Neuropsychiatric Disease and Treatment

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Long-Acting Injectable Antipsychotic Treatment for Schizophrenia in Asian Population: A Scoping Review

Ning Ma[1–3,*], Lei Zhang[4,*], Wufang Zhang[1–3], Yingying He[1–3], Chong Ye[4], Xin Li[4]

[1]Peking University Sixth Hospital, Beijing, People's Republic of China; [2]Peking University Institute of Mental Health, Beijing, People's Republic of China; [3]NHC Key Laboratory of Mental Health (Peking University), Beijing, People's Republic of China; [4]Xi'an Janssen Pharmaceutical Ltd, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ning Ma, Peking University Sixth Hospital, NO. 51 Huayuan North Road, Haidian District, Beijing, 100191, People's Republic of China, Tel +86 010 82801939, Email maning@bjmu.edu.cn

Abstract: Evidence of comparative benefits of long-acting injectable (LAI) antipsychotics in Asian patients with schizophrenia has been inconsistent. This scoping review aimed to synthesize the current evidence in the past ten years and provide an overview of efficacy, safety, treatment adherence, patient attitudes, and healthcare resource utilization of LAI in this population. A systematic search was conducted with a pre-defined search strategy in six electronic databases including Chinese National Knowledge Infrastructure (CNKI), Wanfang, PubMed, Embase, CINAHL, and PsycArticles. A total of 46 studies were included, including 15 cohort studies, 13 single-arm trials, 10 randomized controlled trials, four mirror-image studies, three cross-sectional studies, and one controlled clinical trial. Paliperidone palmitate once-monthly injection (27/46) and risperidone LAI (14/46) were the most frequently investigated LAIs. Compared with oral antipsychotic medications (OAMs), LAIs demonstrated a lower rate of relapse/hospitalization and comparable improvement in efficacy. Adverse events (AEs) were similar between LAIs and OAMs, although types and incidence varied. Significant reduction in the length of hospitalization and number of outpatient visits/inpatient admission was observed after initiation of LAIs. These findings suggest that LAI demonstrated comparable efficacy and safety among Asian populations with schizophrenia in comparison to OAMs. Better adherence and lower relapse were observed in patients receiving LAIs from published evidence. Future research is warranted to better understand the comprehensive performance of LAI in specific population or context.

Plain Language Summary: LAI antipsychotic drugs for the maintenance treatment of schizophrenia have been considered the therapy of choice in case of poor adherence to treatment and frequent relapses. Few review studies focused on the benefits of LAI antipsychotics for schizophrenia in the Asian population have been conducted to date. Therefore, we conducted this scoping review to comprehensively summarize the current published evidence in terms of LAI efficacy, safety, treatment adherence, patient attitudes, and healthcare resource utilization in Asia.

Keywords: long-acting injectable antipsychotics, schizophrenia, Asian, scoping review

Introduction

Schizophrenia is a chronic debilitation[1] that affects approximately 6 to 7 out of 1000 people throughout lifetime.[2,3] Up to 80% patients may have post-treatment relapse within 5 years,[4,5] severely impacting their social and occupational functioning, as well as the quality of life (QoL), resulting in great socioeconomic burden.[6] Antipsychotics have been extensively studied for their effectiveness in treating schizophrenia.[7–13] While current practice recommends constant administration of antipsychotics,[14] the non-adherence rate still remains high.[15] Patients taking oral antipsychotics for schizophrenia have an estimated adherence rate of less than 60%,[16,17] compromising treatment effectiveness and leading

Received: 20 March 2023
Accepted: 7 September 2023
Published: 18 September 2023

to recurrent relapses and hospitalizations. It has been reported that patients who discontinued antipsychotic treatments are five times more likely to relapse than the adherent ones.[18] As the disease progresses, increased relapse frequencies could result in treatment refractoriness and shortened relapse-free period.[19] The focus of schizophrenia treatment has gradually shifted from improving acute symptoms to achieving sustained periods of symptom remission and function recovery.[10]

Schizophrenia relapse rate can be reduced with antipsychotic maintenance treatment.[16] Multiple guidelines and consensus recommended the use of long-acting injectable (LAI) antipsychotics for patients who experience relapse due to non-adherence to antipsychotics.[20–22] In the Chinese expert consensus, second-generation antipsychotics (SGA) have been recommended as a first-line treatment option.[23] The use of LAIs not only maintains stable and effective plasma concentration but also reduces dose-dependent side effects, improves patient's positive symptoms, depressive symptoms, and social functions.[24,25] Compared to oral antipsychotics, LAIs were reported to significantly improve treatment adherence, restore social functioning, and reduce relapse, hospitalization, emergency department visits, and medical costs.[16,26,27] However, some other studies also reported evidence of non-superiority in LAI compared to oral antipsychotics.[28,29]

Despite being available in Asia for over 10 years, LAI antipsychotics have low prescription rate and patient attitudes towards LAI remain important barriers to their use.[30] While global or other population studies have investigated LAI for the maintenance treatment of schizophrenia,[31,32] there has been a significant gap in systematic investigation or summary of published studies on its impact on Asian populations.[33–35] Thus, it is essential to evaluate the overall efficacy/effectiveness, safety, treatment adherence, healthcare resource utilization (HCRU), and patient attitude towards LAIs specifically in this population. Our goal is to fill this research gap by conducting a scoping review to present a comprehensive research landscape on LAI for schizophrenia treatment in the Asian population.

Materials and Methods

We performed a scoping review following Preferred Reporting Items for Systematic Review and Meta-analyses guidelines Extension for Scoping Reviews (PRISMA-ScR).[36] The study was conducted in rigid and comprehensive procedure following the guidance of the Joanna Briggs Institute (JBI) Methodology for Scoping Reviews.[37] Given that we aimed to describe the currently available evidence of LAI antipsychotics in treating Asian population with schizophrenia, our research question was formulated: "What are the clinical effectiveness/efficacy/safety, treatment adherence, patients' attitudes and HCRU of LAI antipsychotics among Asian population with schizophrenia?"

Search Strategy, Eligibility Criteria, and Study Selection

Search terms were developed with the guidance of Population, Concept, and Context framework shown in Supplementary Table 1. The literature search involved six electronic databases including PubMed, Embase, CINAHL, PsycArticles, Chinese National Knowledge Infrastructure (CNKI, in Chinese) and Wanfang (in Chinese). Keywords used in the search and details of the search strategy are shown in Supplementary Table 2. The inclusion criteria were (1) The study population were patients with schizophrenia; (2) Studies related to the clinical evidence of LAI antipsychotics including efficacy/effectiveness, safety, treatment adherence, HCRU and attitude towards LAIs; (3) Studies published in peer-reviewed journals from January 2012 to January 2022. And studies met the following criteria were excluded: (1) Studies published in language other than Chinese or English; (2) Studies without available full text; (3) Chinese studies not published in journals from the list of Peking University Core Journals of China; (4) Studies without quantitative results for patients with schizophrenia in Asia; (5) Non-targeted types of publication including case report, protocol, editorial letter, personal opinions, poster, conference abstract, and dissertation. Literature screening was performed by two reviewers independently in a two-phase process including title/abstract review and full-text review. Discrepancies between two reviewers were resolved by a third reviewer.

Data Extraction and Synthesis

Two reviewers independently extracted data from all eligible articles. Cross-examination of retrieved information was conducted, and disagreements were resolved by a third reviewer. Attempts to contact the authors of the included studies were made if there were any missing or additional data needed. Charting forms were pre-designed for data management to ensure data quality. For each study, data were extracted regarding study characteristics, population characteristics,

treatment or management, and outcome measures. Descriptive statistics were used to summarize findings on treatment and main outcomes. For continuous variables, mean, median, and standard deviation (SD) were extracted, while for categorical variables counts and proportions were extracted.

Results

Literature Screening and Selection

The initial search yielded a total of 523 publication records. Forty-six publications were eventually included in this review, and details are presented (Table 1). The screening and selection flowchart is shown in Figure 1.

Study Population and Design

This scoping review targeted study populations from Asian countries, eventually including studies from China (the mainland,[30,40,56,57,60,62,63,66,75–79,81] Hong Kong,[46] and the Taiwan region[42,43,50,55,68,70,71,74,80]), Japan,[38,48,51,54,58,61,64,82] Korea,[38,44,45,47,49,52,53,59,64,65,67,72,73] Malaysia,[44,47,49,52,53,58,67] Thailand,[47,49,67] and the Philippines.[49,58,67] Eleven of the studies were multicenter studies across different Asian countries. Patients enrolled in the included studies were mostly younger adults or at middle age (median = 36.1 years). All patients were diagnosed at the age of 25.9 to 33.0 years. The proportion of male patients exceeds 50% in most treatment groups in the included studies (median male percentage = 50.9%). Twenty-two studies defined baseline disease stage directly or screened patients by certain PANSS scores. A majority of them (15/20) enrolled patients during acute episode (explicitly defined as acute or derived from PANSS score >60) and five in stable condition (explicitly defined as stable or derived from PANSS score ≤60). Twenty-five studies reported previous treatment at baseline, of which 17 studies enrolled patients who had prior oral antipsychotic medications (OAMs), seven studies reported LAI treatment at baseline, and one study enrolled treatment-naïve patients.

Both clinical trials (24/46) and observational studies (22/46) were identified, including 15 (32.6%) cohort studies, 13 (28.3%) single-arm trials, 10 (21.7%) randomized controlled trials (RCT), 4 (8.7%) mirror-image studies, 3 (6.7%) cross-sectional studies, and 1 (2.2%) controlled clinical trial (CCT). Sample sizes ranged from less than 100 to over 50,000 owing to study designs and data sources. Observational studies tended to include larger sample size. More than half of the observational studies exceeded 1000 patients, and for studies using claims data, the sample sizes even exceeded 10,000.[54,71] The majority of clinical trials and mirror-image studies included less than 1000 patients. Furthermore, the follow-up period varied from weeks to years. Retrospective observational studies had much longer follow-up periods than other study designs, with two studies[68,72] having exceptionally long follow-up of more than 10 years.

Types of LAIs and Comparison Groups

Under the research question, the forty-six included studies involved both first-generation antipsychotics (FGA) and SGA, including OAMs and LAIs. The LAI intervention groups in comparative studies included risperidone, flupentixol, fluphenazine, aripiprazole, haloperidol, clopentixol, zuclopenthixol, paliperidone palmitate (PP, including paliperidone palmitate once-monthly (PP1M), and paliperidone palmitate 3-month formulation (PP3M)). Fifteen studies conducted pre-post LAI treatment comparison, which mostly are single-arm clinical trials and mirror-image studies. Fourteen studies included multiple LAIs or multiple subgroups/settings of population receiving the same LAI. Eighteen studies selected OAM(s) as control group in comparison to LAI and only one study included placebo group. Paliperidone palmitate (27/46) and risperidone long-acting injectable (RLAI) (14/46) were the most frequently investigated LAIs, and the most used OAM control in comparison to LAI is risperidone. Of all the studies included PP, thirteen are single-arm trials, two are mirror-image studies, and ten are RCTs/cohort studies. Two studies[38,39] included PP3M as intervention, and both studies are based on the results from the same RCT.

Table 1 Summary of All Included Studies

Authors and Year of Publication	Study Country or Region	Study Design	Study Period	Sample Size	LAI Group (s)	Comparator	Follow-Up	Main Outcomes	Main Findings
Adam J Savitz_2017[38]	Multi center	RCT	2012–2015	344	PP3M; PP1M	PP3M; PP1M	4 weeks	PANSS; CGI-S; PSP; relapse rate; AE;	PP3M is efficacious in the East Asian subgroup. Although treatment-emergent adverse events were slightly higher in the East Asian subgroup versus the global population, no new safety signals were identified.
Adam J Savitz_2019[39]	Multi center	RCT	2012–2015	995	PP3M; PP1M	PP3M; PP1M	4–12 weeks	PANSS; CGI-S; PSP; AE;	PP3M showed similar efficacy to PP1M in Europeans and non-Europeans, consistent with non-inferiority of PP3M to PP1M observed in overall population. Rates of AEs were higher in non-Europeans. However, weight gain was greater in non-Europeans, especially the Asian population.
Bai Hanping_2015[40]	Wuhan Province	RCT	2012–2014	80	PP1M	OAM-Risperidone	1 years	PSP; MSQ; relapse rate; discontinuation rate;	Long-acting paliperidone palmitate injection in the treatment of patients could improve social function and medication satisfaction, treatment compliance and remission, drug withdrawal, relapse and rehospitalization, so that it can be used in out-of-hospital long-term maintenance treatment of college students with schizophrenia safely and effectively.
Chen-Chung Liu_2013[41]	Taiwan region	Cohort study	2004–2008	92	LAIs; Risperidone; Flupentixol; Fluphenazine c;	Risperidone-Flupentixol-Fluphenazine-OAMs	3 years	Adherence;	Initiating LAIAs during admission for an acute psychotic episode, to a group of patients with an inadequate previous treatment response and poorer compliance, might keep their rehospitalization rates to the level of their oral antipsychotic medication treated counterparts.
Ching-Hua Lin_2020[42]	Taiwan region	Cohort study	2016–2018	1168	LAIs	OAMs	1 year	HCRU; discontinuation rate;	LAIs were found superior to oral antipsychotics (OAPs) in preventing rehospitalization. A continuous increase in second-generation LAI prescription rate may be due to the better side-effect profile of second-generation LAIs compared to first-generation LAIs. More studies investigating the effectiveness of LAIs in elderly patients with schizophrenia are needed in the future.

Chi-Shin Wu_2016[43]	Taiwan region	Cohort study	2004–2008	13,060	Clopentixol/ zuclopentixol; Flupentixol; Fluphenazine; Haloperidol	LAI-Risperidone	1 year	Cost; discontinuation rate;	Patients taking the RLAI may be more effective in some but not all outcome measures; however, risperidone was also associated with higher medical costs in the healthcare setting.
Chiun-Fang Chiou_2015[44]	Multi center	Cohort study	NA	311	PP1M	PP1M-China-Korea-Malaysia	1.5 years	HCRU; Cost;	The results suggest that reductions in hospital utilization cost were associated with PP treatment, likely largely due to increased adherence to treatment.
Dasom Lee_2020[45]	Korea	Mirror-image study	2010–2017	1272	PP1M	Pre-post	8 years	HCRU; Cost;	The high prescription costs for PP may be counterbalanced by the reduced admission costs associated with its use. Economic outcomes for patients treated with LAIs should be investigated further to help healthcare decision-makers and providers to determine the value of LAIs relative to other treatment medications.
David Bin-Chia Wu_2013[46]	Hong Kong	Mirror-image study	2003–2007	191	Risperidone	Pre-post	3 years	HCRU; Cost;	Cost of hospitalization was significantly reduced after RLAI therapy. However, results should be considered as indicative or suggestive only, due to potential channeling bias where certain drug regimens are preferentially prescribed to patients with particular conditions. The findings from our study may be useful in health-care decision making considering treatment options for schizophrenia in resource-limited settings.
Fan Zhang_2015[47]	Multi center	Single arm trial	2010–2013	585	PP1M	Pre-post	1.5 years	PANSS; MSQ; AE;	PP was efficacious and generally tolerable with significant reductions observed in both number of hospitalizations and days spent in hospital.
Fuminari Misawa_2021[48]	Japan	Cohort study	2004–2019	5791	Aripiprazole; Risperidone; PP1M;	OAM-Risperidone /paliperidone	5 years	AE;	LAI-SGAs were not associated with a higher reporting frequency and mortality of NMS compared with oral SGAs, although clinicians need to closely monitor the occurrence of NMS not only during oral SGA treatment, but also, and in particular, in the early stage of LAI-SGA treatment.
Hongyan Zhang_2017[49]	Multi center	Single arm trial	2010–2013	728	PP1M	Pre-post	3.75 years	PSP	Functioning, including employment, was improved after short-term, once-monthly paliperidone palmitate injection, and was sustained to 18 months in Asia–Pacific patients with schizophrenia.

(*Continued*)

https://doi.org/10.2147/NDT.S413371

Table 1 (Continued).

Authors and Year of Publication	Study Country or Region	Study Design	Study Period	Sample Size	LAI Group (s)	Comparator	Follow-Up	Main Outcomes	Main Findings
Hsiao-Fen Hsu_2019[50]	Taiwan region	Cohort study	2006–2015	78	FGA; SGA;	OAMs-Olanzapine, Risperidone, Ziprasidone, and Aripiprazole; LAI-FGA, SGA	3.5 year	HCRU;	We propose that oral and LAI antipsychotics were equally effective when patients received home care services. Our results can serve as a reference for the choice of treatment for patients with schizophrenia in a home care program.
Hsue-Wei Chan_2015[51]	Japan	Cohort study	2011–2012	379	Risperidone	OAMs- Risperidone	1 year	HCRU;	Using RLAI reduces the severity of disease in more difficult patients.
HuaFang Li_2016[52]	Multi center	Single arm trial	2012–2013	212	PP1M	Pre-post	1.5 years	PANSS; CGI-S; PSP; AE; discontinuation rate;	PP was generally tolerable and efficacious in a hospital setting for the treatment of acute exacerbated schizophrenia with significant improvements in psychotic symptoms, social functioning, and severity of illness.
Huafang Li_2018[53]	Multi center	Single arm trial	2012–2013	212	PP1M	Pre-post	13 weeks	PANSS; CGI-S; PSP; AE;	Early initiation of once-monthly paliperidone palmitate in hospitalized patients with acute exacerbation of schizophrenia led to greater improvements in psychotic symptoms with comparable safety than treatment initiation following 1 week of hospitalization.
Huaning Wang_2021[54]	Multi center	Cohort study	2012–2017	57,019	PP1M	OAM-SGAs	1 years	Adherence;	Persistence and adherence were significantly higher in PP1M users than in oral SGAs users across 3 databases comprising patients in 2 countries in Asia.
Hui-Chih Chang_2012[55]	Taiwan region	Mirror-image study	2004–2007	184	Risperidone	Pre-post	1 years	HCRU; Cost;	RLAI treatment was associated with reductions of service uses; however, overall psychiatric service costs were compromised by costs incurred from increased utilization of outpatient service and RLAI medication costs under the context of healthcare in the Taiwan region.

Jie Liu_2022[56]	Shandong Province	Mirror-image study	2016–2019	82	PP1M	Pre-post	2.5 years	HCRU; Cost;	Switching from OAPs to PP1M decreased the household workforce burden without increasing clinical healthcare costs. Direct costs were significantly reduced in patients with ≥ 1 inpatient stay in 1 year pre-PP1M treatment with OAPs after the switch, which decreased by improving adherence to therapy and reducing the number and length of hospital stays, suggesting that those patients may benefit after switching to PP1M.
Jingping Zhao_2017[57]	Multi center	Single arm trial	2013–2015	353	PP1M	Pre-post	4 weeks	PANSS; CGI-S; PSP; MSQ; AE; adherence; patients' attitudes;	Long-term treatment with PP1M was efficacious, and no new safety concerns were identified in Chinese patients with schizophrenia. Overall, the results were comparable with observations from previous studies.
Jun Ishigooka_2015[58]	Multi center	RCT	NA	455	Aripiprazole	OAM-Aripiprazole	26 weeks	PANSS; CGI-S; relapse rate; AE;	Aripiprazole once-monthly is efficacious in maintenance treatment of stabilized schizophrenia, with comparable efficacy and tolerability to oral aripiprazole.
Jun Soo Kwon_2015[59]	Korea	Cohort study	NA	141	PP1M	NA	21 weeks	PANSS; PSP; MSQ; AE;	Switching from oral atypical antipsychotics to paliperidone palmitate because of poor satisfaction significantly improved patient satisfaction, with comparable efficacy and tolerability.
Junli Zhu_2021[30]	Beijing City	Cross-sectional study	2020–2020	496	LAIs	NA	2 months	Adherence; patients' attitudes;	Beijing community patients are not very optimistic about LAI's cognition and willingness. Medication habits play an important role in their medication selection decisions. Intervention such as educate clinicians and patients about LAI and provide free injections to patients can be imposed. The promotion of LAI still has a long way to go.
Le Xiao_2022[60]	Multi center	RCT	2017–2019	436	Aripiprazole	OAM-Aripiprazole	2 weeks	PANSS; CGI-S; PSP; AE;	This study confirmed the efficacy and safety of aripiprazole once-monthly (AOM) for the treatment of Chinese patients with acute schizophrenia. The non-inferiority of AOM to oral aripiprazole was established, with comparable efficacy and tolerability. These findings suggested that AOM could be used as a treatment option for patients experiencing an acute episode of schizophrenia.

(*Continued*)

https://doi.org/10.2147/NDT.S413371 DovePress

Table 1 (Continued).

Authors and Year of Publication	Study Country or Region	Study Design	Study Period	Sample Size	LAI Group (s)	Comparator	Follow-Up	Main Outcomes	Main Findings
Masakazu Hatano_2020[61]	Japan	Cohort study	2004–2018	5226	LAIs	OAMs- FGA, SGA. LAI: Risperidone, paliperidone; Aripiprazole	4.25 years	AE;	Real-world data suggest that LAIs tend to reduce the occurrence of extrapyramidal symptom and neuroleptic malignant syndrome, but a number of other adverse events have potential risks as well as OAPs. In addition, onset of adverse events with LAIs have been shown to be slightly delayed, requiring more careful long-term monitoring.
Mei Qiyi_2016[62]	Jiangsu Province	Single arm trial	2012–2013	156	PP1M	Pre-post	16 months	AE; discontinuation rate;	Gender, the third injection dose, PANSS reduction in acute phase and akathisia may be the main factors to discontinuation of PP treatment.
Miao Xingfang_2014[63]	Shandong Province	Single arm trial	NA	58	PP1M	Pre-post	13 weeks	PANSS; AE;	Paliperidone palmitate is an effective and safe long-acting injection antipsychotic. It shows good efficacy and safety profiles on first episode schizophrenia.
Nagahide Takahashi_2013[64]	Multi center	RCT	2010–2012	324	PP1M	Placebo	21 weeks	PANSS; CGI-S; AE;	PP is efficacious for Asian patients with schizophrenia at the dosing regimen approved in other countries, with a similar safety and tolerability profile.
Nam Young Lee_2014[65]	Korea	Single arm trial	2005–2007	472	Risperidone	Pre-post	1 year	PANSS; CGI-S; AE;	This prospective, open-label study showed improvements in symptom and AEs and a significant increase in BMI during 48 weeks of biweekly RLAI treatment. The rate of study completion was 39.0% and the remission rate among those who completed the study was 65.2%. None of the serious AEs were directly related to the administration of RLAI.
Nan Li_2018[66]	Multi center	Single arm trial	2012–2013	610	PP1M	Pre-post	1 years	PANSS; PSP;	Thus, symptom and functional improvements with caregiver burden reduction were observed in patients, and PANSS reduction at week 5 was commonly associated with favorable outcomes.
Nan Li_2019[67]	Multi center	Single arm trial	2010–2013	470	PP1M	Pre-post	12 months	Other	Switching to PP1M treatment from oral antipsychotics is likely to be associated with a significant reduction in hospitalization risk along with a delay in time to hospitalization and rehospitalization.

Po-Chung Ju_2014[68]	Taiwan region	Cohort study	1996–2009	1755	Risperidone;	OAMs	14 years	Other	Consequently, LAI home-based treatment for the prevention of schizophrenia relapse may lead to substantial clinical and economic benefits.
Qin Guoxing_2013[69]	Zhejiang Province	CCT	2007–2009	70	Risperidone	OAM-Risperidone	2.5 years	PANSS; relapse rate; AE;	Injection of long-active risperidone microsphere and risperidone tables have equivalent efficacy and safety, so it is a good choice for us to use the long-acting antipsychotic drug injection as a maintenance treatment of schizophrenia due to its inherent advantages of coerciveness.
Shiau-Shian Huang_2013[70]	Taiwan region	Cohort study	203–2008	14,610	LAIs; Risperidone; Haloperidol; Flupenthixol;	LAI-Risperidone, haloperidol, flupenthixol; OAM-risperidone, other SGA or FGA	5 years	Other	Except for injectable haloperidol, long-acting injectable antipsychotics seem not to be superior to oral antipsychotics in reducing rehospitalization.
Su-Chen Fang_2020[71]	Taiwan region	Cohort study	2011–2012	40,194	LAIs	OAM-FGA, Risperidone	1 year	HCRU;	Chronic schizophrenia patients who received only LAIs had a lower risk of disease relapse and a reduction in psychiatric service utilization than those receiving only OAPs.
Sung Woo Joo_2019[72]	Korea	Cohort study	2007–2016	6163	Haloperidol; PP1M; Risperidone;	PP1M-Haloperidol-Risperidone	10 years	Discontinuation rate;	Early discontinuation of LAI antipsychotic treatment occurs in a large number of patients with schizophrenia. Intervention strategies for improving the LAI antipsychotics treatment adherence are needed.
Sung-Wan Kim_2013[73]	Korea	Cross-sectional study	2011–2012	99	LAIs	NA	1 years	Patients' attitudes;	In conclusion, attitudes of psychiatrists toward LAI were closely related to the use of LAI. The negative attitudes and reluctance of psychiatrists, rather than patient resistance, may contribute toward the underuse of LAI.
Szu-Jui Fan_2018[74]	Taiwan region	Cohort study	2008–2013	2073	Risperidone	OAM- Risperidone	1 year	HCRU; Cost;	Patients with schizophrenia treated with RLAI had shorter lengths of stay, higher medical costs largely because of increased utilization of outpatient service and hospital admissions, compared with those who took risperidone orally.
Tang Wei_2016[75]	Zhejiang Province	RCT	2012–2014	120	PP1M	OAM-Risperidone	2.5 years	PANSS; PSP; relapse rate; AE;	Long-acting paliperidone palmitate injection in the treatment of the patients with schizophrenia could obviously improve the remission rate.

(*Continued*)

https://doi.org/10.2147/NDT.S413371 DovePress

https://doi.org/10.2147/NDT.S413371 DovePress

Table 1 (Continued).

Authors and Year of Publication	Study Country or Region	Study Design	Study Period	Sample Size	LAI Group (s)	Comparator	Follow-Up	Main Outcomes	Main Findings
Tianmei Si_2015[76]	Multi center	Single arm trial	2012–2013	610	PP1M	Pre-post	1 years	PANSS; CGI-S; PSP; MSQ; AE; adherence; patients' attitudes;	The efficacy and safety data are consistent with other short-term, placebo-controlled studies of paliperidone palmitate conducted in similar populations.
Tianmei Si_2018[77]	Multi center	Single arm trial	2012–2014	362	PP1M	Pre-post	1 year	Relapse rate; AE; adherence;	Continued use of PP1M formulation/LAI antipsychotic was effective in preventing schizophrenia relapses, especially in patients with suboptimal antipsychotic adherence.
Tianmei Si_2019[78]	Multi center	Single arm trial	2010–2013	108	PP1M	Pre-post	3 years	PANSS; PSP; MSQ; AE;	Efficacy of PP1M corroborate findings from earlier studies and no new safety concerns emerged in this Chinese subgroup of patients with schizophrenia.
Wang Jian_2015[79]	Hebei Province	RCT	2013–2013	60	PP1M	OAM-Risperidone	13 weeks	PANSS; CGI-S; PSP;	Palmitic acid Paley piperidone is effective in the treatment of schizophrenia, which is beneficial to the patient's continuous and effective drug treatment and the improvement of the social life function of the patients.
Wen-Yin Chen_2016[80]	Taiwan region	Cross-sectional study	2013–2014	434	FGA; Risperidone;	LAI-FGA	1 years	CGI-S; PSP;	Our results suggest that patients treated with FGA-LAI have more satisfactory subjective experiences compared with patients treated with RIS-LAI and that both FGA-LAI and RIS-LAI treatments can prevent relapses and hospitalization. Additional longitudinal studies determining the long-term benefits of RIS-LAI are warranted.
Xu Qiuxia_2015[81]	Zhejiang Province	RCT	2012–2013	72	PP1M	OAM-Risperidone	14 months	PANSS; PSP; AE;	Palmitic acid Paley piperidone is effective and rapid in the treatment of acute schizophrenia, with significant social functioning improvement, convenience, and satisfaction.
Yosuke Koshikawa_2016[82]	Japan	RCT	2014–2015	30	PP1M; Risperidone;	PP1M; Risperidone;	0.5 years	Other	These results suggest that PP may improve the total social functioning, independent life competence, and performance as compared to the RLAI group. However, these results are preliminary and need independent replication in larger samples before any definitive statement can be made.

Abbreviations: AE, adverse event; AOM, aripiprazole once-monthly; CCT, controlled clinical trial; CGI-S, the Clinical Global Impression - Severity of Illness Scale; FGA, first-generation antipsychotics; HCRU, healthcare resource utilization; LAI, long-acting injectable; MSQ, the Medication Satisfaction Questionnaire; NA, not applicable; OAM, oral antipsychotic medications; OAP, oral antipsychotics; PANSS, the Positive and Negative Syndrome Scale; PP, palmitate paliperidone; PP1M, palmitate paliperidone once-monthly; PP3M, palmitate paliperidone 3-monthly; PSP, the Personal and Social Performance Scale; RCT, randomized controlled trial; RLAI, risperidone long-acting injectable; SGA, second-generation antipsychotics.

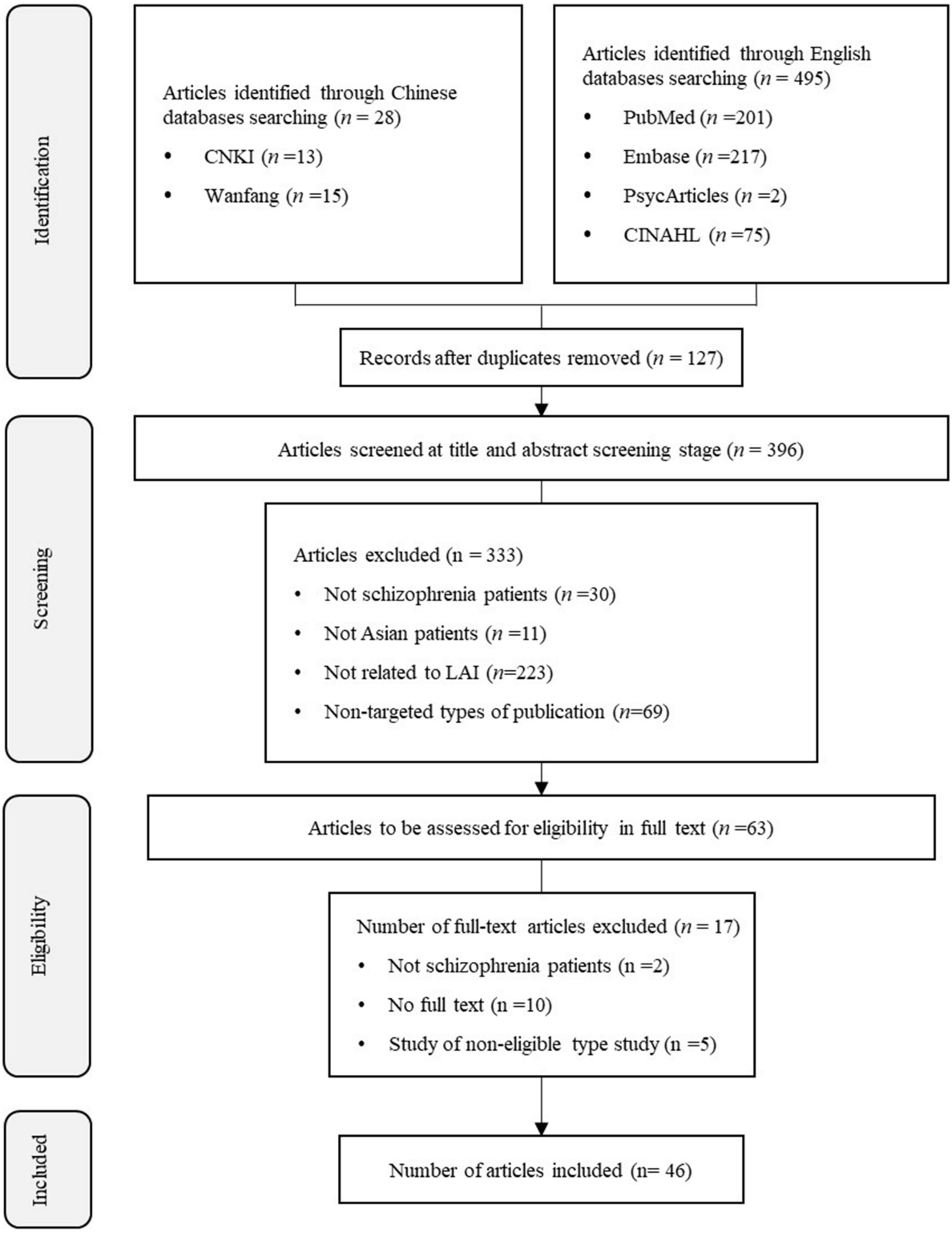

Figure 1 Flowchart of the study selection process.
Abbreviations: LAI, long-acting injectable; CNKI, Chinese National Knowledge Infrastructure.

Outcome Measurements of LAIs

We analyzed the outcome measures of the included studies, including treatment effectiveness or efficacy, safety, HCRU, and patient attitudes and adherence. Clinical trials mostly focused on the investigation of efficacy and safety of LAIs, whereas most reported HCRU results were from observational studies. Twenty-three of the 46 studies (50.0%), including ten single-arm trials and nine RCTs, used clinical rating scales as outcome measurements to assess the efficacy of LAIs. The most frequently used scales included the Positive and Negative Syndrome Scale (PANSS), the Personal and Social Performance Scale (PSP), the Clinical Global Impression-Severity of Illness Scale (CGI-S), and the Medication Satisfaction Questionnaire (MSQ). Other outcomes, such as relapse rate,[38–40,52,55,58,69,75,77] adherence to medications,[40–43,52,54,57,62,77] and discontinuation rate,[40,42,43,52,62] were also used in five cohort studies, four RCTs, and five single-arm trials, among which relapse rate was the most commonly reported. Safety outcomes, such as adverse event (AE) or treatment-emergent adverse event (TEAE), severe adverse event (SAE), and extrapyramidal symptom (EPS), were reported in 21 studies. Twenty studies investigated healthcare resource utilization (HCRU) including the number of inpatient/outpatient visits, lengths of hospital stay, and medical costs of LAIs. All mirror-image studies included in this review reported HCRU.

PANSS, CGI-S, and PSP

Twenty-three of the 46 studies (50.0%) evaluated efficacy of LAIs, of which PANSS (20/46), CGI-S (15/46), and PSP (15/46) were the mostly reported outcome measures in 11 single-arm trials,[47,49,52,53,57,62,63,65,66,76,78] nine RCTs,[38–40,58,60,64,75,79,81] one cohort study,[59] one controlled clinical trial,[69] and one cross-sectional study.[80]

Ten single-arm trials were focused on PP1M treatment and one study on RLAI.[65] Ten single-arm trials evaluated PANSS and all reported significant decreases in PANSS scores from baseline (range of mean change of PANSS score: −6.6 ~ −31.0). Nine single-arm trials reported decreased CGI-S from baseline (range of mean change: −0.19 ~ −3.0) and seven single-arm trials reported improved PSP scores (range of mean change: 14.9 ~ 19.8). Seven out of all single-arm trials reported that enrolled patients had prior OAM, and six reported statistically significant improvement in PANSS score and CGI-S score.

On the other hand, in the 12 comparative studies, eight used OAMs or placebo as controls (four PP1M vs OAM risperidone, two LAI aripiprazole vs aripiprazole OAM, one RLAI vs risperidone OAM, and one PP1M vs placebo). LAIs demonstrated equivalent efficacy in comparison of OAMs by the reported mean change of PANSS (LAI range −2.3~−49.7; OAM range: −2.7~−49.8), CGI-S (LAI range 0~−2.2; OAM range 0~−2.3), or PSP scores (LAI range 15.63~40.2; OAM range 9.4~20.33). Two RCTs, Tang et al[75] and Hanping et al,[40] reported significant improvement in PSP scores in PP1M treatment groups in comparison to OAM risperidone. Tang et al[75] included acute patients with recent onset and no prior treatment, also reported significantly decreased PANSS score in the PP1M treatment group over risperidone OAM. Notably, the enrolled patients in Tang et al[75] and Hanping et al[40] were the youngest among all included studies (mean age 23.8~25.1 years). In other RCTs, even though improvement in PANSS or CGI-S was found after risperidone or aripiprazole treatment was administered, no significant differences were observed between the LAI and OAM.

Relapse Rate and Rehospitalization Rate

A total of 19 studies reported relapse rate and/or rehospitalization rate (five cohort studies,[42,50,51,68,70] five RCTs,[38–40,58,75] four mirror-image studies,[45,46,55,56] three single-arm studies,[52,77,78] one cross-sectional study,[80] and one controlled clinical trial[69]). Of the nine studies reporting results of relapse rate, eight were clinical trials and one was an observational study. Among the 11 studies reporting on readmission rates, two were clinical trials, while nine were observational studies. The reported relapse rates of LAIs ranged from 0.0% to 12.4% and OAMs from 5.9% to 34.0%, while rehospitalization rates of LAIs ranged from 0.0% to 60.29% and OAMs from 20% to 66.1%. Three studies reported relapse rates with statistically significant reduction. Chang et al[55] observed significant reduction in relapse rate after RLAI treatment, whilst Tang et al[75] and Hanping et al[40] reported significantly lower relapse rates in PP1M groups than in OAM risperidone groups (PP1M: 5.4% vs OAM 34%; PP1M 7.5% vs OAM 25%). Four studies compared the rehospitalization rate between LAI and OAM, and three of them reported statistically significant results. Hanping et al,[40] Ju et al[68] and Lin et al[42] observed significant

differences between LAI treatment and OAMs in reducing hospitalization rates (LAI 2.5%, 28.15%, 53.6% vs OAMs 20%, 32.91%, 66.1%, respectively) and prolonging time to rehospitalization.

Patient Adherence, Satisfaction, and Attitude

Nine studies (four cohort studies,[41–43,54] four single-arm studies,[52,57,62,77] and one RCT[40]) reported adherence to LAI with different measurements, including discontinuation rate, time to discontinuation, proportion of days covered (<80% indicates poor adherence), or Medication Adherence Rating Scale (MARS; total score <4 indicates nonadherence). Treatment discontinuation could be attributed to lack of efficacy, intolerability, economic reasons, or self-perception of symptom remission. Out of five studies that reported discontinuation rate, Hanping et al[40] observed significantly lower discontinuation rate in PP1M than in OAM risperidone, and Wu et al[43] (cohort study) found that RLAI is unanimously superior in reducing discontinuation rate than LAI Clopentixol/zuclopentixol, LAI Fluphenazine, LAI Flupentixol, or LAI Haloperidol in short term (90 days) and long term (1 year). Zhao et al,[57] a non-interventional prospective study, demonstrated that LAI PP1M can continuously improve patient adherence assessed by MARS score (mean change = 1.7 at day 64, $p < 0.0001$; mean change = 2.2 at day 176, $p < 0.0001$) and adherence rate (baseline = 46.9%; day 64 = 75.0%; day 176 = 82.3%).

Through this scoping review, patient satisfaction and attitude were found associated with their medication adherence. In the included studies, patient satisfaction was mainly assessed by MSQ, and patient attitudes were collected via qualitative questionnaires. All reported MSQ results (one RCT,[40] one cohort study,[59] and five single-arm trials[47,57,66,76,78]) were extracted from studies on PP1M, and MSQ results were generally improved after the intervention of PP1M. All five single-arm trials yielded significant improvement in patient MSQ scores between pre- and post-PP1M intervention. Hanping et al[40] compared PP1M and OAM risperidone and found that MSQ improvement, decrease of relapse rate and treatment discontinuation rate of PP1M was significantly superior over OAM risperidone. Successfully improved MSQ score after PP1M treatment was reported by Kwon et al[59] regardless of whether administered immediately or delayed for patients switching from OAM to PP1M. Two patient surveys[30,73] and two single-arm studies[57,76] were identified consisting of patient preference of LAI or OAM, preference of injection site, advantages or disadvantages of LAI, and willingness to receive LAI. Few patients naïve to LAI would like to initiate LAI because of the high cost and the intramuscular injection,[30] however, LAI users were more likely to maintain LAIs. Furthermore, after receiving LAI, more patients agreed that it is more effective taking LAI than OAMs with fewer side effects.[76] For patients who have a preference for LAI, not requiring daily consumption was one of the most popular advantages.[30,73]

Healthcare Resource Utilization of LAIs

Twenty studies investigated HCRU including costs of LAIs, 13 of which were conducted in China (nine in the Taiwan region,[41–43,50,55,68,70,71,74,80] three in the mainland,[48,56,78] and one in Hong Kong[46]) and seven in other Asian regions.[44,45,47,51,59,67,72] The most frequently reported outcome regarding HCRU was the length of hospital stay (75%), followed by the number of inpatient visits (40%), medical costs (35%), and the number of acute admissions (30%) and outpatient visits (15%). All but two studies with results of length of hospital stay observed statistically significant reduction. Among three cohort studies compared RLAI vs OAM risperidone, two[46,55] found significantly reduced length of hospitalization in LAI groups. Costs were reported in four mirror-image studies and three cohort studies. Two mirror-image studies, with follow-up times of 1 year[55] and 2.5 years,[56] resulted in increased costs after switching to LAIs, whereas the other two mirror-image studies with follow-up times of 3 years[46] and 8 years[45] yielded significant reduction in costs after switching to LAIs. Chiou et al,[44] a cohort study with patients from China, Korea, and Malaysia, found lower medical costs incurred in patients who received PP1M in China than in Korea or Malaysia, especially in the subgroup with schizophrenia history less than a year. As for the number of outpatient visits and inpatient admissions, all mirror-image studies and single-arm trials reported significant decreases after receiving LAI, and all cohort studies found superiority in LAIs compared to OAMs.

Safety of LAIs

Ten single-arm studies,[47,52,53,57,62,63,65,76–78] seven RCTs,[38,39,58,60,64,75,81,83] three cohort studies[48,59,61] and one controlled clinical trial[69] collected data on safety outcomes. The AE results differed tremendously owing to study design, study

population, duration of intervention, and length of follow-up. Although reported types and incidence of AEs varied across studies, most of them were mild and the incidences of SAE were relatively low (0.0%~9.3%) in both LAI and OAM groups.

One single-arm trial[65] evaluated safety of RLAI with 472 patients followed-up for 1 year, with the overall rate of AE was 49.3%, including insomnia (17.9%), anxiety (8.2%), akathisia (6.3%), agitation (6.3%), constipation (5.7%), headache (5.3%), weight gain (4.8%), and dizziness (4.0%) in descending order, and 25.4% of all the AEs were TEAEs. SAE of RLAI included aggravation of schizophrenia and psychotic symptoms, while they were not directly attributed to RLAI. SAEs that were considered relevant to RLAI included EPS and akathisia.[65] Among the other nine single-arm trials on PP1M, the range of AE rate was wide due to study heterogeneity and 0.3% to 12.0% patients experienced TEAE that led to treatment discontinuation.

The seven RCTs (two PP1M vs OAM risperidone,[75,81] two PP1M vs PP3M,[38,39] two LAI aripiprazole vs aripiprazole OAM,[58,60] and one PP1M vs placebo[64]) resulted no major differences when comparing the AEs of LAI and OAM groups or between PP1M and PP3M, except that one study[81] comparing OAM risperidone and PP1M reported a lower AE rate in PP1M group (33.3% vs 58.3%). The most common TEAEs of PP1M included injection-site pain, insomnia, upper respiratory tract infection, weight gain, nasopharyngitis, and dizziness. Schizophrenia exacerbation was the most common serious TEAE (≥5%) of PP1M. Moreover, the controlled clinical trial also revealed no differences between LAIs and OAMs regarding safety.[69] In the real-world setting, Hatano et al,[61] a retrospective database study, reported that LAI was associated with significantly lower reporting rate than OAM for EPS, neuroleptic malignant syndrome (NMS), and dystonia. For more serious AE, Misawa et al,[48] a retrospective cohort study with a follow-up of 5 years, observed more deaths due to NMS in OAMs than in LAIs (Aripiprazole: oral 13.1% vs LAI 0.0%; risperidone/paliperidone: oral 8.8% vs LAI 7.6%).

Discussion

There is no evidence summary like a comprehensive scoping review of LAIs treatments for Asian population with schizophrenia to date. As of the time we initiated the study, this was the first scoping review focused on LAI treatment in Asian populations diagnosed with schizophrenia. By compiling current publications reporting clinical outcomes, HCRU, and patients' attitudes in Asian patients with schizophrenia who received LAI treatment in both clinical trials and real-world settings, this scoping review provided valuable insights into the efficacy, safety, treatment adherence, patient attitudes, and HCRU of LAI among Asian populations that fills the gap in current knowledge.

After screening a total of 523 articles, we identified 46 articles fulfilling our inclusion criteria. Our study suggests that LAIs were associated with a lower rate of relapse and rehospitalization, comparable improvement in PANSS, CGI-S, and PSP scores, and similar risk of AEs or TEAEs when compared to oral antipsychotics.[31] In addition, significant reduction with length of hospitalization was observed across studies reported HCRU. Studies on patient attitudes toward LAIs showed that patients initiated LAIs have positive attitudes because of LAIs' convenience, while increased effort was needed to overcome the objections and negative attitudes of LAI-naive patients.

During the development of our manuscript, two additional studies out of our search window of Asian population have been published. One self-controlled case series study of 70,396 schizophrenia patients from Hong Kong reported that LAI was associated with a lower risk of disease relapse and hospitalization than oral antipsychotics, without an increased risk of adverse events.[84] Another retrospective study including 19,813 schizophrenia patients from Taiwan found that switching from oral antipsychotics to LAIs during the first 3 years of treatment could improve antipsychotic adherence, decrease relapses, and reduce long-term mortality.[85] This study also compared the long-term effectiveness of patients who switched to LAIs versus those who remained on oral antipsychotics and concluded that early initiation of LAI treatment led to improved long-term outcomes. These findings support the benefits of using LAI in the early stage of schizophrenia. Overall, these two studies provide further evidence supporting the use of LAIs as an effective alternative to oral antipsychotics in the treatment of schizophrenia to maintain treatment adherence and reduce discontinuation rates.

Studies conducted among global populations consistently demonstrate stronger evidence supporting LAIs over oral antipsychotics in preventing relapse and rehospitalization and comparable efficacy between LAIs and oral antipsychotics.[31,86] Paliperidone palmitate injection has been found to prolong relapse-free period in patients significantly compared to oral medications, with patients experiencing an extension of over 200 days of relapse-free period.[11] Another study demonstrated that RLAI could prevent treatment failure even after long-term withdrawal of RLAI medication and

relapse.[19] A systematic review and comparative meta-analysis by Kishimoto et al[31] among a global population reported similar results that LAIs were comparable to oral antipsychotics in most outcomes related to effectiveness and efficacy, and LAIs showed no significant difference to oral antipsychotics regarding most AEs. Moreover, according to Park et al's systematic review and meta-analysis of global population of schizophrenia, patients with LAI SGA treatment showed significantly lower relapse rates than oral SGA patients.[86] They also observed that the decrease in total PANSS score and CGI-S score in the group treated with LAI SGAs was greater than that in the oral SGA group. However, this difference was not significant even after considering inter-group differences caused by the length of the follow-up period.[86] It is worth noting that these findings from the global population may differ from our study's results on the Asian population due to differences in demographic characteristics, medication compliance, and underlying genetic factors. The possible reason for the difference in the performance of PANSS score and CGI-S score between the global and Asian populations when treated with LAI compared with the oral antipsychotic group should be examined in future studies. Additionally, regarding the outcome measurements, quality of life (QoL), evaluated by several studies in non-Asian populations, was rarely assessed among included studies in this scoping review.

As patients enrolled in clinical trials tend to be more adherent and compliant with treatment regimens, minimizing the difference between LAI and OAM, patients treated in real-world clinical practice are more representative. In particular, many studies[87–89] have put in evidence that studies with mirror design and/or naturalistic cohort study in real clinical settings more than RCT can highlight the superior efficacy in preventing relapses of LAI if compared with oral antipsychotic therapy.

Nonetheless, the difference between relapse and rehospitalization should be interpreted with caution.[86] Six studies[44–46,55,56,74] included in our review showed that the use of LAI increased the total cost in the short-term and decreased the total costs in the longer term, which may be explained by a reduction in the utilization of ER or inpatient visits resulting from lower relapse rate and rehospitalization rate resulting from long-lasting efficacy of LAIs. This finding aligns with the study conducted by Shah et al that hospitalization cost reductions could offset the high pharmacy cost of LAIs and contribute to no increase in total healthcare costs relative to oral antipsychotic use.[90] The hospitalization cost reductions could offset the high pharmacy cost of LAIs and contributed to no increase in total healthcare costs relative to oral antipsychotic use.[90]

Although some studies reported a relatively higher incidence of AEs in patients receiving LAI PP, a solid conclusion still could not be drawn due to the reporting bias that might exist because LAI PP1M was the most investigated medication (16/21) with safety measures. Furthermore, the LAI PP1M studies included mild AEs (such as injection-site pain) in the safety analysis, while injection site pain usually emerges at the time of the first or second LAI administration and subsequently resolved in each case,[91] which may have increased the overall rates in appearance.[26]

This review also found that no current studies in the Asian population have adopted LAIs as part of community mental health services.[92] One mirror-image study conducted in Italy collected data from five community mental health centers where patients receive their LAI antipsychotic treatment.[93] It showed that hospitalization and emergency visits are significantly reduced with the use of LAIs, while planned visits are increased in patients treated with LAIs compared with OAMs. Therefore, future studies are needed to confirm the effectiveness of LAIs as part of community management for patients with schizophrenia in the Asian population and evaluate its impact on healthcare resource utilization.

While patient attitude towards LAIs was considered and evaluated, the role of caregivers and psychiatrists in the decision-making process has been relatively underexplored in the previous research. One study showed that only 10% of psychiatrists used LAIs after a first psychotic episode.[26] Although limited availability of LAIs, psychiatrists' attitudes also play an important role in their treatment decision. Thus, further research is warranted to investigate the correlation between psychiatrist attitudes and the use of LAIs. Furthermore, most studies have primarily focused on the direct social and financial impact on the patients, neglecting to thoroughly assess the social and economic impact derived from caregivers. In the long course of the disease, constant hospitalization, leading to income loss or unemployment for patients and their caregivers, is overlooked by researchers.

Additionally, it is noteworthy that the definitions of relapse rate differed among studies, and the follow-up periods are study-specific; thus, direct comparison between studies is inappropriate. Additionally, rehospitalization was considered one of the events indicating relapse in some studies, while it was reported as an independent measurement in others. Further studies are needed to unify the definitions of relapse rates and rehospitalization to enable accurate comparisons across different studies.

While this scoping review included up-to-date information on clinical studies regarding LAIs among the Asian population, we acknowledged the limitations of this study. First, only studies published in English and Chinese in peer-reviewed journals of selected academic databases were included, potentially missing studies published in other languages or databases. Second, only the most frequently utilized outcome assessments were reported, whereas others were not explicitly described because of the great variety of measurement instruments used across different studies. Additionally, given the purpose of this scoping review is to comprehensively summarize current evidence from studies with various designs, settings, and population characteristics, quality assessment as well as statistical pooling of results was not conducted.

Despite these limitations, this study offers several strengths. First, a comprehensive and rigorous search strategy was applied in this review, enabling the retrieval of relevant articles covering various aspects of LAI treatment and identifying current research limitations effectively. Second, the study categorized the research fields of LAI treatment into effectiveness/efficacy, safety, treatment adherence, patients' attitudes, and healthcare resource utilization. This comprehensive summarization of different treatment aspects lays a solid foundation for future investigations into the use of LAIs in this population. It also facilitates the development of more targeted research questions and stricter inclusion criteria for forthcoming studies. Additionally, the outcomes identified in this scoping review could be used to develop key outcome measures, supporting comparability across studies and reducing heterogeneity. Overall, this scoping review provides valuable insights and research directions for future research endeavors concerning the use of LAIs in the Asian population with schizophrenia and serves as an important starting point for further systematic reviews and meta-analyses.

Conclusion

Current evidence revealed that LAI treatments showed advantages regarding improved adherence and reduced relapse compared to oral antipsychotics, with comparable improvement in clinical symptoms and safety in the Asian population. Present results should be interpreted considering the limited publications and heterogeneity in study designs and outcome measures. The finding of this review also provides evidence to researchers and helps underpinning future research areas, including the evaluation of the effectiveness of LAIs as part of community management for patients with schizophrenia, its impact on indirect healthcare resource utilization and the attitudes of healthcare practitioners towards LAIs. A unified definition of relapse and rehospitalization could also be developed for better comparisons across different studies in the future.

Acknowledgments

We thank Dr. Yea-Jen Hsu and Dr. Miaomiao Jia for their support in the interpretation of study results, the revision and editing of the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Xi'an Janssen Pharmaceutical Ltd.

Disclosure

Zhang L, Ye C and Li X are employees of Xi'an Janssen Pharmaceutical Ltd. All other authors have no conflicts of interest to declare in relation to this study.

References

1. Haller CS, Padmanabhan JL, Lizano P, Torous J, Keshavan M. Recent advances in understanding schizophrenia. *F1000Prime Rep*. 2014;6:1.
2. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev*. 2008;30:67–76. doi:10.1093/epirev/mxn001
3. Huang Y, Wang Y, Wang H, et al. Prevalence of mental disorders in China: a cross-sectional epidemiological study. *Lancet Psychiatry*. 2019;6(3):211–224. doi:10.1016/S2215-0366(18)30511-X
4. Harrow M, Jobe T, Faull R. Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis? A 20-year multi-follow-up study. *Psychol Med*. 2014;44(14):3007–3016. doi:10.1017/S0033291714000610
5. Jääskeläinen E, Juola P, Hirvonen N, et al. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull*. 2013;39(6):1296–1306. doi:10.1093/schbul/sbs130
6. Rice DP. The economic impact of schizophrenia. *J Clin Psychiatry*. 1999;60(1):4–6.
7. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962. doi:10.1016/S0140-6736(13)60733-3
8. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *Int J Neuropsychopharmacol*. 2013;16(6):1205–1218. doi:10.1017/S1461145712001277
9. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019;394(10202):939–951. doi:10.1016/S0140-6736(19)31135-3
10. Ventura J, Subotnik KL, Guzik LH, et al. Remission and recovery during the first outpatient year of the early course of schizophrenia. *Schizophr Res*. 2011;132(1):18–23. doi:10.1016/j.schres.2011.06.025
11. Schreiner A, Aadamsoo K, Altamura AC, et al. Paliperidone palmitate versus oral antipsychotics in recently diagnosed schizophrenia. *Schizophr Res*. 2015;169(1–3):393–399. doi:10.1016/j.schres.2015.08.015
12. Excellence NIfHaC. Psychosis and schizophrenia in adults: prevention and management; 2014.
13. Barnes TR, Drake R, Paton C, et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: updated recommendations from the British association for psychopharmacology. *J Psychopharmacol*. 2020;34(1):3–78. doi:10.1177/0269881119889296
14. Kozma CM, Weiden PJ. Partial compliance with antipsychotics increases mental health hospitalizations in schizophrenic patients: analysis of a national managed care database. *Am Health Drug Benefits*. 2009;2(1):31–38.
15. Valenstein M, Blow FC, Copeland LA, et al. Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. *Schizophr Bull*. 2004;30(2):255–264. doi:10.1093/oxfordjournals.schbul.a007076
16. Davis JM. Maintenance therapy and the natural course of schizophrenia. *J Clin Psychiatry*. 1985;46(11):18–21.
17. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv*. 1998;49(2):196–201. doi:10.1176/ps.49.2.196
18. Robinson D, Woerner MG, Alvir JMJ, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;56(3):241–247. doi:10.1001/archpsyc.56.3.241
19. Emsley R, Chiliza B, Asmal L. The evidence for illness progression after relapse in schizophrenia. *Schizophr Res*. 2013;148(1–3):117–121. doi:10.1016/j.schres.2013.05.016
20. Fitzgerald HM, Shepherd J, Bailey H, Berry M, Wright J, Chen M. Treatment goals in schizophrenia: a real-world survey of patients, psychiatrists, and caregivers in the United States, with an analysis of current treatment (long-acting injectable vs oral antipsychotics) and goal selection. *Neuropsychiatr Dis Treat*. 2021;17:3215–3228. doi:10.2147/NDT.S330936
21. Correll CU, Citrome L, Haddad PM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. *J Clin Psychiatry*. 2016;77(suppl 3):1–24. doi:10.4088/JCP.15032su1
22. Reus VI, Fochtmann LJ, Bukstein O, et al. The American psychiatric association practice guideline for the pharmacological treatment of patients with alcohol use disorder. *American Psychiatric Pub*. 2018;175(1):86–90. doi:10.1176/appi.ajp.2017.1750101
23. Group CSC. Expert consensus on long-acting injectable in the treatment of schizophrenia. *Chin J Psychiatry*. 2020;2:99–100.
24. Nasser AF, Henderson DC, Fava M, et al. Efficacy, safety, and tolerability of rbp-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. *J Clin Psychopharmacol*. 2016;36(2):130–140. doi:10.1097/JCP.0000000000000479
25. Ravenstijn P, Remmerie B, Savitz A, et al. Pharmacokinetics, safety, and tolerability of paliperidone palmitate 3-month formulation in patients with schizophrenia: a phase-1, single-dose, randomized, open-label study. *J Clin Pharmacol*. 2016;56(3):330–339. doi:10.1002/jcph.597
26. Kaplan G, Casoy J, Zummo J. Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. *Patient Prefer Adherence*. 2013;7:1171. doi:10.2147/PPA.S53795
27. Okoli CTC, Kappi A, Wang T, Makowski A, Cooley AT. The effect of long-acting injectable antipsychotic medications compared with oral antipsychotic medications among people with schizophrenia: a systematic review and meta-analysis. *Int J Ment Health Nurs*. 2022;31(3):469–535. doi:10.1111/inm.12964
28. Olfson M, Marcus SC, Ascher-Svanum H. Treatment of schizophrenia with long-acting fluphenazine, haloperidol, or risperidone. *Schizophr Bull*. 2007;33(6):1379–1387. doi:10.1093/schbul/sbm033
29. Rosenheck RA, Krystal JH, Lew R, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med*. 2011;364(9):842–851. doi:10.1056/NEJMoa1005987
30. Zhu J, Chen Y, Lu W, et al. Attitudes and Willingness to accept long-acting injections for patients with schizophrenia in Beijing: a cross-sectional investigation based on samples from the communities. *Front Public Health*. 2021;9:770276. doi:10.3389/fpubh.2021.770276
31. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *Lancet Psychiatry*. 2021;8(5):387–404. doi:10.1016/S2215-0366(21)00039-0

32. Schneider-Thoma J, Chalkou K, Dörries C, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2022;399(10327):824–836. doi:10.1016/S0140-6736(21)01997-8
33. Banerjee A. Cross-cultural variance of schizophrenia in symptoms, diagnosis and treatment. *Georgetown Univer J Health Sci*. 2012;6(2):18–24.
34. Stauffer VL, Sniadecki JL, Piezer KW, et al. Impact of race on efficacy and safety during treatment with olanzapine in schizophrenia, schizophreniform or schizoaffective disorder. *BMC Psychiatry*. 2010;10(1):1–11. doi:10.1186/1471-244X-10-89
35. Coppola D, Liu Y, Gopal S, et al. A one-year prospective study of the safety, tolerability and pharmacokinetics of the highest available dose of paliperidone palmitate in patients with schizophrenia. *BMC Psychiatry*. 2012;12(1):1–14. doi:10.1186/1471-244X-12-26
36. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;169(7):467–473. doi:10.7326/M18-0850
37. A E, M Z. JBI Reviewer's Manual; 2017. Available from: https://reviewersmanual.joannabriggs.org/. Accessed September 12, 2023.
38. Savitz AJ, Xu H, Gopal S, et al. Efficacy and safety of paliperidone palmitate three-monthly formulation in East Asian patients with schizophrenia: subgroup analysis of a global, randomized, double-blind, Phase III, noninferiority study. *Neuropsychiatr Dis Treat*. 2017;13:2193–2207. doi:10.2147/NDT.S134287
39. Savitz AJ, Xu H, Gopal S, et al. Efficacy and safety of paliperidone palmitate 3-month versus 1-month formulation in patients with schizophrenia: comparison between European and non-European population. *Neuropsychiatr Dis Treat*. 2019;15:587–602. doi:10.2147/NDT.S189668
40. Hanping B, Qianjun Y, Juncheng Z. Paliperidone palmitate in the treatment of 40 college students with schizophrenia (Article in Chinese). *J Herald of Medicine*. 2015;4:483–486.
41. Liu CC, Shan JC, Chiang CL, et al. Initiating long-acting injectable antipsychotics during acute admission for patients with schizophrenia--A 3-year follow-up. *J Formos Med Assoc*. 2015;114(6):539–545. doi:10.1016/j.jfma.2013.01.004
42. Lin C-H, Chen F-C, Chan H-Y, Hsu -C-C. A comparison of long-acting injectable antipsychotics with oral antipsychotics on time to rehospitalization within 1 year of discharge in elderly patients with schizophrenia. *Am J Geriatr Psychiatry*. 2020;28(1):23–30. doi:10.1016/j.jagp.2019.08.005
43. Wu CS, Cheng IC, Feng J, Chen CL. Comparison of treatment effectiveness and medical costs for different long-acting injectable antipsychotics in patients with schizophrenia in Taiwan: a nationwide population-based cohort study. *Schizophr Res*. 2016;173(1–2):37–44. doi:10.1016/j.schres.2016.02.037
44. Chiou CF, Wang BC, Caldwell R, et al. The cost reduction in hospitalization associated with paliperidone palmitate in the People's Republic of China, Korea, and Malaysia. *Neuropsychiatr Dis Treat*. 2015;11:1989–1994. doi:10.2147/NDT.S86722
45. Lee D, Lee BC, Choi SH, Kang DH, Jon DI, Jung MH. Effects of paliperidone palmitate on healthcare utilization and costs for patients with schizophrenia: a claim-based mirror-image study in South Korea. *Clin Psychopharmacol Neurosci*. 2020;18(2):303–310. doi:10.9758/cpn.2020.18.2.303
46. Wu DB, Lee EH, Chung WS, et al. Cost analysis of risperidone long-acting injection in the treatment of schizophrenia and schizoaffective disorders in Hong Kong: an approach using generalised estimating equations. *Psychiatry Res*. 2013;210(3):745–750. doi:10.1016/j.psychres.2013.07.012
47. Zhang F, Si T, Chiou CF, et al. Efficacy, safety, and impact on hospitalizations of paliperidone palmitate in recent-onset schizophrenia. *Neuropsychiatr Dis Treat*. 2015;11:657–668. doi:10.2147/NDT.S77778
48. Misawa F, Okumura Y, Takeuchi Y, Fujii Y, Takeuchi H. Neuroleptic malignant syndrome associated with long-acting injectable versus oral second-generation antipsychotics: analyses based on a spontaneous reporting system database in Japan. *Schizophr Res*. 2021;231:42–46. doi:10.1016/j.schres.2021.02.016
49. Zhang H, Turkoz I, Zhuo J, Mathews M, Tan W, Feng Y. Paliperidone palmitate improves and maintains functioning in Asia-Pacific patients with Schizophrenia. *Adv Ther*. 2017;34(11):2503–2517. doi:10.1007/s12325-017-0638-0
50. Hsu HF, Kao CC, Lu T, Ying JC, Lee SY. Differences in the effectiveness of long-acting injection and orally administered antipsychotics in reducing rehospitalization among patients with schizophrenia receiving home care services. *J Clin Med*. 2019;8(6):823. doi:10.3390/jcm8060823
51. Chan HW, Huang CY, Feng WJ, Yen YC. Risperidone long-acting injection and 1-year rehospitalization rate of schizophrenia patients: a retrospective cohort study. *Psychiatry Clin Neurosci*. 2015;69(8):497–503. doi:10.1111/pcn.12294
52. Li H, Turkoz I, Zhang F. Efficacy and safety of once-monthly injection of paliperidone palmitate in hospitalized Asian patients with acute exacerbated schizophrenia: an open-label, prospective, noncomparative study. *Neuropsychiatr Dis Treat*. 2016;12:15–24. doi:10.2147/NDT.S83651
53. Li H, Li Y, Feng Y, et al. Impact of time of initiation of once-monthly paliperidone palmitate in hospitalized Asian patients with acute exacerbation of schizophrenia: a post hoc analysis from the PREVAIL study. *Neuropsychiatr Dis Treat*. 2018;14:1107–1117. doi:10.2147/NDT.S157399
54. Wang H, Zhang Y, Liu J, et al. Persistence with and adherence to paliperidone palmitate once-monthly injection for schizophrenia treatment in China and Japan. *J Clin Psychiatry*. 2021;83(1). doi:10.4088/JCP.20m13850
55. Chang HC, Tang CH, Huang ST, McCrone P, Su KP. A cost-consequence analysis of long-acting injectable risperidone in schizophrenia: a one-year mirror-image study with national claim-based database in Taiwan. *J Psychiatr Res*. 2012;46(6):751–756. doi:10.1016/j.jpsychires.2012.02.019
56. Liu J, Wang Q, Su L, Yang L, Zou L, Bai L. A health economics study of long-acting injectable once-monthly paliperidone palmitate in schizophrenia: a one-year mirror-image study in China. *BMC Psychiatry*. 2022;22(1):95. doi:10.1186/s12888-022-03728-2
57. Zhao J, Li L, Shi J, et al. Safety and efficacy of paliperidone palmitate 1-month formulation in Chinese patients with schizophrenia: a 25-week, open-label, multicenter, Phase IV study. *Neuropsychiatr Dis Treat*. 2017;13:2045–2056. doi:10.2147/NDT.S131224
58. Ishigooka J, Nakamura J, Fujii Y, et al. Efficacy and safety of aripiprazole once-monthly in Asian patients with schizophrenia: a multicenter, randomized, double-blind, non-inferiority study versus oral aripiprazole. *Schizophr Res*. 2015;161(2–3):421–428. doi:10.1016/j.schres.2014.12.013
59. Kwon JS, Kim SN, Han J, et al. Satisfaction of immediate or delayed switch to paliperidone palmitate in patients unsatisfied with current oral atypical antipsychotics. *Int Clin Psychopharmacol*. 2015;30(6):320–328. doi:10.1097/YIC.0000000000000093
60. Xiao L, Zhao Q, Li AN, et al. Efficacy and safety of aripiprazole once-monthly versus oral aripiprazole in Chinese patients with acute schizophrenia: a multicenter, randomized, double-blind, non-inferiority study. *Psychopharmacology*. 2022;239(1):243–251. doi:10.1007/s00213-021-06044-x
61. Hatano M, Kamei H, Shimato A, Yamada S, Iwata N. Trend survey on adverse event profiles of antipsychotic long-acting injections and oral agents using the Japanese adverse drug event report database. *Psychiatry Res*. 2020;291:113249. doi:10.1016/j.psychres.2020.113249
62. Qiyi M, Kui C, Jianhong S, Guangya Z, Yong Y, Yingcui H. Predictor of discontinuation with paliperidone palmitate in patients with schizophrenia (Article in Chinese. *Chin J Psychiatry*. 2016;49(6):373–377.

63. Xingfang M, Qian W, Jie L, Ludong B. An open-label study on the efficacy of paliperidone palmitate in patients with acute schizophrenia (Article in Chinese). *Chin J New Drugs*. 2014;23(19):2280–2283.
64. Takahashi N, Takahashi M, Saito T, et al. Randomized, placebo-controlled, double-blind study assessing the efficacy and safety of paliperidone palmitate in Asian patients with schizophrenia. *Neuropsychiatr Dis Treat*. 2013;9:1889–1898. doi:10.2147/NDT.S54051
65. Lee NY, Kim SH, Cho SJ, et al. A prospective, open-label study to evaluate symptomatic remission in schizophrenia with risperidone long-acting injectable in Korea. *Int Clin Psychopharmacol*. 2014;29(5):279–287. doi:10.1097/YIC.0000000000000030
66. Li N, Feng Y, Lu H, et al. Factors related to improvement of symptoms, function, and caregiver burden in Chinese patients with schizophrenia after switching to paliperidone palmitate once-monthly from oral antipsychotics. *Neuropsychiatr Dis Treat*. 2018;14:825–837. doi:10.2147/NDT.S158353
67. Li N, Zhuo JM, Turkoz I, Mathews M, Feng Y, Tan W. A post hoc analysis on hospitalization risk in Asian patients with schizophrenia switching to once-monthly paliperidone palmitate from oral antipsychotics. *Expert Opin Pharmacother*. 2019;20(16):2033–2039. doi:10.1080/14656566.2019.1650022
68. Ju PC, Chou FH, Lai TJ, et al. Long-acting injectables and risk for rehospitalization among patients with schizophrenia in the home care program in Taiwan. *J Clin Psychopharmacol*. 2014;34(1):23–29. doi:10.1097/JCP.0b013e3182a6a142
69. Guoxing Q, Jianguang G, Guoqiang T. Clinical controlled study on the effect of risperidone microsphere on schizophrenia (Article in Chinese). *Chin Gen Pract*. 2013;16(3):308–309.
70. Huang SS, Lin CH, Lohel W, Yang HY, Chan CH, Lan TH. Antipsychotic formulation and one-year rehospitalization of schizophrenia patients: a population-based cohort study. *Psychiatr Serv*. 2013;64(12):1259–1262. doi:10.1176/appi.ps.201200506
71. Fang SC, Liao DL, Huang CY, Hsu CC, Cheng SL, Shao YJ. The effectiveness of long-acting injectable antipsychotics versus oral antipsychotics in the maintenance treatment of outpatients with chronic schizophrenia. *Hum Psychopharmacol*. 2020;35(3):e2729. doi:10.1002/hup.2729
72. Joo SW, Shon SH, Choi G, Koh M, Cho SW, Lee J. Continuation of schizophrenia treatment with three long-acting injectable antipsychotics in South Korea: a nationwide population-based study. *Eur Neuropsychopharmacol*. 2019;29(9):1051–1060. doi:10.1016/j.euroneuro.2019.07.138
73. Kim SW, Lee YH, Jang JE, et al. Comparison of attitudes toward long-acting injectable antipsychotics among psychiatrists and patients. *Int Clin Psychopharmacol*. 2013;28(2):80–86. doi:10.1097/YIC.0b013e32835d30ae
74. Fan SJ, Lu N, Chang HC, Tang CH, Huang KC. Health service utilization and medical costs among patients with schizophrenia receiving long-acting injectable risperidone versus oral risperidone: a nationwide retrospective matched cohort study in Taiwan. *Int Clin Psychopharmacol*. 2018;33(4):204–212. doi:10.1097/YIC.0000000000000213
75. Wei T, Fuyin Y, Na W, Jianshe P, Jinliang Z, Wenjie T. A comparative study of paliperidone palmitate injections and risperidone on long-term effects and prognosis for the first-episode schizophrenic patients. *Chin J Psychiatry*. 2016;49(2):76–80.
76. Si T, Zhang K, Tang J, et al. Efficacy and safety of flexibly dosed paliperidone palmitate in Chinese patients with acute schizophrenia: an open-label, single-arm, prospective, interventional study. *Neuropsychiatr Dis Treat*. 2015;11:1483–1492. doi:10.2147/NDT.S81760
77. Si T, Li N, Lu H, et al. Impact of paliperidone palmitate one-month formulation on relapse prevention in patients with schizophrenia: a post-hoc analysis of a one-year, open-label study stratified by medication adherence. *J Psychopharmacol*. 2018;32(6):691–701. doi:10.1177/0269881118772449
78. Si T, Zhuo J, Feng Y, Lu H, Hong D, Zhang L. Long-term efficacy and safety of paliperidone palmitate once-monthly in Chinese patients with recent-onset schizophrenia. *Neuropsychiatr Dis Treat*. 2019;15:1685–1694. doi:10.2147/NDT.S191803
79. Jian W, Li ZX, Wei L, et al. Clinical effect of paliperidone palmitate and risperdal consta in the treatment of patients with schizophrenia. *Chin J Clin Pharmacol*. 2015;12:1124–1126.
80. Chen WY, Lin SK. Comparison of subjective experiences and effectiveness of first-generation long-acting injectable antipsychotics and risperidone long-acting injectables in patients with schizophrenia. *J Clin Psychopharmacol*. 2016;36(5):492–495. doi:10.1097/JCP.0000000000000555
81. Qiuxia X, Jushui S, Shikai W, Xilong J, Weigang G, Xiongkai D. Paliperidone palmitate injection in the treatment of 36 cases of acute schizophrenia (Article in Chinese). *Herald Med*. 2015;10:1304–1307.
82. Koshikawa Y, Takekita Y, Kato M, et al. The comparative effects of risperidone long-acting injection and paliperidone palmitate on social functioning in schizophrenia: a 6-month, open-label, randomized controlled pilot trial. *Neuropsychobiology*. 2016;73(1):35–42. doi:10.1159/000442209
83. Savitz AJ, Xu H, Gopal S, Nuamah I, Mathews M, Soares B. Efficacy and safety of paliperidone palmitate 3-month formulation in Latin American patients with schizophrenia: a subgroup analysis of data from two large phase 3 randomized, double-blind studies. *Braz J Psychiatry*. 2019;41(6):499–510. doi:10.1590/1516-4446-2018-0153
84. Wei Y, Yan VK, Kang W, et al. Association of long-acting injectable antipsychotics and oral antipsychotics with disease relapse, health care use, and adverse events among people with schizophrenia. *JAMA network open*. 2022;5(7):e2224163–e2224163. doi:10.1001/jamanetworkopen.2022.24163
85. Fang S-C, Huang C-Y, Shao Y-HJ. Long-term outcomes of early use of long-acting injectable antipsychotics in schizophrenia. *J Clin Psychiatry*. 2022;83(4):41243. doi:10.4088/JCP.21r14153
86. Park S-C, Choi MY, Choi J, et al. Comparative efficacy and safety of long-acting injectable and oral second-generation antipsychotics for the treatment of schizophrenia: a systematic review and meta-analysis. *Clin Psychopharmacol Neurosci*. 2018;16(4):361–375. doi:10.9758/cpn.2018.16.4.361
87. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry*. 2011;168(6):603–609. doi:10.1176/appi.ajp.2011.10081224
88. Fagiolini A, Alfonsi E, Amodeo G, et al. Switching long acting antipsychotic medications to aripiprazole long acting once-a-month: expert consensus by a panel of Italian and Spanish psychiatrists. *Expert Opin Drug Saf*. 2016;15(4):449–455. doi:10.1517/14740338.2016.1155553
89. Di Lorenzo R, Ferri P, Cameli M, Rovesti S, Piemonte C. Effectiveness of 1-year treatment with long-acting formulation of aripiprazole, haloperidol, or paliperidone in patients with schizophrenia: retrospective study in a real-world clinical setting. *Neuropsychiatr Dis Treat*. 2019;15:183–198. doi:10.2147/NDT.S189245
90. Shah A, Xie L, Kariburyo F, Zhang Q, Gore M. Treatment patterns, healthcare resource utilization and costs among schizophrenia patients treated with long-acting injectable versus oral antipsychotics. *Adv Ther*. 2018;35(11):1994–2014. doi:10.1007/s12325-018-0786-x

91. Suzuki H, Inoue Y, Gen K. A study of the efficacy and safety of switching from oral risperidone to risperidone long-acting injection in older patients with schizophrenia. *Ther Adv Psychopharmacol*. 2012;2(6):227–234. doi:10.1177/2045125312457585
92. Altamura AC, Aguglia E, Bassi M, et al. Rethinking the role of long-acting atypical antipsychotics in the community setting. *Int Clin Psychopharmacol*. 2012;27(6):336–349. doi:10.1097/YIC.0b013e328357727a
93. Latorre V, Papazacharias A, Lorusso M, et al. Improving the "real life" management of schizophrenia spectrum disorders by LAI antipsychotics: a one-year mirror-image retrospective study in community mental health services. *PLoS One*. 2020;15(3):e0230051. doi:10.1371/journal.pone.0230051