val, OLZ and QTP as second-line strategy [22], while the CINP-BD 2017 [21] guideline suggested FX or Li, and Li + CBZ, MS + QTP, MS + OLZ and MS + ARP combinations. Adding RIS LAI, CBZ, LTG and N-acetylcyteine was for later intervention. WFSBP 2013 [27]

Table 6. Maintenance treatment across practice guidelines

Guidelines	First-line treatment	Next-step intervention	Later intervention
KMAP-BP 2022 [17]	Preventing mania: MS, MS + AAP, ARP, QTP, OLZ Preventing depression: MS + (AAP or LTG), LTG, AAP, MS, AAP + LTG, 2MSs	Preventing mania: MS + LTG, 2MSs, AAP + LTG, MS + AAP + LTG, LTG Preventing depression: MS + AAP + LTG	Preventing mania: MS + AAP + AD, AAP + AD, MS + AD Preventing depression: MS + AAP + AD, MS + AD, AAP + AD
BAP 2016 [18]	Li	If mania predominates; Val, OLZ, QTP, RIS LAI, CBZ, OXC If depression predominates; LTG, QTP	Combination therapy, AD, CLZ, Maintenance ECT
CANMAT 2018 [19]	Li, QTP, Val, LTG, ASP, QTP + Li (or Val), ARP + Li (or Val), ARP, ARP OM	OLZ, RIS LAI, RIS LAI (adj), CBZ, PAL, LUR + Li (or Val), ZIP+ Li (or Val)	ARP + LTG, OFC, CLZ (adj), gabapentine (adj)
CINP-BD-2017 [21]	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 [22]	Li	Val, OLZ, QTP	
RANZCP 2020 [24]	Preventing mania: ARP, Li, Val, QTP, ASP, Li + QTP, Val + QTP, Li + ARP Preventing depression: LTG, Li, Val, QTP, ASP, Li + QTP, Val + QTP, Li + ARP	Preventing mania: PAL, RIS, OLZ, CBZ, 2MSs, MS + OLZ (or RIS or ZIP) Preventing depression: 2MSs, MS + OLZ, MS + LTG, LTG + ARP (or OLZ or QTP or FX or LUR)	OFC
WFSBP 2012 [27]	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 2022, Korean Medication Algorithms for Bipolar Disorder 2022; BAP 2016, The British Association for Psychopharmacology Guidelines for Treatment for Bipolar Disorder 2016; CANMAT 2018, Canadian Network for Mood and Anxiety Treatments 2018; NICE 2014, National Institute for Health and Clinical Excellence Treatment for Bipolar Disorder; RANZCP 2020, The 2020 Royal Australianand New Zealand College of psychiatrists clinical practice guidelines for mood disorders; WFSBP 2012, World Federation of Societies of Biological Psychiatry guidelines for the biological treatment of bipolar disorders: maintenance; MS, mood stabilizer; AAP, atypical antipsychotics; ARP, aripiprazole; QTP, quetiapine; OLZ, olanzapine; LTG, lamotrigine; AD, antidepressant; Li, lithium; Val, various kinds of valproic acid; ASP, asenapine; ARP OM, aripiprazole once-monthly; RIS LAI, risperidone long-acting injectable; adj, adjunctive; LUR, lurasidone; CBZ, carbamazepine; PAL, paliperidone; OXC, oxcarbazepine; CLZ, clozapine; ECT, electroconvulsive therapy; RIS, risperidone; FX, fluoxetine; ZIP, ziprasidone; OFC, olanzapine-fluoxetine complex.

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 a number of 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 [6,21,41]. In this review, we compared the recommendations of KMAP-BP 2022 [17] 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 mood stabilizer or AAP monotherapy and combination therapy as equivalent first-line modalities, while MS + AAP combination therapy for psychotic severe manic episodes was ranked as TOC in KMAP-BP 2022. This may reflect that Korean experts are generally doubtful regarding the clinical effectiveness of monotherapy, and instead laid an emphasis on the superiority of combination therapy over monotherapy in terms of efficacy for mania, a conclusion based on results from clinical trials and meta-analyses [42-47].

The WFSBP 2009 guidelines [25], BAP 2016 [18] and CINP-BD-2017 [21] recommend Val as the only first-line MS medication. This result seems to reflect concerns regarding the safety of Li. However, guidelines have also advised that Val should not be used for women of child bearing potential because of its unacceptable risk of teratogenesis and impaired intellectual development of the fetus [18,21,23,25,48].

NICE 2014 guidelines do not recommend Li or Val as first-line treatment strategies in drug-naïve manic patients [22]. However, newly published KMAP-BP 2022 [17], as well as RANZCP 2020 [24] and CANMAT 2018 [19] recommended Li and Val as first-line MS agents for treating manic episodes. This discrepancy is 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.

ARP, OLZ and QTP were first-line AAPs for manic episodes across guidelines, However, CANMAT 2018 [19], CINP-BD-2017 guideline [21] and RANZCP 2020 [24] recommended OLZ as a second-line strategy. This might reflect safety concerns, as well as tolerability and adherence issues [49,50]. However, OLZ and RIS showed superior antimanic effects over other AAPs in a meta-analysis [51], and OLZ and QTP monotherapy are known to reduce the overall risk of relapse [19,52]. The authors recommend that these diverse opinions should be considered in clinical practice. Additionally, ASP and CAR were recommended as first-line options in newly published guidelines [19,21,24].

In cases of non-response or incomplete response to first-line strategies, guidelines recommended switching or adding another first-line agent. KMAP-BP 2022 [17] also recommended switching from an MS or AAP to a different agent of the same type. However, triple combinations such as MS + 2AAPs or Li + Val + AAP were also suggested as next-step interventions for severe psychotic mania. In severe mania, a closed inpatient setting is common, and rapid symptom improvement is often the first goal. Despite concerns about the safety concern of the polypharmacy, there is a report that suggests the initial triple combination reduced the overall use of neuroleptics and shortened the hospital stay in severe manic patients [53]. Also, the fact that the TOC in Korea for severe psychotic mania is MS + AAP may be one reason. ECT and CLZ were recommended in most guidelines, while chlorpromazine, clonazepam, tamoxifen and rTMS were only recommended in CANMAT 2018 [19].

KMAP-BP 2022 recommended monotherapy of MS or AAP as the first-line strategy for only mild to moderate depression. MS + AAP, MS + LTG and AAP + LTG combinations were preferred for moderate depression to severe psychotic cases. However, other guidelines recommended monotherapy and combination therapy to approximately similar degrees in the first-line strategy for bipolar depression. Additionally, RANZCP 2020 guideline's first-line strategy was a monotherapy of Li, LTG, Val, QTP, LUR and CAR, and also CINP guideline only recommended QTP, LUR and OFC as a first-line. Although MS and AAP monotherapy were supported by higher degrees of evidence for bipolar depression, Korean experts preferred combination treatment over monotherapy for treating bi-

polar depression as in mania. This might be because a high proportion (70.1%) of the Korean experts who participated in KMAP-BP 2022 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 2022 and other guidelines (e.g., expert consensus vs. evidence-based). Furthermore, polypharmaceutical approaches to psychotropic medication appear to be increasingly common in clinical practice [54], suggesting that it is difficult to apply research-based findings to real clinical fields.

In KMAP-BP 2022, the use of ADs in depressive episodes was limited as a secondary option and only for combined use, and these results were similar to those of other guidelines [19,21,24]. These results reflect the controversy and debate surrounding the use of ADs for bipolar depression due to potentially increased risk of harms, such as affective switching, higher suicide risk, and increased risk of development of mixed states/rapid cycling, and a limited evidence for their efficacy [55,56]. Moreover, two recent meta-analyses [57,58] reported that adjunctive ADs in bipolar depression yield only small, non-significant benefits without increased risk of switching into mania. The most recent meta-analysis concluded that their findings were supportive of guideline recommendations to use adjunctive AD as a second-line or lower-category treatment [58].

Strict prohibition of AD monotherapy and increasing preference for LTG were found in all guidelines. This increasing preference for LTG seems to reflect the finding that LTG is more effective than placebo in LTG monotherapy and in adjunctive therapies [59]. However, adjunctive AD use with MS or AAP was also widely recommended.

ARP, QTP and OLZ were recommended as first-line monotherapies (mild to moderate episodes) or adjunctive therapy for bipolar depression in KMAP-BP 2022. However, ARP was categorized a 3rd-line recommendation by CANMAT 2018 and CINP-BD 2017 guidelines. This reflects some results showing that ARP monotherapy is not superior to placebo [60,61]. However, due to partial agonism at the dopamine 2 receptor, aripiprazole is unlikely to result in affective flattening or cognitive problems determined by dopamine antagonism in the mesocortical pathways. Indeed, it has been observed that ARP is unlikely to precipitate depression, and has a relatively favorable tolerability profile, with a lower risk for weight gain, dyslipidemia, diabetes, and hyperprolactinemia in bipolar disorder [62]. Another meta-analysis suggested that ARP monotherapy could be effective for treatment of acute depression because combined data from two negative studies revealed a significant effect [55,63]. Reportedly in Korea, the proportion of patients with bipolar depression prescribed with ARP increased from 1.4% (2004－2006) to 8.5% (2011－2014), but the mean initial and maximum dose was 15 mg/day and 30 mg/day respectively in 2004－2006 and 6.3 mg/day and 16.8 mg/day respectively in 2011－2014 [64]. The high preference for, 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. Additionally, low doses of aripiprazole, (5 mg or less), were reportedly more effective and better tolerated than higher ones for treating bipolar depression [65] and it was suggested clinicians should start treatment with a very low dose and give patients time to respond.

In KMAP-BP 2022, 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 strategies in other guidelines, such as CBZ (or OXC), ADs, modafinil, eicosapentaenoic acid, rTMS, ketamine, light therapy/sleep deprivation, levothyroxine, N-acetylcysteine, pramipexle, armodafinil, and L-sulpiride [19,21,24]. This variety of options may reflect the difficulty in treating bipolar depression.

In the KMAP-BP 2022 guidelines the initial treatment strategy for mixed mania was MS + AAP, MS monotherapy and AAP monotherapy; for mixed depression, MS + AAP, LTG + AAP, LTG + MS, MS monotherapy, AAP monotherapy and LTG monotherapy; and for mixed features without predominance, MS + AAP, MS monotherapy, AAP monotherapy and LTG monotherapy. Val, Li, ARP, OLZ, QTP and LTG were the mostly preferred medications for mixed features [17]. We found that recommendations for mixed features were similar to those for manic episodes, and with a preference for monotherapy. These recommendation trends are also found in other treatment guidelines [18,20-22,24,28]. ARP, OLZ and QTP were the most preferred AAPs for mixed features in KMAP-BP 2022, but other guidelines recommended sev-

eral different AAPs such as ARP, QTP, OLZ, ASP, CAR and LUR for mixed features. This discrepancy may reflect the particular circumstances in Korea where highly ranked agents recommended by CANMAT 2021 and RANZCP 2020 including ASP, CAR and LUR, have not been introduced.

Other guidelines did not recommend any specific treatment modality for rapid cycling. Of all, only CINP-BD 2017 recommended ARP, QTP and Val to be used as the first-line treatment while OLZ and Li were recommended as a second-line strategy [21]. In KMAP-BP 2022, MS + AAP, LTG + MS, LTG + AAP (currently depressed), and monotherapy of MS and AAPs (QTP, ARP, OLZ, RIS) were the first-line treatment strategies [17]. Changing MS and adding another MS or AAP, and ECT were the second-line approach for treating rapid-cycling patients. Val, Li, QTP, ARP and OLZ were preferred in any episode, and RIS was an additional first-line agent for currently manic, while LTG was, for currently depressed, in KMAP-BP 2022. These results as preferred monotherapies are inconsistent with the findings of a previous study indicating that MS monotherapy had limited effect on rapid cycling while a combination of Li and Val was found to be more effective than Li or Val alone [66]. However a recent growing body of data shows that AAP treatment is also effective for rapid cycling bipolar disorder [67-69].

In a recent systematic review [70], the role of combination therapy was unclear in rapid cycling, and the usefulness of ARP, OLZ, QTP, Val or LMT monotherapy was suggested.

In contrast to KMAP-BP 2022, other guidelines did not discuss strategies for treating rapid cycling bipolar disorder, or discuss them as part of refractory bipolar disorder. This might be due to inadequate research dealing with this condition. Direct comparisons across guidelines will be possible once a 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 2022 [17], MS, MS + AAP, MS, AAP, LTG, MS + LTG, LTG + AAP and 2MSs were recommended as the first-line strategy in maintenance treatment, and Val, Li, ARP, QTP, OLZ and LTG were most preferred. However, among MS, Val was not a first-line agent in BAP 2016 [18], NICE 2014 [22], CINP-BD-2017 [21] or WFSBP 2012 [27] guidelines. Despite the relapse preventing effect of Li and Val being widely understood, there were some arguments regarding their safety. Clinicians should be aware of these issues in clinical applications.

KMAP-BP 2022 [17] and CINP-BD-2017 guidelines [21] recommended OLZ as a first-line agent in maintenance treatment while other guidelines [18,19,22,24, 27] placed it as second-line. RIS and PAL were first-line agents only in the CINP-BD-2017 [21] guideline. It was regarded as second-line in KMAP-BP 2022 [17], BAP 2016 [18], CANMAT 2018 [19], RANZCP 2020 [24] and WFSBP 2012 [27]. However, it was not included in NICE 2014 [22]. There are no randomized controlled trials evaluating bipolar maintenance treatment with RIS, and there are some cautions about OLZ's long-term metabolic side-effects. However, RIS LAI and OLZ were preferred either as monotherapies or in combination with MS in recently published guidelines [18,19,21,24], and this was based on previous results showing its positive effects in preventing bipolar episodes [71-73]. As well, recently published systemic reviews have reported positive results in relapse prevention effects by RIS LAI, PAL LAI and OLZ in bipolar disorder [74,75]. Clinicians might wish to consider this point. ARP OM also showed efficacy and safety during maintenance treatment [74-77], and it was recommended as first-line in CANMAT 2018 [19].

There were no substantial differences between KMAP-BP 2022 and the other treatment guidelines. In particular, the increased preference for AAPs, LTG and monotherapy was similar across all guidelines. However, a strong preference for combination therapy was characteristic of KMAP-BP 2022, predominantly for the treatment of psychotic mania, mixed mania and psychotic depression.

LIMITATIONS

The KMAP-BP 2022 guideline [17] is an expert consensus set of guidelines while the other guidelines were evidence-based ones. Some treatment strategies in KMAP-BP 2022 might not have been rated as first-line options despite evidence demonstrating their effectiveness. Evidence-based treatment evaluations are 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 peer re-

viewed studies can help clinicians evaluate the actual effect of a treatment on patient outcomes. However, most of the experimental data in evidence-based guidelines were derived from strictly designed randomized controlled trials and they might not reflect the complexity of real clinical situations. This suggests that there may be some discrepancies between the findings of randomized controlled trials and the results observed in real-world practice. On the other hand, KMAP-BP 2022 has not been compared with expert consensus guidelines, but it is due to the lack of a recently published one.

KMAP-BP 2022 has limitations as a set of expert consensus guidelines. Hence, we made efforts to compensate for these limitations by opening public hearings at the Academic Conference of the Korean College of Neuropsychopharmacology and by opening a results announcement and panel discussion at the Academic Conference of the Korean Society for Affective Disorders. Despite the limits of expert opinion, our current comparison showed that there were no major differences in overall treatment recommendations between KMAP-BP 2022 and other guidelines. Furthermore, the recommendations of KMAP-BP 2022 aligned well with current changes in the pharmacotherapy of bipolar disorder based on newer evidence. However, we also found some differences between KMAP-BP 2022 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 appear, they may prompt modifications to some of these guidelines. This algorithm could not provide recommendations for new drugs such as ASP, CAR or LUR which come highly recommended with strong evidences in other algorithms [19,21,24], because they, as of this writing, are not yet introduced in South Korea.

Finally, we have reason to believe that KMAP-BP 2022 provides useful information to Korean clinicians regarding their clinical decision-making, and that the guideline will be well administered in Korean clinical practice.

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■ Conflicts of Interest

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

■ Author Contributions

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