

# Korean Medication Algorithm for Schizophrenia 2019, Second Revision: Treatment of Psychotic Symptoms

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**Objective:** In 2001, the Korean College of Neuropsychopharmacology and the Korean Society for Schizophrenia Research developed the Korean Medication Algorithm Project for Schizophrenia (KMAP-SPR 2001, revised 2006) through a consensus of expert opinion. The present study was carried out to support the second revision of the KMAP-SPR.

**Methods:** Based on clinical guidelines and studies on the treatment of psychotic symptoms in schizophrenia, the Executive committee completed a draft of KMAP-SPR 2019. To obtain an expert consensus, a Review committee of 100 Korean psychiatrists was formed and 69 responded to a 30-item questionnaire. Based on their responses, the KMAP-SPR 2019 was finalized.

**Results:** The revised schizophrenia algorithm now consists of 5 stages. At Stage 1, monotherapy with atypical antipsychotics was recommended by expert reviewers as the first-line strategy. At Stage 2, most reviewers recommended the use of typical or atypical antipsychotic drugs not used at Stage 1. At Stage 3, many reviewers agreed with the administration of clozapine. At Stage 4, a combination of clozapine and other agents such as antipsychotics, mood stabilizers, antidepressants, or electroconvulsive therapy was recommended. At Stage 5, most reviewers recommended combined treatment with an antipsychotic other than clozapine; and a mood stabilizer, antidepressant, or electroconvulsive therapy. At any stage, prescribing long-acting injectable antipsychotics at the discretion of the clinician was recommended.

**Conclusion:** Compared with previous versions, the KMAP-SPR 2019 now recommends using clozapine earlier in treatment-refractory schizophrenia. In addition, the use of long-acting injectable antipsychotics is now considered to be available at any stage.

**KEY WORDS:** Schizophrenia; Algorithm; Drug therapy; Consensus; Practice guideline.

## INTRODUCTION

Medication algorithms can help clinicians make decisions by providing a wealth of information about psycho-

tropic medications and research data [1]. Although treatment algorithms and clinical practice guidelines have been published in many countries, the guidelines for pharmacological treatment can vary from country to country because national health systems, economic situations, and cultural environments can differ. Most medication algorithms rely on the evidence of randomized controlled trials, but incorporating expert consensus is also important because this can lead to an algorithm reflective of national characteristics [2,3].

In order to develop medication algorithms suitable for

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clinical situations in Korea, the Korean College of Neuropsychopharmacology (KCNP) and the Korean Society for Schizophrenia Research (KSSR) developed the Korean Medication Algorithm Project for Schizophrenia (KMAP-SPR) through a consensus of expert opinion in 2001, which was updated in 2006. However, since the publication of KMAP-SPR 2006, several international clinical guidelines have been revised [4-9], new antipsychotic drugs have been developed [10-12], and studies have been published supporting the use of long-acting injectable antipsychotics (LAIs) in first-episode schizophrenia [13]. Accordingly, the KCNP and KSSR have now created a second revision, the KMAP-SPR 2019, to reflect changes in expert opinion regarding the treatment of psychotic symptoms in patients with schizophrenia.

Common to the KMAP-SPR series is a three-part organization: 1) treatment of psychotic symptoms, 2) treatment of comorbidities, and 3) treatment of adverse effects from antipsychotic medication. We aimed to determine an expert consensus on a draft revision of KMAP-SPR that reflected developments since 2006, for incorporation into a finalized second revision, with emphasis on Part 1).

## METHODS

### Executive Committee

This committee performs several practical tasks for medication algorithm development. There are two chairpersons, one of whom is head director of the KCNP and the other, head director of the KSSR. In addition to the chairpersons, the Committee includes three KCNP members and four KSSR members. The Executive committee recruits the members of the Review committee.

The Executive committee completed a draft version of KMAP-SPR 2019 based on various clinical guidelines and on published studies on the treatment of psychotic symptoms in schizophrenia. To gather expert opinion, they also wrote a questionnaire about the draft version and circulated it to the Review committee for comments.

### Review Committee

The Executive committee recruited 100 Korean psychiatrists who were life-long members of KCNP or KSSR and had more than 10 years of clinical experience in the field of schizophrenia. Through discussion, candidates who were considered clinically and investigatively ex-

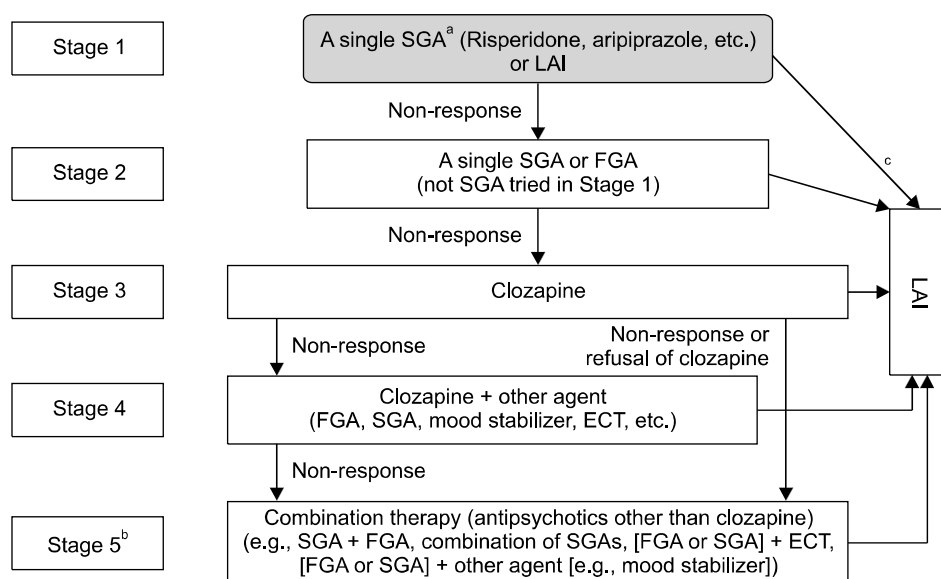
perienced in the field were selected by the Executive committee. The questionnaire was mailed to members of this committee and responses were received from 69 (69.0%) members. The respondents worked in a wide variety of clinical settings, including university hospitals (n = 50), general/psychiatric hospitals (n = 17), and private psychiatric clinics (n = 2).

### Questionnaire

The KMAP-SPR 2019 questionnaire was similar to that used to develop the KMAP-SPR 2006, with some modifications. To take advantage of both evidence-based and expert-consensus guidelines, the questionnaire was structured as requests for comments on the draft of KMAP-SPR 2019, which was based only on evidence at that stage. Specifically, the questions asked how satisfied the reviewers were with the treatments recommended at each stage, or what treatments they would prefer. Degree of satisfaction was measured on a five-point scale. Five indicated "very satisfied," 4 indicated "usually satisfied", 3 indicated "moderate", 2 indicated "usually unacceptable" and 1 indicated "absolutely unacceptable". In questions answered with 1 or 2 points, the reviewers were asked to give their recommendations as free-form statements. The questionnaire had 30 questions. Fifteen concerned either the overall composition of the medication algorithm or the treatment of psychotic symptoms, and the remainder concerned treatment of comorbidities and adverse effects. The new modifications of the questionnaire were: In Stage 1, the Executive committee proposed monotherapy with second-generation antipsychotics (SGAs) as the first-line treatment, and asked the reviewers which SGA they prefer. In Stage 4, the Executive committee proposed as the treatment of choice a combination therapy consisting of clozapine plus other treatments such as first-generation antipsychotics (FGAs), SGAs, mood stabilizers, antidepressants, or nonpharmacological treatments such as electroconvulsive therapy (ECT). The reviewers were also asked which treatment option they would prefer to combine with clozapine.

### Public Hearing

On April 20, 2018, at the Spring Conference of the Korean Society for Neuropsychiatry, a public hearing for the development of the KMAP-SPR 2019 was held. Various proposals raised at the hearing were reviewed by



**Fig. 1.** Korean Medication Algorithm for Schizophrenia 2019: treatment of psychotic symptoms.

SGA, second generation antipsychotics; LAI, long-acting injectable antipsychotics; FGA, first generation antipsychotics; ECT; electroconvulsive therapy.

<sup>a</sup>Other SGAs including olanzapine, amisulpride, quetiapine, ziprasidone, paliperidone, blonanserin, zotepine are approved and used currently in South Korea. <sup>b</sup>Depending on the clinical situation, it is possible to move to Stage 5 at any Stage. <sup>c</sup>Depending on the clinical judgment, LAI can be considered at any Stage; Depending on the clinical situation, it is possible to skip to the further stage.

the Executive committee and the KMAP-SPR 2019 was then finalized.

### Data Analysis and Development of Medication Algorithms

For each question, we counted how many reviewers gave particular scores. If a question received more than 4 points, it was considered that the reviewer was generally satisfied with the treatment option being proposed. If more than 50% of the respondents gave more than 4 points, it implies that the reviewers reached a consensus on the question. Recommendations at each stage were based on a draft prepared by the Executive committee based on various clinical guidelines and published studies, but amendments have been made if expert consensus was not reached on a particular item.

### Ethics

The present study was conducted according to the Declaration of Helsinki. All reviewers received a pre-determined fee for their participation.

## RESULTS

### Overview

As shown in Figure 1, the medication algorithm for treatment of psychotic symptoms consists of five stages. In order not to limit clinical judgment, however, clinicians can skip a stage depending on the clinical situation. As far as possible, antipsychotic monotherapy is recommended. The new parts of the KMAP-SPR 2019 are revisions to Stage 2 and the criteria for LAIs (Table 1).

### Stage 1

The Executive committee had proposed SGA monotherapy as the first-line treatment for psychotic symptoms. In addition, they had proposed LAIs at Stage 1 if tolerance to oral medication is demonstrated. The reviewers favored risperidone (29.9%), aripiprazole (28.4%), olanzapine (16.4%), and paliperidone (14.9%) for SGA monotherapy at Stage 1 (Table 2).

### Stage 2

The Executive committee had proposed that if there is no response to the SGA selected at Stage 1, another SGA or FGA monotherapy can be tried at Stage 2. Of the 69 reviewers who answered the question for Stage 2, 62 were

**Table 1.** Comparisons of treatment strategies for psychotic symptoms between the Korean Medication Algorithm for Schizophrenia 2006 and 2019

First revision in 2006		Second revision in 2019
Stage 1	SGA	SGA
Stage 2	SGA (not tried in Stage 1) or FGA With no response to a single trial of SGA or FGA, another trial of a different generation antipsychotic drug can be done	SGA (not tried in Stage 1) or FGA With no response to a single trial of SGA or FGA, proceed to Stage 3
Stage 3	Clozapine	Clozapine
Stage 4	Clozapine + other agent (FGA/SGA, MS, ECT, etc.)	Clozapine + other agent (FGA/SGA, MS, ECT, etc.)
Stage 5	Combination therapy	Combination therapy
LAI	No response due to non-compliance	Depending on the clinical judgment

SGA, second generation antipsychotics; FGA, first generation antipsychotics; MS, mood stabilizer; ECT, electroconvulsive therapy; LAI, long-acting injectable antipsychotics.

**Table 2.** Preference rate and ranking of antipsychotics for Stage 1

Antipsychotics	First place	Second place	Third place
Risperidone	29.9% (1)	14.9% (4)	10.4% (4)
Aripiprazole	28.4% (2)	16.4% (3)	25.4% (1)
Olanzapine	16.4% (3)	34.3% (1)	13.4% (3)
Paliperidone	14.9% (4)	17.9% (2)	9.0% (6)
Blonanserin	4.5% (5)	1.5% (7)	3.0% (7)
Amisulpride	3.0% (6)	6.0% (5)	23.9% (2)
Quetiapine	3.0% (7)	6.0% (5)	10.4% (4)
Ziprasidone	-	-	1.5% (8)

Data are presented as preference rate (ranking).  
-, not available.

satisfied (usually satisfied 37, very satisfied 25). According to the KMAP-SPR 2006, if there is no response to a single trial of SGA or FGA, another different-generation antipsychotic drug can be tried. However, according to the KMAP-SPR 2019, if there is no response to a single trial of SGA or FGA monotherapy, proceeding to Stage 3 is recommended.

### Stage 3

The Executive committee had proposed clozapine monotherapy as the treatment of choice at Stage 3. Of the 69 reviewers who answered the question for Stage 3, 48 were satisfied (usually satisfied 45, very satisfied 3). Because there should be no response to two adequate trials of antipsychotic drugs before proceeding to Stage 3, reaching Stage 3 can be considered treatment resistance. When asked whether to test serum clozapine levels at this point, 35 out of 67 respondents (52.2%) were opposed.

### Stage 4

The Executive committee had proposed that when patients do not show an adequate response to clozapine,

**Table 3.** Preference of combination strategies for Stage 4

Strategies	Preference rate
Clozapine + SGA	91.0%
Clozapine + MS	6.0%
Clozapine + ECT	1.5%
Clozapine + LAI	1.5%

SGA, second generation antipsychotics; MS, mood stabilizer; ECT, electroconvulsive therapy; LAI, long-acting injectable antipsychotics.

**Table 4.** Preference of atypical antipsychotics for Stage 4

Antipsychotics	First place	Second place	Third place
Amisulpride	36.5% (1)	26.0% (2)	20.0% (2)
Aripiprazole	32.7% (2)	28.0% (1)	17.8% (3)
Risperidone	23.1% (3)	12.0% (4)	28.9% (1)
Paliperidone	5.8% (4)	20.0% (3)	8.9% (5)
Olanzapine	1.9% (5)	6.0% (5)	6.7% (6)
Quetiapine	-	6.0% (5)	-
Blonanserin	-	2.0% (7)	11.1% (4)
Ziprasidone	-	-	6.7% (6)

Data are presented as preference rate (ranking).  
-, not available.

combination therapy with clozapine plus other treatments is the treatment of choice. The other agents are FGA, SGA, mood stabilizers, antidepressants, or non-pharmacological treatments such as ECT. As shown in Table 3, 91.0% of reviewers preferred a combination of clozapine and an SGA at this stage. The SGAs most preferred for combination with clozapine were amisulpride (36.5%), aripiprazole (32.7%), and risperidone (23.1%) (Table 4).

### Stage 5

The Executive committee had proposed that there is no treatment of choice for treatment-resistant patients who

refuse to take clozapine or who do not respond to clozapine. Therefore, at Stage 5, various combination therapies including an SGA combined with an FGA, a combination of SGAs, an FGA/SGA with ECT, or an FGA/SGA combined with another agent (e.g., mood stabilizer, antidepressant) can be tried. Of the 69 reviewers who answered the question for Stage 5, 60 were satisfied (usually satisfied 43, very satisfied 17).

### LAI

In the KMAP-SPR 2006, LAIs were recommended only in cases of no treatment response due to drug non-compliance. The draft revision recommended that LAIs be prescribed at any stage at the clinician's discretion after tolerance to oral medication is verified. Of the 69 reviewers who answered the question on LAIs, 59 were satisfied (usually satisfied 27, very satisfied 32).

### Switching Strategy

The Executive committee had proposed that the preferred switching strategy be "overlap and taper," which means continuing the same dose of the first antipsychotic while gradually increasing that of the second to a therapeutic level and then tapering the first. Of the 69 reviewers who answered the question on switching strategy, 55 were satisfied (usually satisfied 49, very satisfied 6).

## DISCUSSION

### Evidence-based vs. Consensus-based Guidelines

Guidelines on treatment fall into two types: expert consensus and evidence-based, each with advantages and disadvantages. The consensus among experts has the advantage of reflecting national characteristics such as health care policy, the economic situation, and ethnicity. Expert consensus statements can also provide practice-based evidence in the absence of high-quality research evidence. However, expert-consensus guidelines have in common a difficulty in guaranteeing validity. On the other hand, most evidence-based guidelines rely on randomized controlled trials (RCTs) with strict inclusion and exclusion criteria that apply only to the specific populations so defined, and conclusions from RCTs often cannot be generalized to the diverse populations seen in clinical practice. The present guideline is based mostly on expert consensus, but the recommendations for Stage 1 and

Stage 4 are based on new research. Since this guideline combines expert consensus with research evidence, it will be necessary to make further revisions if warranted by new knowledge, new high-level evidence, or experience over time, all of which must be monitored on an ongoing basis.

### Stage 1

As in the KMAP-SPR 2001 and 2006, SGA monotherapy is the first-line treatment strategy for psychotic symptoms in the KMAP-SPR 2019. It has been widely accepted that SGAs should be used as the first-line drug. However, paradigms changed after some large-scale studies such as Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) [14] and Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study (CULASS) [15] emphasized that certain SGAs are not superior to certain FGAs regarding effectiveness. Despite these findings, we decided to use SGA as the first-line treatment for the following two reasons: First, FGAs have a high risk of extrapyramidal side effects. These side effects are one of the major causes of poor drug compliance and decreased quality of life [16,17]. In particular, FGAs are known to produce numerous irreversible side effects such as tardive dyskinesia, as well as life-threatening side effects such as neuroleptic malignant syndrome. At present, the most important known principle for preventing tardive dyskinesia is to minimize exposure to FGAs. Second, a meta-analysis showed that SGAs were superior to FGAs regarding relapse prevention [18].

### Stage 2

According to the KMAP-SPR 2006, after a single trial of an SGA or FGA, another antipsychotic of a different generation can be tried, but in the KMAP-SPR 2019, a single trial of any SGA or FGA is recommended at Stage 2. This is consistent with other clinical guidelines such as the Schizophrenia Patient Outcomes Research Team (PORT) psychopharmacological treatment recommendations [4], The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia [6], The National Institute for Health and Care Excellence (NICE) guideline [9], and The Royal Australian and New Zealand College of Psychiatrists clinical practice guideline [7], which recommends a trial of clozapine if there is no response to two trials of different antipsychotics.

In the KMAP-SPR 2006, the use of FGAs at Stage 2 was limited to patients who had shown a good response to FGAs in the past. However, since CATIE and CUTLASS have shown that the difference in treatment effects between SGA and FGA may not be significant, whether to use FGAs at Stage 2 is left to the judgment of the clinician.

### Stage 3

If no treatment response is achieved at Stage 2, clozapine monotherapy is recommended at Stage 3. Treatment resistance is usually defined when patients with schizophrenia continue to experience clinically significant psychotic symptoms after 2 adequate trials of different antipsychotics [19]. Moreover, almost all clinical guidelines [4-9] suggest that clozapine be offered to patients with treatment-resistant schizophrenia, and this is consistent with KMAP-SPR 2019. Many clinical guidelines recommend the determination of clozapine plasma levels to guide dosage and check drug compliance, but more than half of the reviewers objected to monitoring clozapine levels. This is probably because of limited availability of testing; clozapine plasma level monitoring is not implemented in many hospitals in South Korea.

### Stage 4

At Stage 4, a combination of an SGA and clozapine was the most preferred treatment. This is consistent with a recent meta-analysis, which demonstrated that this combination is modestly beneficial in patients not responding to clozapine alone [20]. However, little evidence was found for preferring one SGA over another in combination with clozapine. The reviewers preferred amisulpride, aripiprazole, and risperidone. In other research, patients who were only partially responsive to clozapine monotherapy and who received amisulpride or placebo for 6 weeks showed the beneficial effect of augmented amisulpride in the secondary measures (e.g., Clinical Global Impression) [21]. In a study comparing the effectiveness of clozapine/amisulpride and clozapine/quetiapine in patients partially responsive to clozapine, the improvement associated with amisulpride was significantly greater than that seen with quetiapine [22]. When clozapine was combined with aripiprazole, researchers observed an improvement in negative symptoms [23], or a significant improvement in positive symptoms and general psychopathology [24]. Studies on the combination of clozapine

with risperidone were reported most often, but findings have been mixed: significant improvement [25,26] or no proven improvement [27-29].

### Stage 5

Little evidence is available to support combinations of non-clozapine antipsychotics [30], although this is common in clinical practice. Since controlled studies on combination therapy are by nature difficult to conduct, few studies have reported on combinations of antipsychotics other than those involving clozapine in treatment resistant schizophrenia [30]. At Stage 5, an SGA/FGA plus ECT, or an SGA/FGA plus another agent such as a mood stabilizer can be tried, but these treatments are likewise not based on controlled studies. However, the effects of treatment are believed to vary considerably across individuals, involving substantial improvement in some and worsening in others, although proven evidence for this is lacking. Because polypharmacy is a risk factor for severe side-effect burden [31], caution should be exercised in prescribing more than three kinds of drugs despite no apparent therapeutic benefit.

### LAI

In the KMAP-SPR 2006, LAIs were used in cases of poor drug compliance, but the KMAP-SPR 2019 allows clinicians to use it at their discretion. This recommendation is based on the advantages of LAIs over oral antipsychotics, namely improved compliance to medication and prevention of the worsening of symptoms and relapses associated with the discontinuation of treatment [13]. Non-compliance is very common during the early stages of treatment; approximately 40% of patients stop taking their antipsychotic medication within 1 year and about 75% stop taking the medication within 2 years [32]. In patients with schizophrenia, non-compliance is problematic because it can lead to exacerbation of symptoms and relapses [33]. LAIs is an important treatment option to compensate for non-compliance by making it easier to detect non-compliance and by enabling early intervention [34]. Several meta-analyses demonstrated that LAIs were superior to oral antipsychotics in preventing rehospitalization and relapse [35,36]. Furthermore, a study of patients with first-episode schizophrenia showed that LAIs were associated with significantly lower relapse and rehospitalization rates than those of oral antipsychotics [37].

### Advantages and Limitations

Several limitations of this study should be acknowledged. First, the study is based on a consensus of Korean experts rather than experimental evidence. Most available evidence is from RCTs. However, RCTs may not apply to real-life clinical situations because they have strict inclusion/exclusion criteria and highly controlled settings. Therefore, we drafted the revision with reference to recent clinical studies and other guidelines based on experimental evidence, but we also consulted with experts to ensure that the algorithm reflected actual clinical situations. Second, the size of the Review committee may be too small to provide a valid consensus by some criteria. However, we decided that a sample of 69 psychiatrists is sufficient based on the fact that there are only 4,525 psychiatrists in South Korea. Third, the draft algorithm made no distinction between first-episode and multiple-episode patients. Because these two kinds of patient have different treatment outcomes and clinical features, several guidelines provide different treatment recommendations for first- and multiple-episode patients [6,7]. This option should be considered in future KMAP-SPR revisions.

To our knowledge, the KMAP-SPR 2019 is the most recent guideline revision based on both recent findings and expert consensus. Moreover, the guidelines are easy to understand and apply clinically, and the treatment options allow for the exercise of judgement by the clinician. We hope that the KMAP-SPR 2019 will provide clinicians with useful information to help them in making important decisions in difficult clinical situations.

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### Conflicts of Interest

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

### Author Contributions

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