

Achieving better outcomes for schizophrenia patients in Hong Kong: Strategies for improving treatment adherence

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Abstract

Recent research on second-generation long-acting injectable antipsychotics (LAI SGAs) has proven its effectiveness in minimizing medication nonadherence problem and reducing relapses. Administered by medical professionals, making quick detection of nonadherence possible, long-acting injectable antipsychotics (LAIs) facilitate immediate intervention and recovery process, and thus are favored by psychiatrists. Despite a higher initial cost with LAIs, the subsequent schizophrenia-related health costs for hospitalizations and outpatients are greatly reduced. With reference to guidelines published by psychiatric associations around the globe, this article looks at scenarios in Hong Kong on the management of severe mentally ill patients with regard to the use of a host of psychosocial interventions as well as LAI SGAs as a preferable treatment. In particular, it examines the benefits of using LAI SGAs for Hong Kong patients who demonstrated high nonadherence treatment rates due to their social environment. It assesses the rationale behind the early usages of LAI SGAs, which help to provide better recovery outcomes for patients.

KEYWORDS

antipsychotic agents, Hong Kong, paliperidone palmitate, patient compliance, schizophrenia

1 | INTRODUCTION

In Hong Kong, there are more than 40 000 diagnosed schizophrenia patients, of which around half will be provided with outreach support in the community over the next few years.¹ Health Authority (HA), as a major specialist service provider for people with mental disorders in Hong Kong, provides psychiatric services ranging from inpatient facilities, day hospitals, and specialist outpatient (SOP) clinics to community outreach services. Among these services, SOP clinics serve the

largest proportion of patients within the population (89%).¹ The clinics had served 26 747 new patients in 2008-09 and provided a total of 647 864 outpatient attendances in the same year. Moreover, the workload in these clinics has increased by 19% since 2003-04.¹ The increase in the burden of mental illness suggests that the HA will need to enhance its SOP and community services for rehabilitation further to accommodate the rising number of utilizations. In addition, the support of mental health promotion, including prevention, early detection, and treatment, are important in maintaining a healthy society.¹⁻³

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Although regular intake of medication is the key to preventing relapse for patients with mental illness, treatment nonadherence and relapse remain the major problems for many schizophrenia patients,⁴ indicating that there is a need to improve severe mental illness (SMI) management for better long-term treatment outcomes.

Meanwhile, advances in psychosocial and pharmacological interventions continue to improve the management of schizophrenia.⁵⁻⁷ Second-generation antipsychotics (SGAs) have become the foundational interventions for schizophrenia as they offer good treatment efficacy with superior tolerability relative to first-generation antipsychotics (FGAs), especially in diminishing the development of extrapyramidal side effects.⁸ Because of this advantage and other reasons, for instance, the once biweekly or monthly injection schedule, SGA long-acting injectable antipsychotics (LAIs) further minimize the medication nonadherence problem, which often results in relapses and poses as a major barrier to optimal recovery.

A recent study revealed that 41% of Hong Kong psychiatrists would prefer to switch to or add on a LAI.⁴ Despite such preferences, the use of LAI is restricted due to resource limitations and stringent SMI management (eg, for the year 2011, 5.5% of Hong Kong's GDP was spent on health care, but only 0.24% was distributed to mental health).⁹

The aim of this article is to provide directions for Hong Kong on improving the SMI management for schizophrenia patients in the near future. The advantages and preferences of LAI SGAs over FGAs and current issues related to the management of SMI are discussed.

2 | METHODS

An expert panel from the Hong Kong Association of Psychosocial Rehabilitation (HKAPR) was formed to study on current issues related to the management of schizophrenia. Based on the scientific evidence in the literature and the clinical experience encountered by the healthcare professionals, recommendations for the improvement of SMI management were provided in the hope of achieving better treatment outcomes for patients.

A systematic literature search was performed using the PubMed database with the keywords "schizophrenia", "first-generation antipsychotics", "second-generation antipsychotics", "long-acting injectable antipsychotics", "oral antipsychotics", "serious mental illness" and "medication adherence". Approximately 1000 articles published from January 1981 to June 2016 resulted from the searches. A total of 61 articles and relevant references cited in those articles were selected for further review. In addition, the Hospital Authority Mental Health Service Plan for Adults 2010-2015¹ was included. All articles selected in this article were published in English.

2.1 | Impact of schizophrenia and better treatment outcomes on the society

The onset of schizophrenia peaks between the age of 20 and 24 in men, and between the age of 25 and 29 in women, with another

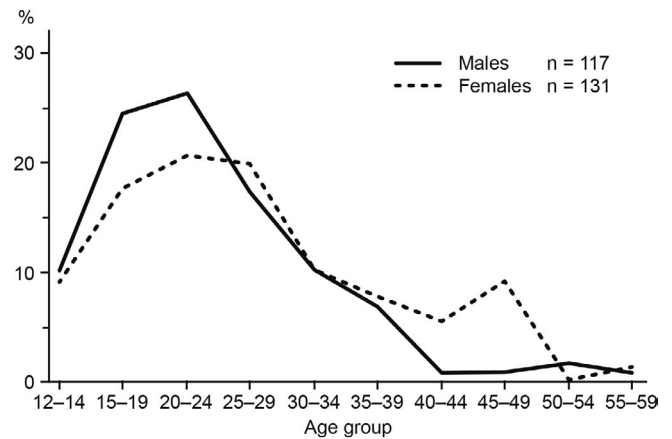


FIGURE 1 Age distribution of onset of schizophrenia (first sign of mental disorder) for men and women. From Häfner et al, 1998¹⁰

small peak after age 45 (Figure 1).¹⁰ Patients with schizophrenia often deny their mental problems; however, the disease progressively causes deterioration in their daily life functioning, such as occupation, hygiene, self-management, and their family and social relationships. All these negatively impact on the patients' quality of life (QoL) and the people around them.¹¹ In addition to the deterioration, sudden and unexpected personality changes, social stigmatization, and discrimination from other people could make patients less adherent to treatments and hence more prone to relapses.¹¹

Generally, if longer remission can be achieved and relapses can be prevented early in the course of the illness, the brain tissue loss and the decline in functioning can be minimized.^{12,13} This would increase the chance that the patients will reintegrate into the society and allow for more opportunities for patients to rebuild relationships and regain functions early.

2.2 | Voices, concerns, and myths from patients

A study conducted by Caroli et al¹⁴ found that 39% of patients with schizophrenia did not believe they had mental illness. Only 28% realized that they were diagnosed with schizophrenia. Indeed, the name of their disease was unknown to 37% of the patients, and 35% believed that their illness was mainly other psychological problems such as depression.¹⁴ Moreover, patients with schizophrenia who received an injectable treatment were concerned with the details of the injection procedures. 37% of the patients stated that they were unable to recall being given any details on the advantages and possible side effects of the injectable treatment.¹⁴ Additionally, Potkin et al¹⁵ showed that patients refused to receive the injectable treatment mainly due to fear and were concerned with the damaging and side effects of the therapy.¹⁵

For patients in Hong Kong, a cohort study revealed that patients' symptom severity, psychosocial functioning, self-esteem, and duration of illness were associated with their own perceived stigmatization.¹⁶ Those who experienced stigmatization was mainly due to their inadequate knowledge of mental illness, ineffective communication,

and misunderstandings about the disease mostly learnt from their relatives and the mass media, thus resulting in a feeling of inferiority and more stress for the patients. The study also showed that the perceived stigmatization from patients significantly increased over 1 year with deteriorated self-esteem and mental state. These perceptions can, in turn, increase the patients' relapse rates.¹⁶

To address the patients' concerns and promote advanced recovery among people with SMI, shared decision-making (SDM) should be implemented. Patients with schizophrenia may wish to be involved in decisions about their treatment.¹⁴ In a recovery-oriented mental healthcare system, instead of just focusing on interventions that reduce symptoms, the process should be directed to the conceptualization of personal recovery in mental health (ie, the CHIME framework: Connectedness, Hope, and Optimism about the future, Identity, Meaning in life, and Empowerment).^{17,18} Interventions that target these recovery outcomes, such as the illness management and recovery program (IMR), can be implemented to teach illness self-management strategies to people with SMI.¹⁸ To overcome the ethical and cultural challenges of implementing SDM, two approaches are suggested: (a) social marketing: a citizen-centered mental health system oriented around the preferences of service users, in which partnership is the foundation rather than an add-on feature; (b) hospitality industry: an approach where clinicians work in partnership with service users to ensure that they have a positive experience.¹⁹

2.3 | Voices, concerns, and myths from family and caregivers

A study conducted with the caregivers from Hong Kong, who had family members with mental illness, showed that their QoL was significantly lower than that of other Chinese populations.²⁰ Results indicated that caregivers who were younger had chronic illness, and a lower level of education and more dissatisfaction with mental health services were associated with more burdens and poorer QoL. Particularly, caregiver characteristics and beliefs were strongly associated with caregiver's QoL.²⁰

Indeed, the insight, concerns, and characteristics of the family members have a great influence on the patients' treatment adherence. The environmental and cultural contexts of the clinical setting and family dynamic are important areas to consider when using medication interventions in Hong Kong.²¹ For example, some family members do not believe in Western Medicine, or prefer Traditional Chinese Medical practices to Western Medicine.²¹ The traditional views of mental illness held by some families/carers may present a barrier to achieving treatment adherence, suggesting that in Hong Kong it may be beneficial to modify medication training to include specific family work approaches aimed to explore the cultural beliefs of mental illness and its management.²¹

Moreover, the distorted perspectives of some caregivers may present barriers to using psychotropic medications, including the recent LAIs.²² According to a research aimed to study the perspectives

of healthcare providers (psychiatrists, nurses, social workers, and therapists) about LAIs in the United States, caregivers were mostly concerned about potentially damaging the therapeutic relationship and possible side effects when discussing about initiating LAIs.¹⁵ A study of community mental health nurses in the United Kingdom revealed that about one-third of the nurses believed that LAIs were old-fashioned, about 40% felt that LAIs were stigmatizing and coercive, and about one-quarter of those surveyed felt that LAIs compromised patient autonomy.²³

Despite these concerns, the majority of healthcare providers (especially those in the mental health professions) had positive attitudes toward LAIs.^{15,24-26} In a study of 4120 nurses from Europe, Middle East, and Africa, almost all respondents (92%) felt that ensuring continuous medication with an LAI antipsychotic would yield long-term patient benefits.²⁵ Similarly, based on a study conducted to assess the psychiatric nurses' attitudes to depots in Hong Kong, 82.7% agreed that patient's adherence is better with depots than with oral antipsychotics (AP).²⁴

2.4 | Standard treatment algorithm and patient journey to recovery

The classical treatment goal for treating schizophrenia included symptom reduction and control, preventing relapses and increasing adaptive functioning so that the patient can be reintegrated into the community.²⁶ Pharmacotherapy is the mainstay of schizophrenia management. Nonetheless, the very first step of treatment should be a detailed and thorough assessment and an accurate diagnosis for schizophrenia followed by appropriate pharmacological treatment.²⁷ The international guidelines (such as the American Psychiatric Association and the Maudsley Prescribing Guidelines) suggested trial of a single SGA for first episode of schizophrenia.

Although there are no strict local guidelines for the treatment duration of schizophrenia, psychiatrists should judge on a case-by-case basis. Patients who previously remitted while on medications for a continuous period of time cannot be warranted to be in full remission if the antipsychotics were stopped.²⁸ For patients with first-episode psychosis (FEP), AP treatment is often discontinued after 1 year of good response. However, a study conducted in Hong Kong demonstrated that patients with FEP who were given placebo in the following year had a much higher rate of relapse than those who received maintenance treatment, suggesting the importance of treatment continuity.^{27,29}

Furthermore, in the past two decades, the traditional hospital-based care in Hong Kong has evolved toward community-based care for mental patients, including those who are suffering from schizophrenia. To further enhance the support to patients discharged from hospital, a proactive and assertive model of community services adopting the case management approach was started in 2010. In addition to the conventional community psychiatric nursing service (CPNS), three rehabilitation programs including Intensive Care Team (ICT), Personalized Care Program (PCP), and Community

Psychiatric Service (CPS) were implemented. Standardized protocols are followed, and services are provided after assessing patients' risks and needs. The case managers can be nurses, occupational therapists, or trained social workers. They work closely with the carers, psychiatrists and other mental health professionals, nongovernmental organizations (NGOs), and other rehabilitation agencies that provide services to patients. This community treatment model allows intensive psychosocial interventions for patients with schizophrenia to be carried out in the community and optimized their treatment outcomes and recovery.³⁰

2.5 | Clinical and social importance of treatment adherence

Nonadherence is a vital problem in treating schizophrenia patients, which has been reported to be as high as 50% with the use of oral AP.^{31,32} In Hong Kong, the self-reported nonadherence rate was 30%.²¹ Because nonadherence can lead to a high risk of relapse with subsequent clinical and social implications,²⁷ a phase-specific review of treatment regimen should be conducted regularly.

The negative effects of relapse on brain tissues have been well documented in several studies.^{12,13,33} Brain tissue loss has been linked to functional significance, which is related to the severity of the psychotic symptoms and cognitive impairment,¹³ implying that frequent relapses will worsen the patient's chance on achieving normal daily life. Additionally, there is an increased risk of hospitalization due to relapses, which will further contribute as social burden on patients, their families, and the society. It may also increase the safety concerns on the society due to an increased risk of dangerous behaviors such as suicide or homicide if the mental state was unstable.^{12,13,27,33}

Indeed, the chance of relapse is increased if pharmacotherapy or illness management plan discontinues, and with each relapse, recovery can be slowed, and the course of illness worsened.³⁴⁻³⁷ A study conducted by Robinson et al³⁸ showed that FEP patients who discontinued treatment were almost five times more likely to experience relapse than adherent patients. Also, the illness became more resistant to treatment and more difficult for patients to achieve functional recovery.³⁸ Additionally, a 15-year prospective study from the Netherlands revealed that the chronicity of psychotic symptoms for patients gradually increased from 27% to 47% between the first and the fourth episodes, and relapses occurred with a high risk of suicide.³⁹ The data from these studies clearly support the need for an adequate relapse prevention program for mentally ill patients.

2.6 | Assessing drug adherence

In Hong Kong, the patient's medication adherence is mainly assessed indirectly. For example, counting the number of pills that remain in the patient's medication bottles or vials is a common method for measuring adherence.^{32,34} However, it can be a barrier to build rapport with

the patient because the patient may feel that she/he is being pressured or not trusted by the healthcare workers. Furthermore, the patient can still discard some of the pills before hospital visits to pretend that she/he is following the treatment regimen. Besides checking the serum drug levels, there is no accurate way of assessing the medication adherence, and specific serum drug testing may be burdensome and impractical for routine clinical services.^{27,34} Nevertheless, there are a few commonly used adherence rating scales for the assessment of drug adherence including the Drug Attitude Inventory (DAI),^{40,41} the Medication Adherence Rating Scale (MARS),⁴¹ and the Brief Adherence Rating Scale (BARS).⁴² The DAI is a commonly used instrument that contains 10/30 items focusing on subjective attitudes toward antipsychotics; the MARS is a 10-item self-reported inventory which is based on the DAI; and the BARS is a clinician-administered adherence instrument. These rating scales demonstrate good sensitivity and specificity in identifying nonadherent outpatients.²⁷

One way to improve medication adherence is to adopt a *concordance approach* in introducing treatment options to the patients. The term "concordance" relates to a consultation process in which prescription is based on partnership because patients are more likely to be committed to the treatment regimen and adhere to the decision that she/he has actively made for herself/himself.⁴³ Concordance between the clinician and the patient should be the goal of all SDM encounters.⁴⁴ Three key steps to achieving SDM in clinical practice are as follows: (a) Choice talk, referring to the step of making sure that patients know that reasonable options are available, (b) Option talk, referring to providing more detailed information about options, and (c) Decision talk, referring to supporting the work of considering preferences and deciding what is best.⁴⁵

2.7 | Use of LAIs to address the adherence problem

Survey results published by the South China Morning Post (SCMP) stated that people in Hong Kong who work long and inflexible hours are more vulnerable to mental illnesses.^{46,47} Long working hours, as well as the lack of private working spaces for most of the workers, can be very troublesome for patients to strictly adhere to taking pills several times a day. Moreover, patients will also have to deal with the stigma or enquiries regarding the medication from their coworkers. These factors will contribute to patients' nonadherence to the oral drugs.

Most of the frequent causes of treatment failure are due to adherence problems.^{48,49} Patients will initially prefer to take oral drugs, but as their symptoms subside, they often would reduce the amount of drugs taken on their own. Patients may also stop treatment at the first sign of side effect that causes inconvenience.⁵⁰

Depending on the specific drug, LAI SGAs only need to be administered once every 2-4 weeks. Additionally, LAIs can be used to address the adherence issues. The treatment not only decreases the patient's burden of daily pill-taking, but also alerts the healthcare workers of patient's nonadherence as LAIs are administered by healthcare workers directly.²² Compared with oral AP, the use of a LAI SGA agent was associated with better QoL outcomes and lower

caregiver burden.⁵¹ Initially, patients might be reluctant for LAIs, but as they are stabilized over the long-term treatment, their attitude may change. By lowering the caregiver's burden on checking patients' adherence to daily pill-taking, the potential conflict between them may also be reduced.

Compared with the oral medication, LAIs have several advantages. Firstly, they are administered by mental health professionals that have the potential of increasing therapeutic contacts. This contact allows for easy and quick detection of nonadherence which facilitates immediate intervention. Secondly, it decreases the risk of accidental or deliberate overdose. Thirdly, the parenteral route avoids first-pass metabolism in the liver, which reduces the risk of drug-drug interactions. Last but not least, injections offer stable plasma concentrations that avoid high fluctuations and reduce the risk of drug levels wavering below or above the desired range.⁵²

Long-acting injectable antipsychotics are known to be at least as effective as oral AP; however, LAIs are associated with a significantly lower percentage of relapse and treatment discontinuation, with a significantly higher percentage of remission (Figure 2).²² Based on a hospital database analysis for 4 years, LAI SGAs were also associated with lesser rehospitalization and emergency room visits compared with oral AP.⁵³

2.8 | Early interventions with LAIs

Empowerment and interpersonal support are important components in the recovery process for schizophrenia patients.⁵⁴ Moreover, both pharmacological and psychosocial treatments should be offered as early interventions, as these therapies can improve patients' prognosis and help prevent their illness chronicity.⁵⁵ Several rationales for using LAIs early in the treatment of schizophrenia are as follows²²: (a) neuroprotective potential: LAIs promote intracortical myelination and may exert a neuroprotective effect when used in patients with FEP; (b) relapse reduction: A significantly lower relapse rate was observed with the LAIs; and (c) Adherence and overall illness management were easily fostered with the LAIs. The three

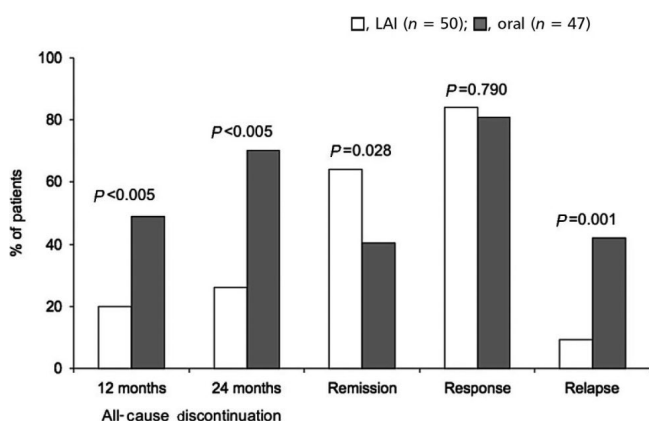


FIGURE 2 Outcomes after treatment with LAI or oral antipsychotics. From Stevens et al, 2016²²

most commonly used modalities of psychosocial interventions, namely, cognitive behavioral therapy (CBT), family intervention, and psychoeducation, also demonstrated a significant reduction of relapse during a 12-month follow-up study.⁵⁵ Compared to medication alone, an integrated treatment approach consisting of pharmacotherapy, psychosocial treatment, and psychoeducation also resulted in higher medication adherence, suggesting that this approach could effectively help patients learn the necessary skills about symptoms and medication management, which, in turn, could help prevent relapse.⁵⁶

Indeed, several professional associations have issued guidelines with recommendation of the early use of LAIs. In 2009, the National Institute for Health and Clinical Excellence (NICE) guidelines stated that clinicians should consider offering depot/LAI antipsychotic medications to patients with schizophrenia who would “prefer such treatment after an acute episode and where avoiding covert nonadherence to antipsychotic medication is a clinical priority” within the treatment plan.^{48,52} The French Association for Biological Psychiatry and Neuropsychopharmacology (AFBPN) also specifically recommended systematic offering of LAIs as first-line treatment to schizophrenia patients who needed maintenance treatment.^{48,52}

In Hong Kong, the consensus statements on adherence issues in schizophrenia²⁷ also stated that “LAI atypical antipsychotics should be considered as an option among indicated patients early in the course of illness in improving adherence” and “Adjunctive psychosocial interventions should be considered to be an integral part of the personalized care package to improve adherence.” Additionally, the recent recommendations for the optimal care of patients with recent-onset psychosis developed by experts from the Asia-Pacific region, Europe, and South Africa⁵⁷ stated that “LAI APs may play a role in relapse prevention via increased rates of adherence and should be considered as an early-stage treatment.” The recommendations also suggested that psychosocial therapies should be used in conjunction with continuous antipsychotic therapy: “Psychosocial therapies should be implemented early to prevent deterioration of psychosocial and cognitive functions.”⁵⁷

2.9 | Advantages and preference of LAI SGAs over LAI FGAs

Compared with the older FGA medications, SGAs have been generally associated with a reduced risk of tardive dyskinesia and treatment-related extrapyramidal syndrome (EPS) which are common side effects of FGAs.⁵⁸ Indeed, 28 neurotoxicity studies have reported the various destructive effects of haloperidol, one of the prototypic FGAs, on brain tissues,⁵⁹ whereas some of the SGAs are associated with neuroprotective effects.⁶⁰ In a review article, some SGAs have been shown to improve cell survival, enhance neurogenesis, and even prevent or reverse the effects of haloperidol-induced toxicity.⁶⁰

Overall, the advantages of LAI SGAs can be translated to a more cost-effective treatment strategy. As shown by the results of a

FIGURE 3 Differences in mean hospitalization and outpatient costs. From Lin et al, 2013⁶¹

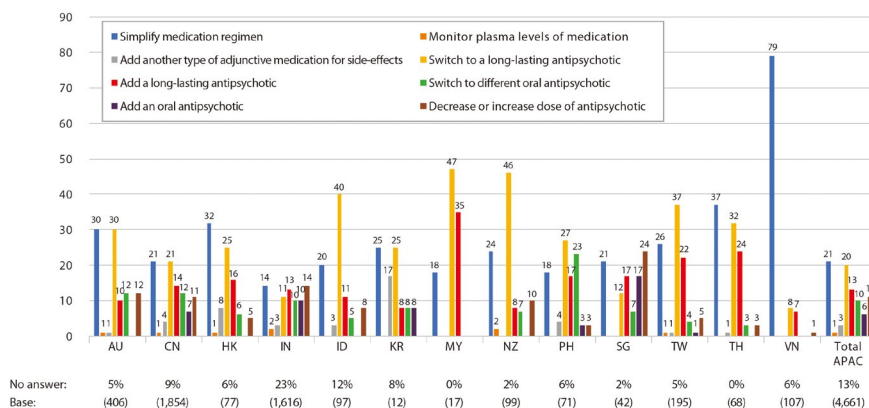
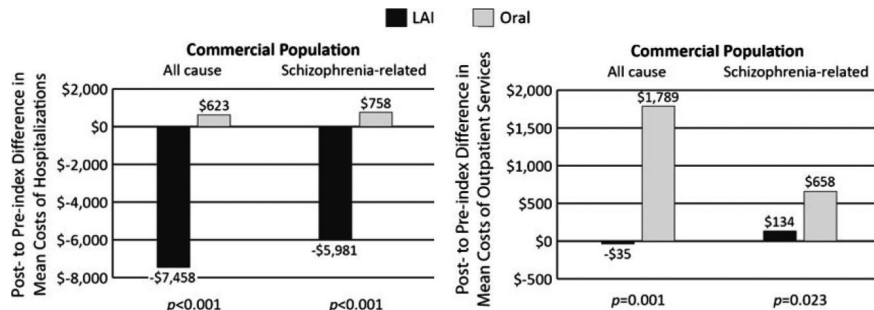


FIGURE 4 The preferred pharmacological approach for psychiatrists in 13 Asia-Pacific countries to address an adherence problem in their patients. Modified from Olivares et al, 2013.⁴ APAC, Asia-Pacific; AU, Australia; CN, People's Republic of China; HK, Hong Kong; ID, Indonesia; IN, India; KR, Korea; MY, Malaysia; NZ, New Zealand; PH, Philippines; SG, Singapore; TH, Thailand; TW, Taiwan; VN, Vietnam

real-world study, the initial drug costs were higher with LAIs, but the subsequent schizophrenia-related health costs for hospitalizations and outpatient services were higher in patients using oral AP (Figure 3).⁶¹ This provides indirect evidence that nonadherence is strongly associated with an increased risk of relapses and hospitalizations, and generally greater costs of care.⁶¹

2.10 | LAI SGAs-to-LAI FGAs ratio

The advantages of LAI SGAs clearly demonstrate a need to increase its use in place of LAI FGAs or oral AP. Evidence has shown that among the 13 Asia-Pacific countries, one in three psychiatrists (33%) expressed preference to switch to or add on a LAI.⁴ Indeed, 41% of the psychiatrists in Hong Kong showed the same preference for addressing an adherence problem in their patients (Figure 4).⁴ An increase in ratio of LAI SGAs-to-LAI FGAs would presumably provide many beneficial treatment outcomes to patients.

3 | CONCLUSION

In light of the advantages of LAI SGAs over both oral AP and LAI FGAs described in this article, the HKAPR panel would like to provide directions for Hong Kong on improving the SMI management

for schizophrenia patients within the near future. The proposed recommendations include the implementation of shared decision-making programs, as well as the increase in LAI SGA-to-FGA ratio as described above. The enhancement of LAI SGAs would significantly lead to better drug adherence for patients, leading to better clinical and psychosocial treatment outcomes, not to mention that neurotoxicity and side effects in patients would be significantly decreased. Also, due to better medication adherence, the implementation of LAI SGAs would reduce the rate of relapse and treatment discontinuation, thus increasing the percentage of remission. Additionally, the increase in ratio of LAI SGAs would help reduce the social burden of patients because a decrease in relapses would reduce brain tissue damage. Considering all these factors, the schizophrenia-related healthcare costs for hospitalizations and outpatient visits would be decreased. The reduction of hospitalization and relapse rates would therefore result in workload reduction for healthcare workers, who could then better align their objectives toward effective psychosocial treatment and reintegrating patients into the community. Ultimately, the augmentation of LAI SGAs would lead to a higher quality of care for patients as a result of better treatment adherence.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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