

Guidance on the clinical understanding and use of long-acting injectable antipsychotics in Schizophrenia: Hong Kong Consensus Statements

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Abstract

Aims: There is increasing evidence showing the importance of long-acting injectable antipsychotics in the management of schizophrenia, especially in terms of improving patient medication compliance. A panel of experienced clinicians in Hong Kong mapped out a set of consensus statements with an aim to facilitate the understanding and use of long-acting injectable antipsychotics among local physicians.

Methods: Eight discussion areas regarding long-acting injectable antipsychotics were selected by the chairman of the consensus group. A series of meetings were held for the panelists to discuss the published literature and their clinical experience, followed by the drafting of consensus statements. At the final meeting, each consensus statement was voted on anonymously by all members based on its practicability of recommendation in Hong Kong.

Results: A total of 12 consensus statements on the rational use of long-acting injectable antipsychotics were established and accepted by the consensus group.

Conclusion: The consensus statements aim to provide practical guidance for Hong Kong physicians on the use of long-acting injectable antipsychotics in schizophrenia patients. These statements may also serve as a reference for doctors in other parts of the Asia-Pacific region.

KEYWORDS

consensus statements, guidance, long-acting injectable antipsychotics, schizophrenia

1 | INTRODUCTION

Long-acting injectable antipsychotics (LAIs) are important to improve the management of schizophrenia. A recent consensus statement by the Hong Kong Association of Psychosocial Rehabilitation indicates that there is growing concern about the need to tackle adherence issues in schizophrenia patients.¹ An Asia-Pacific survey

revealed that 41% of Hong Kong psychiatrists prefer to switch or add a long-lasting antipsychotic to address the adherence problem in their patients.² In addition, there is evidence showing that cultural beliefs about mental illness and its treatment are an area for consideration in Hong Kong.³ This article aims to present the consensus statements established by a local expert panel, which is expected to facilitate the understanding and use of LAIs among Hong Kong

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physicians. Furthermore, these statements can hopefully act as a reference for doctors treating patients with schizophrenia in other parts of the Asia-Pacific region.

2 | METHOD

A consensus group of 11 Hong Kong physicians experienced in the management of schizophrenia were convened to formulate consensus statements on the rational use of LAIs, based on their clinical experience and the published literature. Eight discussion areas of LAIs were identified by the chairman of the consensus group, as follows: (a) characteristics; (b) special features; (c) comparison between first- and second-generation antipsychotic LAIs; (d) efficacy; (e) special clinical uses; (f) tolerability and safety; (g) contraindications; and (h) patient education. A literature search was done on the PubMed database with the following keywords: 'first-generation antipsychotics', 'long-acting injectable antipsychotics', 'paliperidone', 'risperidone', 'schizophrenia', and 'second-generation antipsychotics'. Only articles published between 1996 and 2015 were included.

The consensus group utilized the modified Delphi technique^{4,5} to hold a series of expert focus meetings (Figure 1). Each of the above discussion areas was presented by two panel members, including their clinical experience and the relevant literature, followed by comments contributed by other members. After all the areas were discussed, consensus statements were drafted based on the panelists' comments and the published evidence. At the final meeting, each consensus statement was voted on anonymously by all members. With a method adapted from Ooi et al,⁶ each statement was assessed as per its practicability of recommendation in Hong Kong. A consensus statement was accepted only if $\geq 80\%$ of the members selected "accept completely" (option A) or "accept with some reservation" (option B) for practicability (Table 1).

3 | RESULTS

A total of 12 consensus statements regarding the rational use of LAIs were established and accepted by the consensus group.

Statement 1: The currently available second-generation antipsychotic (SGA) LAIs in Hong Kong, paliperidone LAI (PLAI) and risperidone LAI (RLAI), differ in their formulations. An initial loading dose regimen of PLAI is required to achieve a rapid onset of actions and shorter time to achieve steady-state levels. For RLAI, no loading dose is necessary, but at least 3 weeks of oral supplementations are required.

Voting results: A: 63%, B: 37%, C: 0%, D: 0%, E: 0%

Although aripiprazole LAI was recently approved for use in Hong Kong, it was not discussed by the consensus group because of its

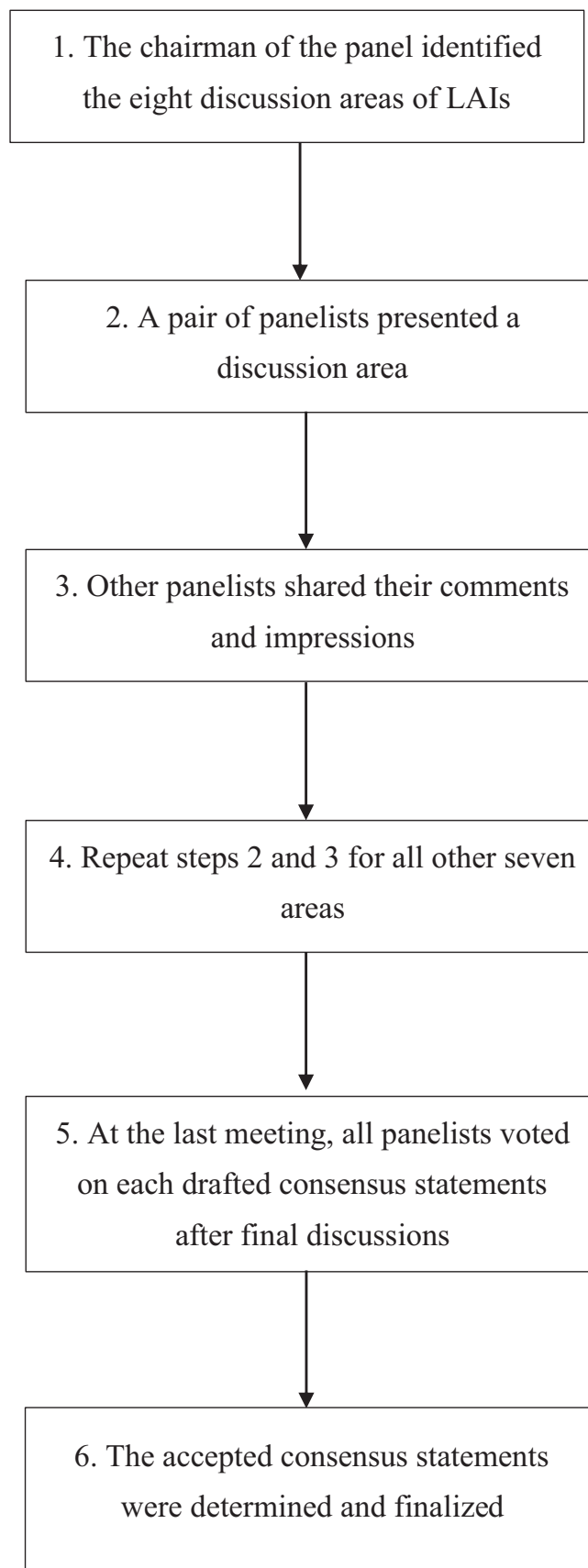


FIGURE 1 Process of consensus meetings

TABLE 1 Grading system for consensus statements⁶

Quality of evidence	Classification of recommendation	Practicability of recommendation
I: Evidence obtained from at least one randomized controlled trial	A: There is good evidence to support the statement	A: Accept completely
II-1: Evidence obtained from well-designed control trials without randomization	B: There is fair evidence to support the statement	B: Accept with some reservation
II-2: Evidence obtained from well-designed cohort or case-control study	C: There is poor evidence to support the statement but recommendation made on other grounds	C: Accept with major reservation
II-3: Evidence obtained from comparison between time or places with or without intervention	D: There is fair evidence to refute the statement	D: Reject with reservation
III: Opinion of respected authorities, based on clinical experience and expert committee	E: There is good evidence to refute the statement	E: Reject completely

Note: Modified from the Canadian Task Force on the Periodic Health Examination.

unavailability during the meeting timeframe. Olanzapine LAI is currently not commercially available in the locality. Therefore, the SGA LAIs mentioned in this article only included PLAI and RLAI, both of which had been available locally before the consensus group was established.

Paliperidone LAI is prepared as an aqueous suspension of nanocrystals of paliperidone palmitate.^{7,8} With an increased surface area, the nanomolecules allow for rapid release, which shortens the time to a steady plasma level of active paliperidone after intramuscular injection.⁷ This kinetic property can also facilitate an initial loading regimen to reach therapeutic antipsychotic levels in schizophrenia patients, without the need for oral antipsychotics (oral APs).⁸ As per the results of some placebo-controlled trials,⁹ starting or loading doses (ie, 150 mg equivalents [mg eq.] on day 1 and 100 mg eq. on day 8) are recommended to be administered in the deltoid muscle. Maintenance doses (ie, 25-150 mg eq/4 wk) can be administered in the deltoid or gluteal muscle.

As for RLAI, it is a water-based formulation of risperidone-impregnated microspheres, which make loading impossible, and a lag period of about 3 weeks is observed during the drug-releasing process.^{7,8} Therefore, at least 3 weeks of supplemental oral APs should be prescribed initially to maintain a sufficient drug level.^{7,8}

Statement 2: Compared with first-generation antipsychotic (FGA) LAIs, SGA LAIs are associated with a lower incidence of tardive dyskinesia and extrapyramidal syndrome; however, clinicians should beware of the increased risk for metabolic adverse events and weight gain.

Voting results: A: 50%, B: 50%, C: 0%, D: 0%, E: 0%

According to a number of reviews,¹⁰⁻¹² the incidence of movement disorders, including tardive dyskinesia and extrapyramidal syndrome, is lower in patients receiving SGA LAIs, compared with those

treated with FGA LAIs. This finding is generally consistent with the clinical experience of the consensus members.

However, some studies have shown that oral SGAs are associated with an increased risk of metabolic side effects and weight gain.¹² These kinds of adverse events and other long-term undesirable effects should be further investigated in patients receiving SGA LAIs.¹¹ Physicians should be aware of the risk of metabolic events and weight gain in patients receiving SGA LAIs.

Statement 3: In terms of cognitive performance, SGA LAIs are preferred over oral antipsychotics and FGA LAIs. SGA LAIs are suggested to preserve white matter brain volume and provide a greater degree of neuroprotection.

Voting results: A: 63%, B: 37%, C: 0%, D: 0%, E: 0%

Two studies found that, compared with oral risperidone, RLAI may enhance the development of intracortical myelin and improve the myelination trajectory in first-episode schizophrenia patients, possibly leading to a better cognitive function.^{13,14} An open-label trial revealed that a switch from haloperidol decanoate to RLAI may boost cognitive performance in patients.¹⁵ A review also found that SGA LAIs can be administered at an early stage of schizophrenia to better preserve cognitive capabilities of patients.¹⁶

In an *in vitro* study,¹⁷ risperidone and paliperidone were shown to possibly protect against apoptosis, while haloperidol induces it. The difference may be associated with their capacity to induce extrapyramidal symptoms. However, more studies are required to confirm the neuroprotective effect of SGA LAIs.

Statement 4: Contraindications to SGA LAIs are dependent on an individual patient's risk factors for the pharmacokinetics of the specific drug. PLAI and RLAI

should be avoided in patients with severe renal or hepatic impairment.

Voting results: A: 37%, B: 63%, C: 0%, D: 0%, E: 0%

SGA LAIs are contraindicated in patients who are hypersensitive to the products and in the elderly with dementia-associated psychosis.^{18,19} Doctors should beware of other risk factors of individual patients, such as impaired renal or hepatic function, before prescribing an SGA LAI. It should be noted that PLAI is not recommended in patients having moderate or severe renal impairment (ie, creatinine clearance [CrCL] <50 mL/min),²⁰ while RLAI should not be used in patients with severe renal impairment (ie, CrCL < 30 mL/min).¹⁸ Owing to the lack of clinical evidence, neither PLAI nor RLAI is recommended in patients suffering from severe hepatic impairment.^{18,20,21}

Statement 5: SGA LAIs are not recommended in patients who are unresponsive and/or unable to tolerate the oral formulations. Cautions should be exercised in special patient groups such as children, pregnant women, the elderly, and patients with physical comorbidities.

Voting results: A: 100%, B: 0%, C: 0%, D: 0%, E: 0%

Before receiving SGA LAIs, patients should establish tolerability with the corresponding oral formulations, that is, risperidone or paliperidone.^{18,19} It is not recommended to initiate SGA LAIs in patients who are unresponsive and/or intolerant to oral risperidone or paliperidone. In view of the absence of well-received clinical evidence, the safety issues of SGA LAIs regarding special populations, which include pediatric patients, pregnant women, the elderly, and patients with physical comorbidities, may be a concern.^{18,19,22} A benefit-risk analysis should be cautiously considered prior to the initiation of SGA LAIs in those special patient groups. More importantly, SGA LAIs are contraindicated in elderly patients who suffer from dementia-related psychosis.^{20,21} For other elderly patients, dose adjustment of SGA LAIs may be needed depending on their renal function.^{20,21}

Statement 6: Regardless of illness stage, SGA LAIs should be considered in all patients with schizophrenia as a shared decision-making process in view of the vast evidence supporting the benefits on treatment outcome.

Voting results: A: 75%, B: 25%, C: 0%, D: 0%, E: 0%

As suggested in a number of reviews,^{16,23-25} LAIs should be considered in all schizophrenia patients through a shared decision-making process, irrespective of their stage of disease or adherence issues. Compared with oral APs, LAIs are found to be more beneficial to patients in terms of the more favorable safety profiles and significant improvements in patients' psychotic symptoms, quality of life, and functioning.^{26,27}

In particular, several randomized controlled trials showed that, in comparison with oral APs, RLAI was associated with reductions in side effects, relapse, and hospitalization, as well as better adherence and enhanced clinical improvement.²⁸⁻³⁰ Some large-scale observational studies also revealed the advantages of RLAI over other treatment options. A French study found that, after a 12-month follow-up, schizophrenia patients treated with RLAI had a 34% reduction in the hospitalization rate compared with those receiving other treatments, including FGA LAIs.³¹ In a 24-month prospective study,³² compared with oral APs, RLAI was found to significantly improve treatment retention (81.8% for RLAI vs 63.4% for oral APs) and Clinical Global Impression Severity scores (-1.14 for RLAI vs -0.94 for oral APs) in patients with schizophrenia. In addition, a nationwide cohort study conducted in Finland showed that, among patients discharged from their first hospitalization for schizophrenia, the all-cause discontinuation was significantly lower in those receiving RLAI compared with those treated with oral risperidone (hazard ratio = 0.44, 95% confidence interval 0.31-0.62).³³ It is noted that most of the current studies were conducted on RLAI, rather than PLAI, as the latter has only been approved for use for a relatively short period of time. Although it might be expected that PLAI and RLAI have comparable clinical benefits, further specific studies on PLAI are warranted.

Statement 7: The use of SGA LAIs to enhance treatment adherence may be a reasonable choice at the early phase of treatment for first-episode schizophrenic patients.

Voting results: A: 75%, B: 25%, C: 0%, D: 0%, E: 0%

The treatment adherence of first-episode schizophrenia patients may be affected by their sensitivity to medication-related adverse effects and inadequate insight about, or acceptance of, their illness.^{34,35} Thus, the early stage of treatment may be pivotal in determining their disease progression in terms of clinical and psychosocial symptoms.^{36,37}

The results of several studies have suggested that SGA LAIs (primarily RLAI as it was the first to be marketed) are beneficial for first-episode schizophrenia patients. In an open-label study on a group of first-episode patients treated with RLAI, 72% of them completed the trial, showing a relatively low discontinuation rate.^{38,39} Moreover, 84% of them achieved a reduction of at least 50% on the Positive and Negative Syndrome Scale (PANSS) score, while 64% acquired a remission status as per the Remission in Schizophrenia Working Group (RSWG) remission criteria.³⁹ Another open-label study showed that, compared with oral risperidone, RLAI significantly reduced the relapse rate and enhanced medication adherence in first-episode patients.⁴⁰ Compared with other oral APs, RLAI was also found to be associated with improved acceptance and adherence in first-episode patients.³⁴

Based on the above clinical evidence and other research reviews,⁴¹⁻⁴⁴ the consensus group agreed that SGA LAIs may be a reasonable option for first-episode schizophrenia patients in the early

treatment stage, in order to improve medication adherence and other clinical outcomes.

Statement 8: The role of LAIs should be considered for patients in the acute phase or with demonstrated signs of relapse, particularly in those with serious mental illness, lack of insight, lack of supportive carers, or for whom there are doubts about medication adherence.

Voting results: A: 88%, B: 12%, C: 0%, D: 0%, E: 0%

According to several major overseas guidelines and expert consensus,^{23,25,45-48} LAIs should be considered in schizophrenia patients with relatively severe conditions, such as those with signs of relapse, lack of insight, deficient family/social support, or adherence issues. The consensus group thereby recommend that local physicians should consider the use of LAIs instead of oral APs among such patients, so as to improve symptom control, relapse risk, and medication adherence.

Statement 9: For outpatients, in addition to those listed for the inpatients, LAIs are recommended to be used for patients that demonstrate signs of relapse and for whom there are doubts about medication adherence.

Voting results: A: 63%, B: 37%, C: 0%, D: 0%, E: 0%

As shown in the Finnish cohort study on patients discharged from hospitalization due to schizophrenia,³³ those treated with LAIs had a significantly lower risk of re-hospitalization compared with those treated with oral APs. An observational study also found that RLAI was correlated with reductions in both the number and days of hospitalization in schizophrenia patients compared with oral risperidone.³² The guidelines set by a group of French experts on psychiatry recommend SGA LAIs as first-line treatment for patients receiving outpatient care.²⁵ Based on the available evidence, the consensus group recommend that LAIs should be prescribed for patients in the outpatient setting who have signs of relapse and potential adherence issues, so as to reduce their hospitalization risk.

Statement 10: Because substance misuse predicts nonadherence to oral medications, the use of LAIs is recommended to enhance treatment adherence in schizophrenia patients with comorbid substance misuse.

Voting results: A: 100%, B: 0%, C: 0%, D: 0%, E: 0%

Substance misuse was found to be closely related to nonadherence to oral APs in patients with schizophrenia.^{49,50} A set of clinical guideline recommendations derived from a literature review propose that LAIs are able to ensure treatment adherence in patients with comorbid substance misuse.⁴⁶ The guideline from the National Institute for Health and Care Excellence (NICE) in the UK also

recommends the use of LAIs in managing nonadherence problems among schizophrenia patients with coexisting substance misuse.⁵¹ The consensus group therefore agreed that, for the sake of medication adherence, LAIs are preferable to oral APs for schizophrenia patients with comorbid substance misuse.

Statement 11: The attitudes of the patients and their relatives toward LAIs should be addressed, and misconceptions are to be clarified via education, as part of the decision-making process, tailored to the individual patient's need.

Voting results: A: 75%, B: 25%, C: 0%, D: 0%, E: 0%

According to a cross-sectional study,⁵² patients currently on oral APs had a significantly lower preference for LAIs than those currently on LAIs. The researchers noted that possible patients' concerns over the perceived forceful nature of LAI initiation should be addressed to tackle LAI underutilization. Other reasons why patients are negative toward LAIs may include the fear of autonomy restriction and the pain of injections.⁵³ Some patients may also confuse LAIs with a short-acting emergency intramuscular dose, resulting in an undesirable perception of LAIs.⁵⁴ To increase patient acceptance of LAIs and diminish the negative image and stigma related to LAIs, clinicians should educate and inform patients and relatives sufficiently about this treatment option as part of a shared decision-making process.⁵³⁻⁵⁵ Even if patients refuse LAIs initially, further discussion on LAIs at subsequent appointments could help them better understand the benefits.^{46,54}

Statement 12: Preclinical studies have shown the neurotoxicity of FGAs (especially haloperidol) and the neuroprotective effect of SGAs; clinicians should consider these when prescribing LAIs.

Voting results: A: 100%, B: 0%, C: 0%, D: 0%, E: 0%

Numerous preclinical studies on animal and human tissues showed that FGAs, in particular haloperidol, may cause neuron apoptosis and brain tissue destruction by reducing the number of cells in the prefrontal cortex, suggesting the presence of potential neurotoxicity.^{17,56,57} In contrast, SGAs, including olanzapine, risperidone, and paliperidone, were found to possibly enhance cell survival and neurogenesis in the prefrontal cortex, leading to a neuroprotective effect of apoptosis prevention.^{17,57-59} In view of the current evidence, psychiatrists should beware of the possible difference in the mechanisms of action on brain tissues between FGAs and SGAs.

4 | DISCUSSION

Long-acting injectable antipsychotics, particularly SGA LAIs, have been found to be more beneficial than oral APs in multiple aspects of treatment of schizophrenia patients, including clinical symptom control, enhancement of treatment adherence, and reduction of

relapse rate and hospitalization risk. LAIs are also applicable for patients in different stages of illness. In view of the importance of LAIs in the management of schizophrenia, the consensus group, through the discussion of the available literature and the panelists' clinical experiences, established the above consensus statements, aiming to facilitate the rational use of LAIs among Hong Kong physicians.

Several limitations of these consensus statements have been noted. First, aripiprazole LAI, the latest approved SGA LAI in Hong Kong, was not discussed because it was not yet approved during the establishment of the consensus group. Its use in the locality should be further investigated by other local experts. Second, from the literature review, the clinical data on PLAI were significantly fewer than those on RLAI because of its rather short period of time on the market. More evidence regarding PLAI, especially from the local setting, is warranted to better assess its usage and properties. Third, local clinical trials on the use of LAIs are relatively scarce. Additional local data are required to further explore the pros and cons of LAIs among different types of schizophrenia patients in Hong Kong.

In conclusion, the consensus statements were formulated based on the available evidence from individual studies, expert consensus, and major overseas guidelines, combined with the insights of the panelists. These statements aim to provide a practical guidance for local physicians on the use of LAIs in patients with schizophrenia.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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