

# Comparative Efficacy and Safety of Long-acting Injectable and Oral Second-generation Antipsychotics for the Treatment of Schizophrenia: A Systematic Review and Meta-analysis

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We aimed to compare the efficacy and safety of long-acting injectable (LAI) and oral second-generation antipsychotics (SGAs) in treating schizophrenia by performing a systematic review and meta-analysis. MEDLINE, EMBASE, PsycINFO, CINAHL, and the Cochrane Library, as well as five Korean databases, were systemically searched to identify studies published from 2000 to 16 April 2015, which compared the efficacy and safety of LAI and oral SGAs. Using data from randomized controlled trials (RCTs), meta-analyses were conducted. In addition, the GRADE (the Grading of Recommendations, Assessment, Development and Evaluation) approach was applied to explicitly assess the quality of the evidence. A total of 30 studies including 17 RCTs and 13 observational studies were selected. The group treated with LAI SGAs was characterized by significantly lower relapse rates, longer times to relapse and fewer hospital days, but also by a higher occurrence of extrapyramidal syndrome and prolactin-related symptoms than that in the group treated with oral SGAs. Our findings demonstrate that there is moderate to high level of evidence suggesting that in the treatment of schizophrenia, LAI SGAs have higher efficacy and are associated with higher rates of extrapyramidal syndrome and prolactin-related symptoms. Additionally, the use of LAI SGAs should be combined with appropriate measures to reduce dopamine D<sub>2</sub> antagonism-related symptoms.

**KEY WORDS:** Efficacy; Long-acting injectable; Safety; Schizophrenia; Second-generation antipsychotics.

## INTRODUCTION

In terms of the global burden of mental disorders, schizophrenia has been identified as an important mental

health issue by the Grand Challenges in Global Mental Health Initiative.<sup>1-4)</sup> Antipsychotic medication non-compliance occurs in 80% or more of patients with schizophrenia, and can last for substantial periods of time, despite recommendations from clinical psychiatrists.<sup>5)</sup> The European Schizophrenia Health Outcome Study (SOHO) demonstrated that non-compliance was associated with recurrence risk, hospitalization rate, and suicidal risk, among more than 7,000 patients with schizophrenia.<sup>6)</sup> In addition, antipsychotic non-compliance has been shown to be significantly associated with an increased risk of re-hospitalization, emergency room visits, homelessness, and symptom exacerbation.<sup>7)</sup> Hence, “long-acting injectable” (LAI) or depot antipsychotics have been proposed as one of the most promising potential alternative

**Received:** February 1, 2018 / **Accepted:** March 5, 2018

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treatments to overcome non-compliance in patients with schizophrenia. A meta-analysis of 10 randomized clinical trials lasting at least 12 months, and including 1,700 patients with schizophrenia showed that LAI antipsychotics are associated with significant reductions in relapses and dropouts due to the lack of efficacy when compared with oral antipsychotics.<sup>8)</sup>

The efficacy and tolerability profiles of LAI and oral antipsychotics have been compared in several studies using a systematic review and/or meta-analysis approach.<sup>9-17)</sup> Most of the systematic reviews and meta-analyses conceptualized LAI and oral antipsychotics as the intervention and the comparator, respectively, without regard for whether the medications were classified as first-generation antipsychotics (FGAs) or second-generation antipsychotics (SGAs). In terms of FGAs and SGAs, “atypicality”, which is associated with SGAs, can be defined as a favorable antipsychotic effect with a reduced risk of extrapyramidal side effects.<sup>18-21)</sup> Moreover, LAI FGAs are rarely used in real-world psychiatry and, particularly in the United States, only haloperidol decanoate and fluphenazine decanoate are used.<sup>22)</sup> However, since most of the systematic reviews and meta-analyses concerning the efficacy and safety of LAI antipsychotics have been evaluated without regard for the distinction of LAI FGAs and SGAs, to our knowledge, the comprehensive efficacy and safety of LAI SGAs in real-world settings have not been well reported. In addition, extrapyramidal side effects and other adverse effects may be associated with discontinuation of antipsychotics in patients with schizophrenia.<sup>15,23)</sup> The present systematic review and meta-analysis aimed to compare overall profiles for both efficacy (relapse rate, time to relapse, hospitalization rate, remission rate, hospital days, non-compliance, quality of life, and changes in symptom severity) and safety (all cause discontinuation, extrapyramidal side effects, abnormal involuntary movements, and other variables) of LAI and oral SGAs among schizophrenia patients.

## METHODS

### Study Overview

A systematic search was performed using international databases including MEDLINE, EMBASE, the Cochrane Library, CINAHL, and PsycINFO, and also several Korean domestic databases, including KoreaMed, Korean Medicine

Database (KMBASE), Korean Studies Information Service System (KISS), National Digital Science Library (NDSL), and the Research Information Sharing Service (RISS), with a date range limit for publications from 2000 to 16 April 2015. The key questions and the PICO framework (Patient, Intervention, Comparator, Outcome)<sup>24)</sup> were defined with the advice of an expert group of psychiatry specialists in the field of schizophrenia research (KYH, WSH, CYC, BKY, LSK, PSC, and LSH). Extensive searches of the databases using the terms “schizophrenia,” “long acting injection,” and each of the generic names of the SGAs, as defined by Tandon *et al.*,<sup>25)</sup> were performed. Terms were related to the databases’ index terms, such as Medical Subject Headings (MeSH) and Emtree.

### Eligibility Criteria

Articles that met the following criteria were included: 1) study subjects were adults with schizophrenia (including initial and relapsed patients); 2) the intervention and the active comparator were LAI and oral SGAs, respectively; 3) at least one of the predetermined outcomes was reported; 4) the study was designed as a randomized controlled trial (RCT), non-RCT, cohort study, case-control study, or mirror-image study; and 5) articles were published in English or Korean. Articles that met the following criteria were excluded: 1) reports on animal trials or pre-clinical studies, and non-original research articles such as reviews, editorials, letters, and comments; 2) articles not published in English or Korean, and those with duplicate subjects (studies using the same outcome indicators and publishing in duplicate) were also excluded.

### Outcome Measures

Relapse rate, non-compliance rate, time to relapse, hospitalization rate, remission rate, hospital days, quality of life, and changes in assessment scales, including the Clinical Global Impression-Severity (CGI-S),<sup>26)</sup> Positive and Negative Syndrome Scale (PANSS),<sup>27)</sup> and the Montgomery-Asberg Depression Rating Scale (MADRS)<sup>28)</sup> were used as measures of efficacy. The discontinuation rate, drug-related side effects, and changes in assessment scales, including the Extrapyramidal Symptom Rating Scale (ESRS),<sup>29)</sup> and the Abnormal Involuntary Movement Scale (AIMS)<sup>30)</sup> were used as safety measures.

### Selection of Studies and Quality Assessment

Study selection was initially conducted by the researchers in pairs (CMY, PSC, THJ, CJ, PCM, SJK, PE, and LSH). Namely, screening of all studies by title and abstract, and selection of studies according to the eligibility criteria were conducted by independent pairs of investigators. Selected studies were then discussed and agreed upon in consensus meetings, with consultation from the expert group. The literature selection process was conducted in accordance with the “preferred reporting items for systematic reviews and meta-analysis protocols” (PRISMA-P) 2015 statement.<sup>31)</sup> Quality assessment of the selected studies was conducted using the Cochrane Risk of Bias Tools<sup>32)</sup> for the RCTs, and the revised risk of bias tool for non-randomized studies (RoBANS),<sup>33)</sup> for the observational studies. Quality assessments were conducted by independent pairs of investigators and a consensus was achieved by discussion, with consultation from the expert group.

### Data Extraction and Management

According to the pre-defined data extraction format, researchers worked in pairs to extract data from the selected studies. Detailed data, including patient characteristics and primary and secondary outcomes, were extracted from the selected studies. Continuous variables such as mean change from baseline, median range and standard deviation were converted according to the formula described in the *Cochrane Handbook for Systematic Reviews of Interventions*.<sup>32)</sup> The extracted data were synthesized in terms of quantity and quality.

### Data Synthesis and Analysis

The data analyses were conducted in terms of both research type (RCT vs. observational study) and medication type (LAI vs. oral antipsychotic). The standardized mean difference (SMD) or relative risk (RR) and 95% confidence interval (CI) from each of the individual RCTs were calculated, and meta-analysis using the fixed effect model was fitted. The fixed effect model assumed that all of the studies had the same treatment effect, and variation in research findings was assumed to be caused by sampling variation or random effects. Along with an evaluation of publication bias, sensitivity analysis and subgroup analysis were also conducted. The publication bias test (funnel plot asymmetry) was only used when at least 10 studies

were included in the meta-analysis. Heterogeneity of effects was evaluated using the Higgins  $I^2$  statistic. All statistical analyses were performed using Cochrane RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and R Software (R version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria), including meta packages.

### Level of Evidence

The level of evidence was evaluated using the methodology developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group.<sup>33)</sup> The GRADE methodology first evaluates the importance of individual outcomes and then determines the level of evidence for each individual outcome as high, moderate, low, or very low. The factors associated with reducing the level of evidence in terms of the risk of bias were as follows: if the presence of performance bias was considered in an association with the open-label designed studies, the level of evidence was reduced by one level. The Summary of Findings table using the GRADE methodology contained a maximum of seven findings, ranked by importance. Measures of clinical efficacy included relapse rate, time to relapse, hospitalization rate, remission rate, hospital days, non-compliance, and quality of life. Measures of safety outcomes included all-cause discontinuation rate, drug-related side effects, ESRS, AIMS, and other side effects. The level of evidence was evaluated using the methodology developed by the GRADE working group.<sup>34)</sup> Confidence in the estimate of effect was categorized into four levels, including very low, low, moderate and high. Factors associated with lowering the level of evidence were risk of bias, inconsistency, indirectness, imprecision, and publication bias. For the observational studies, factors associated with heightening the level of evidence were a large magnitude of effect, a dose-response gradient, and an effect of plausible residual confounding. Evidence summary of findings tables for each research question were prepared using GRADEpro (McMaster University, Hamilton, ON, Canada; available at: <http://ims.cochrane.org/revman/other-resources/gradepr/download>).

## RESULTS

### Study Characteristics

A total of 3,062 articles were retrieved from the databases. After exclusion of duplicates, 1,933 articles remained. According to the selection criteria, 17 RCTs and 13 observational studies were selected.<sup>35-64</sup> All selection steps are presented as a PRISMA flowchart. Finally, the 17 RCTs are selected for our meta-analysis (Fig. 1).

In terms of the geographical locations in which the studies were conducted, most of the studies (70.6%) were conducted internationally (eight studies were conducted globally, three studies were conducted in Europe, and one study was conducted in Asia), 17.6% of studies were conducted in North America (three studies were conducted in the United States), 5.9% were conducted in Europe (one study was conducted in the United Kingdom), and 5.9% were conducted in Asia (one study was conducted in Taiwan). In addition, the follow-up periods for 37% and 36% of articles were two years and less than one year, respectively. The periods for 17%, 7%, and 3% of the studies were between one and two years, three years, and five years, respectively. All studies were published between 2005 and 2015 (Table 1).

The LAI antipsychotics used as the intervention treatments in the selected articles included risperidone LAI (70.6%), olanzapine LAI (17.6%), and aripiprazole LAI

(11.8%). Oral antipsychotics used as active comparators included aripiprazole (23.5%), olanzapine (23.5%), quetiapine (17.6%), and risperidone (11.8%), with an unspecified oral SGA used in the remainder of the studies (23.5%) (Table 1).

### Risk of Bias Assessment of Selected Studies

Risk of bias for the 17 RCTs was assessed using the Cochrane Risk of Bias Tool.<sup>30</sup> Random sequence generation, allocation concealment, incomplete outcome, and selective reporting showed approximately low risks of bias. In contrast, blinding of participants and blinding of outcome assessment showed a high or an unclear risk of bias.

Risk of bias for the 13 observational studies was assessed using the revised RoBANS tool. The results for the risk of bias were as follows: the blinding of outcome assessment presented a high or unclear risk of bias in the prospective studies, whereas participant comparability, selection of participants, and confounding variables presented relatively high risks of bias in the retrospective studies. Blinding of outcome assessment and confounding variables presented unclear risks of bias in the mirror-image studies (Fig. 1).

### Efficacy Outcomes

A summary of the efficacy outcomes, including relapse rate, non-compliance, time to relapse, hospitalization

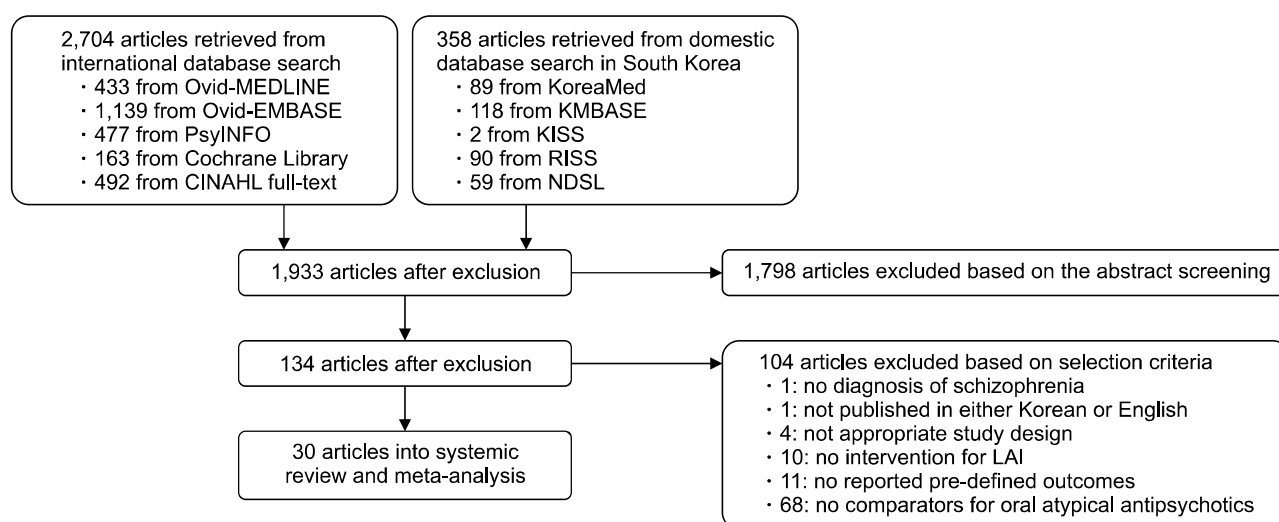


Fig. 1. Disposition of the selected articles for a systemic review and meta-analysis.

KMBASE, Korean Medicine Database; KISS, Korean Studies Information Service System; RISS, the Research Information Sharing Service; NDSL, National Digital Science Library (NDSL); LAI, long-acting injectable.

Table 1. Overview of the selected articles

Author (year)	Study design	Country	Study subjects	Follow-up period	Antipsychotics (n)		Funding
					Intervention group	Control group	
Ascher-Svanum <i>et al.</i> (2013) <sup>35</sup>	RCT	Europe	Adults with schizophrenia	2 yr	Olanzapine depot (598)	Olanzapine (322)	1
Bai <i>et al.</i> (2006) <sup>36</sup>	RCT	Taiwan	Adults with schizophrenia	12 wk	Risperidone consta (25)	Risperidone (25)	3
Barrio <i>et al.</i> (2013) <sup>37</sup>	Case-control	Spain	Adults with schizophrenia	2 yr	Risperidone consta (26)	Olanzapine, Risperidone, Aripiprazole, Perphenazine, Paliperidone (26)	4
Beauclair <i>et al.</i> (2007) <sup>38</sup>	Retrospective cohort	Canada	Patients with schizophrenia or schizoaffective disorder	3 yr	Risperidone consta (69)	Oral SGAs (93)	1
Buckley <i>et al.</i> (2015) <sup>39</sup>	RCT	US	Adults with schizophrenia or schizoaffective disorder	30 mo	Risperidone consta (153)	Oral SGAs (152)	2
Chue <i>et al.</i> (2005) <sup>40</sup>	RCT	International	Adults with schizophrenia	12 wk	Risperidone consta (319)	Risperidone (321)	1
de Arce-Cordon <i>et al.</i> (2012) <sup>41</sup>	RCT	International	Adults with schizophrenia or schizoaffective disorder	2 yr	Risperidone consta (329)	Aripiprazole (45)	1
Detke <i>et al.</i> (2014) <sup>42</sup>	RCT	International	Adults with schizophrenia	2 yr	Olanzapine depot (264)	Olanzapine (260)	1
Fe Bravo-Ortiz <i>et al.</i> (2011) <sup>43</sup>	Prospective cohort	Spain	Patients with schizophrenia	6 mo	Risperidone consta (1,085)	Oral SGAs (467)	1
Fleischhacker <i>et al.</i> (2014) <sup>44</sup>	RCT	International	Adults with schizophrenia	38 wk	Aripiprazole depot (265)	Aripiprazole (266)	1
Gaebel <i>et al.</i> (2010) <sup>45</sup>	RCT	International	Adults with schizophrenia or schizoaffective disorder	2 yr	Risperidone consta (329)	Quetiapine (337)	1
Huang <i>et al.</i> (2013) <sup>46</sup>	Retrospective cohort	Taiwan	Patients with schizophrenia or schizoaffective disorder	5 yr	Risperidone consta (207)	Risperidone and other SGAs (6,302)	2
Ishigooka <i>et al.</i> (2015) <sup>47</sup>	RCT	Asia	Adults with schizophrenia	1 yr	Aripiprazole depot (228)	Aripiprazole (227)	1
Keks <i>et al.</i> (2007) <sup>48</sup>	RCT	Europe	Patients with schizophrenia or schizoaffective disorder	53 wk	Risperidone consta (247)	Olanzapine (300)	1
Kim <i>et al.</i> (2008) <sup>49</sup>	Non-RCT	Korea	Adults with schizophrenia	2 yr	Risperidone consta (22)	Risperidone (28)	2
Lang <i>et al.</i> (2010) <sup>50</sup>	Retrospective cohort	US	Adults with schizophrenia	3 yr	Long-acting injectable SGAs (643)	Oral SGAs (7,790)	1
Llorca <i>et al.</i> (2006) <sup>51</sup>	Mirror-image study	Europe	Patients with schizophrenia or psychotic disorders	6 mo	Risperidone consta (130)	Oral SGAs (130)	1
Macfadden <i>et al.</i> (2010) <sup>52</sup>	RCT	International	Adults with schizophrenia or schizoaffective disorder	2 yr	Risperidone consta (177)	Aripiprazole (172)	1
McDonnell <i>et al.</i> (2011) <sup>53</sup>	RCT	International	Adults with schizophrenia	24 wk	Olanzapine depot (599)	Olanzapine (322)	1
Rouillon <i>et al.</i> (2013) <sup>54</sup>	RCT	Europe	Adults with schizophrenia or schizoaffective disorder	2 yr	Risperidone consta (329)	Quetiapine (337)	1
Schmauss <i>et al.</i> (2007) <sup>55</sup>	Mirror-image study	Europe	Adults with schizophrenia or psychotic disorders	6 mo	Risperidone consta (572)	Risperidone (572)	4
Schmauss <i>et al.</i> (2010) <sup>56</sup>	Mirror-image study	Germany	Adults with schizophrenia or schizoaffective disorder	12 wk	Risperidone consta (205)	Risperidone, Olanzapine, Quetiapine, Amisulpride, Ziprasidone (205)	1

Table 1. Continued

Author (year)	Study design	Country	Study subjects	Follow-up period	Antipsychotics (n)		Funding
					Intervention group	Control group	
Smeraldi <i>et al.</i> (2013) <sup>(57)</sup>	RCT	International	Adults with schizophrenia or schizoaffective disorder	2 yr	Risperidone consta (329)	Quetiapine (337)	1
Spill <i>et al.</i> (2010) <sup>(58)</sup>	Mirror-image study	Germany	Adults with schizophrenia or schizoaffective disorder	18 mo	Risperidone consta (119)	Oral SGAs (63)	1
Suzuki and Gen (2012) <sup>(59)</sup>	Prospective cohort	Japan	Inpatients with chronic schizophrenia	2 yr	Risperidone consta (18)	Risperidone (17)	4
Suzuki <i>et al.</i> (2012) <sup>(60)</sup>	Prospective cohort	Japan	Patients with chronic schizophrenia	24 wk	Risperidone consta (11)	Risperidone (10)	4
Weiden <i>et al.</i> (2009) <sup>(61)</sup>	RCT	US	Adults with schizophrenia or schizoaffective disorder	2 yr	Risperidone consta (19)	Oral SGAs (11)	1
Weiden <i>et al.</i> (2012) <sup>(62)</sup>	RCT	US	Adults with schizophrenia or schizoaffective disorder	2 yr	Risperidone consta (19)	Oral SGAs (11)	1
Willis <i>et al.</i> (2010) <sup>(63)</sup>	Mirror-image study	Sweden	Patients with schizophrenia or psychotic disorders	1 yr	Risperidone consta (164)	Oral SGAs (164)	1
Wykes <i>et al.</i> (2013) <sup>(64)</sup>	RCT	UK	Adults with schizophrenia	12 wk	Risperidone consta (26)	Oral SGAs (24)	1

RCT, randomized controlled trial; SGA, second-generation antipsychotic.

Funding source: 1, industry; 2, public; 3, industry and public; 4, none or declare of conflict of interest.

rate, remission rate, quality of life, hospital days, and other variables are shown in Table 2.

### Relapse Rate

Because the findings of Rouillon *et al.*<sup>54)</sup> and Gaebel *et al.*<sup>45)</sup> were obtained from the same subjects, the relapse rate reported in Gaebel *et al.*<sup>45)</sup> was considered a major measure and the findings in Rouillon *et al.*<sup>54)</sup> were excluded from the meta-analysis. Ultimately, only six studies were used for this analysis. Overall, the group treated with LAI SGAs showed significantly lower relapse rates than did the oral SGAs group (RR, 0.85; 95% CI, 0.74 to 0.99).

In the subgroup based on the length of the follow-up period, the relapse rate in the LAI SGAs group was 17% lower than that in the group treated with oral SGAs, in studies lasting  $\geq 1$  year (RR, 0.83; 95% CI, 0.71 to 0.97). However, there were no significant differences in relapse rates in studies lasting  $\leq 1$  year (RR, 1.03; 95% CI, 0.66 to 1.60). In addition, there were no significant differences between the groups with the relatively long and short follow-up periods ( $\chi^2=0.78$ , degree of freedom [df]=1,  $p=0.38$ ) (Table 2).

### Non-compliance

Although non-compliance was described in two articles, both of the articles investigated the same study subjects. Therefore, only the findings of Weiden *et al.*<sup>62)</sup> were used and no meta-analyses were conducted. Weiden *et al.*<sup>62)</sup> compared non-compliance between schizophrenia patients treated with risperidone long-acting injection and oral SGAs. In their study, non-compliance was defined as "the complete discontinuation of all antipsychotic medication for more than 14 consecutive days." There was no significant difference in non-compliance among patients treated for less than one year (RR, 0.58; 95% CI, 0.09 to 3.35), patients treated for one year (RR, 0.79; 95% CI, 0.47 to 1.31), and patients treated for more than one year (RR, 0.92; 95% CI, 0.51 to 1.66) (Table 2).

### Time to Relapse

Time to relapse (days) was reported in two articles. Both studies used risperidone long-acting injection as the intervention and conducted follow-up assessments for 24 months. In the study by de Arce Cordón *et al.*,<sup>41)</sup> the pro-

portion of schizophrenia patients was 83% in the intervention group and 82.2% in the control group. In the study by Macfadden *et al.*,<sup>52)</sup> all the subjects were schizophrenia patients in the groups treated with LAI and oral SGAs. The mean disease duration of schizophrenia in the study by de Arce Cordón *et al.*<sup>41)</sup> was 9.9 years in the group treated with LAI SGAs and 8.1 years in the group treated with oral SGA-treated group, respectively, the study of Macfadden *et al.*,<sup>52)</sup> included patients that experienced at least two episodes of relapse in the past two years as the study subjects. In results of the meta-analysis, we found that the group treated with LAI SGAs had significantly longer time to relapse than did the group treated with oral SGAs (SMD, 0.42; 95% CI, 0.29 to 0.54) (Table 2).

### Hospitalization Rate

Hospitalization rate was reported in three articles. Rehospitalization was defined as the subjects' psychiatric admission associated with psychotic and/or other psychiatric symptoms occurred after randomization in all studies. Weiden *et al.*<sup>62)</sup> reported separate findings for one-year and two-year follow-up periods. In results of the meta-analysis, there was no statistically significant difference in the hospitalization rates of the groups treated with LAI and oral SGAs (RR, 0.83; 95% CI, 0.62 to 1.11;  $I^2=29\%$ ).

In the subgroup analysis, there were no significant differences according to the follow-up period. In addition, considering inter-group differences caused by the follow-up duration, there was no significant difference ( $\chi^2=0.04$ ,  $df=1$ ,  $p=0.84$ ) (Table 2).

### Remission Rate

Remission rate was reported in five articles.<sup>41,44,47,48,57)</sup> Most of the studies used the schizophrenia remission criteria proposed by Andreasen *et al.*,<sup>65)</sup> although Keks *et al.*<sup>48)</sup> defined remission as a 20% or more decline in the total PANSS score. Since the remission criteria of Andreasen *et al.*<sup>65)</sup> and Keks *et al.*<sup>48)</sup> were similar, in the data synthesis, the remission rates reported in each of the studies were used without modification. The meta-analysis showed no significant difference in remission rates for the groups treated with LAI or oral SGAs (RR, 1.07; 95% CI, 0.99 to 1.15;  $I^2=70.5\%$ ).

In subgroup analysis, based on follow-up duration, the remission rate for the group treated with LAI SGAs was

Table 2. Summary of the efficacy outcomes

Efficacy measure	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of subjects (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oral SGAs	Risk with LAI SGAs				
Relapse rate	Study subjects 211 per 1,000 Moderate	179 per 1,000 (156 to 209)	RR=0.85 (95% CI, 0.74 to 0.99)	2,886 (6 RCTs)	⊕⊕⊕○ Moderate*	Long-term follow-up (RR=0.83; 95% CI, 0.71 to 0.97)
Time to relapse	226 per 1,000 The mean time to relapse was 0.	192 per 1,000 (167 to 223) The mean time to relapse in the intervention group was 0.42 standard deviations more (0.29 more to 0.54 more).	-	1,003 (2 RCTs)	⊕⊕⊕○ Moderate <sup>†</sup>	SMD=0.42 (95% CI, 0.29 to 0.54)
Hospitalization rate	Study subjects 99 per 1,000 Moderate	82 per 1,000 (61 to 110)	RR=0.83 (95% CI, 0.62 to 1.11)	1,518 (4 RCTs)	⊕⊕⊕○ Moderate <sup>‡</sup>	
Remission rate	352 per 1,000 Study subjects 521 per 1,000 Moderate	292 per 1,000 (218 to 390) 558 per 1,000 (516 to 599)	RR=1.07 (95% CI, 0.99 to 1.15)	2,161 (5 RCTs)	⊕⊕⊕○ Moderate*	Long-term follow-up (RR=1.42; 95% CI, 1.18 to 1.71)
Hospital days	532 per 1,000 The mean of hospital days was 0.	570 per 1,000 (527 to 612) The mean of hospital days in the intervention group was 0.11 standard deviations fewer (0.22 fewer to 0.01 fewer).	-	1,444 (2 RCTs)	⊕⊕⊕○ Moderate*	SMD=-0.11 (95% CI, -0.22 to -0.01)
Non-compliance	RR for short term (< 1 yr)=0.58 (95% CI, 0.09 to 3.55) RR for long term (> 1 yr)=0.92 (95% CI, 0.51 to 1.66)		-	(1 RCT)	⊕⊕⊕○ Moderate <sup>§</sup>	Not significant
Quality of life	Significantly increased from baseline to final change, in both intervention and control group.		-	(2 RCTs)	⊕⊕⊕○ Moderate <sup>  </sup>	

CI, confidence interval; SGAs, second-generation antipsychotics; LAI, long-acting injectable; RR, relative risk; RCTs, randomized controlled trials.

Quality of the evidence: \*open-label trial; <sup>†</sup>high heterogeneity ( $I^2=90\%$ ); <sup>‡</sup>confidence interval including non-significance (RR=1); <sup>§</sup>not sufficient for optimal information size; <sup>||</sup>differences in the scale-directions for outcome measurement.



significantly greater than that for the oral SGAs group, in studies lasting  $\geq 1$  year (RR, 1.42; 95% CI, 1.18 to 1.71) (Table 2).

### Quality of Life

Quality of life measures were reported in two articles.<sup>35,41</sup> Since the two studies used quite different assessment scales to measure quality of life, we could not synthesize the data quantitatively. In other words, the relatively high scores on the Schizophrenia Quality of Life Scale (SQLS)<sup>66</sup> which was used in the study by de Arce Cordón *et al.*,<sup>41</sup> indicate a relatively low quality of life, whereas the relatively high scores in the Heinrichs Carpenter Quality of Life Scale (HQLS),<sup>67</sup> which was used in the study by Ascher-Svanum *et al.*,<sup>35</sup> indicate a high quality of life. However, in all the groups treated with LAI and oral SGAs, the mean changes between the initial and final values were significant, and there were no inter-group comparisons (Table 2).

### Hospital Days

“Hospital days” was defined as the duration of psychiatric admission associated with psychotic and/or other psychiatric symptoms in patients with schizophrenia. Two articles were included in the meta-analysis, and both studies used olanzapine long-acting injection as the intervention treatment. Detke *et al.*<sup>42</sup> evaluated hospital days associated with schizophrenia for a two-year follow-up period, and Ascher-Svanum *et al.*<sup>35</sup> evaluated hospital days for a six-month follow-up period. The mean hospital days for the group treated with LAI SGAs was significantly shorter than that for the oral SGAs group (SMD,  $-0.11$ ; 95% CI,  $-0.22$  to  $-0.01$ ) (Table 2).

### Positive and Negative Syndrome Scale (PANSS)

Total score on the PANSS was reported in nine studies included in the meta-analysis. The groups treated with LAI and oral SGAs were compared in terms of the mean change in the total score on the PANSS before and after SGA medications. In the meta-analysis, the decrease in total PANSS score in the group treated with LAI SGAs was greater than that in the oral SGAs group. However, this difference was not significant (SMD,  $-0.05$ ; 95% CI,  $-0.12$  to  $0.12$ ).

In subgroup analysis according to follow-up period, the decrease in total PANSS score was greater in the group

treated with LAI SGAs than in the oral SGAs group. However, again, this difference was not significant. In addition, considering inter-group differences caused by the follow-up period, there was no significant difference ( $\chi^2=1.59$ ,  $df=1$ ,  $p=0.21$ ) (Table 2).

### Clinical Global Impression Scale (CGI-S)

Scores on the CGI-S were reported in eight studies included in the meta-analysis. The groups treated with LAI and oral SGAs were compared in terms of the mean change in score on the CGI-S before and after treatment with SGA medications. In the meta-analysis, the decrease in the CGI-S score in the group treated with LAI SGAs was greater than that in the oral SGAs group. However, this difference was not significant (SMD,  $-0.05$ ; 95% CI,  $-0.13$  to  $0.04$ ;  $I^2=35.5\%$ ).

In the subgroup analysis, according to follow-up period, there was no significant difference. In addition, considering inter-group differences caused by the follow-up period, there was no significant difference ( $\chi^2=0.57$ ,  $df=1$ ,  $p=0.45$ ) (Table 2).

### Montgomery-Asberg Depression Rating Scale (MADRS)

Scores on the MADRS were reported in two articles. Both studies were included in the ConstaTRE study.<sup>40</sup> de Arce Cordón *et al.*<sup>41</sup> used risperidone long-acting injection for intervention and oral aripiprazole for control and Smeraldi *et al.*<sup>57</sup> used risperidone long-acting injection for intervention and oral quetiapine for control for the follow-up period of 24 months. In the meta-analysis, the decrease in the MADRS score was significantly greater in the group treated with LAI SGAs than in the group treated with oral SGAs (SMD,  $-1.69$ ; 95% CI,  $-2.95$  to  $-0.43$ ) (Table 2).

### Safety Outcomes

A summary of the safety outcomes, including all-cause discontinuation rate, drug-related side effects, ESRS, AIMS, and other side effects are shown in Table 3.

### All-cause Discontinuation Rate

All-caused discontinuation rates were described in three articles included in the meta-analysis. Olanzapine long-acting injection was used in the study of Detke *et al.*<sup>42</sup> and aripiprazole long-acting injection was used in

Table 3. Summary of the safety outcomes

Safety measure	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of subjects (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oral SGAs	Risk with LAI SGAs				
All cause discontinuation	Study subjects 393 per 1,000 Moderate	366 per 1,000 (322 to 413)	RR=0.93 (95% CI, 0.82 to 1.05)	1,510 (3 RCTs)	⊕⊕⊕○ Moderate*	
ESRS	335 per 1,000 The mean score on the ESRS in the intervention group was 0. ESRS was 0.	311 per 1,000 (275 to 352) The mean score on the ESRS in the intervention group was 0.01 standard deviations fewer (0.15 fewer to 0.12 more).	-	1,014 (2 RCTs)	⊕⊕⊕○ Moderate*	
Drug-related adverse events	Study subjects 523 per 1,000 Moderate	534 per 1,000 (513 to 555) 690 per 1,000 (663 to 718)	RR=1.02 (95% CI, 0.98 to 1.06)	4,055 (6 RCTs)	⊕⊕⊕○ Moderate*	Subgroup significance: Any adverse event (RR=1.02, 95% CI, 0.98 to 1.06) Serious adverse event (RR=0.90, 95% CI, 0.70 to 1.16)
AIMS	The mean score on the AIMS was 0.	The mean score on the AIMS in the intervention group was 0.02 standard deviations fewer (0.14 fewer to 0.09 more).	-	1,257 (4 RCTs)	⊕⊕⊕○ Moderate*	
Other adverse effects	Study subjects 82 per 1,000 Moderate	96 per 1,000 (86 to 107) 79 per 1,000 (71 to 89)	RR=1.17 (95% CI, 1.05 to 1.31)	14,147 (10 RCTs)	⊕⊕⊕⊕ High	Subgroup significance: Prolactin-increased (RR=2.48, 95% CI, 1.60 to 3.84)
EPSE-related effects	Study subjects 83 per 1,000 Moderate	134 per 1,000 (106 to 170) 139 per 1,000 (110 to 176)	RR=1.61 (95% CI, 1.27 to 2.04)	2,608 (6 RCTs)	⊕⊕⊕⊕ High	

CI, confidence interval; SGAs, second-generation antipsychotics; LAI, long-acting injectable; RR, relative risk; RCTs, randomized controlled trials; ESRS, Extrapyramidal Symptom Rating Scale; AIMS, Abnormal Involuntary Movement Scale; EPSE, extrapyramidal side effects.  
Quality of the evidence: \*open-label trial.

the other two studies. In the meta-analysis, the group treated with LAI SGAs had a lower discontinuation rate than did the oral SGAs group. However, this difference was not significant (RR, 0.93; 95% CI, 0.82 to 1.05) (Table 3).

#### Extrapyramidal Symptom Rating Scale (ESRS)

Scores on the ESRS were reported in two studies. In the meta-analysis, the decreased score in the ESRS score was greater in the group treated with LAI SGAs than in the oral SGAs group (SMD,  $-0.01$ ; 95% CI,  $-0.15$  to  $0.12$ ) (Table 3).

#### Drug-related Side Effects

In the meta-analysis, there was no statistically significant difference between the two groups in terms of all drug-related side effects (RR, 1.02; 95% CI, 0.98 to 1.07) or severe drug-related side effects (RR, 0.90; 95% CI, 0.70 to 1.16) (Table 3).

#### Abnormal Involuntary Movement Scale (AIMS)

Scores on the AIMS were reported in two studies. In the meta-analysis, the decrease in the AIMS score was greater in the group treated with LAI SGAs than in the oral SGAs group, although this difference was not statistically significant (SMD,  $-0.02$ ; 95% CI,  $-0.14$  to  $0.09$ ) (Table 3).

#### Other Adverse Effects

Extrapyramidal side effects occurred significantly more often in the group treated with LAI SGAs than in the group treated with oral SGAs (RR, 1.61; 95% CI, 1.27 to 2.04), whereas there was no significant difference between the two groups in terms of all other drug-related adverse effects (Table 3). Prolactin-related side effects also occurred more often in the group treated with LAI SGAs than in the group treated with oral SGAs (RR, 2.48; 95% CI, 1.60 to 3.84). However, there was no significant difference between the two groups in terms of the incidence of other adverse effects, including akathisia, insomnia, and weight gain (Table 3).

## DISCUSSION

In summary, with respect to outcome measures, the group treated with LAI SGAs was characterized by a significantly lower relapse rate, longer time to relapse, and

fewer hospital days than the group treated with oral SGAs. However, there were no significant differences in hospitalization rate, remission rate, or non-compliance between the two groups. In terms of outcome measures, subgroup analysis limited to the studies lasting  $\geq 1$  year showed that the group treated with LAI SGAs was characterized by significantly lower relapse rate and higher remission rate than the oral SGAs group. In addition, in terms of safety outcome measures, the group treated with LAI SGAs was characterized by higher rates of extrapyramidal syndrome and prolactin-related symptoms than the group treated with oral SGAs. However, there was no significant difference in the all-cause discontinuation rate between the two groups.

In the context of comparing the efficacy of LAI and oral antipsychotics in relapse prevention, the study findings were somewhat consistent as follows: Our study showed that the mean relapse prevention rate for schizophrenia patients treated with oral SGAs was significantly lower than that for patients treated with LAI SGAs. However, a meta-analysis limited to the studies lasting  $\leq 1$  year showed that there were no significant differences in the relapse rate between patients treated with oral versus LAI SGAs. In findings similar to ours, superiority of LAI antipsychotics to oral antipsychotics for relapse prevention was supported by several naturalistic and mirror-image studies.<sup>68-73</sup> For example, the rehospitalization risk in schizophrenia or schizoaffective disorder patients treated with LAI antipsychotics was significantly lower than that in those patients treated with oral antipsychotics, in a nationwide cohort of the United States patients.<sup>70</sup> In addition, in a systematic review limited to mirror-image studies,<sup>71</sup> the group treated with LAI antipsychotics was characterized by significantly lower hospitalization rate than was the group treated with oral antipsychotics.

In contrast to our findings, a previous meta-analysis, which included 21 RCTs ( $n=5,176$ ) for both LAI FGAs and SGAs,<sup>11</sup> reported that there were no significant differences in the outcome measures, including relapse prevention, between the groups treated with LAI and oral antipsychotics (12 studies; RR, 0.93; 95% CI, 0.80 to 1.08;  $p=0.35$ ). In the subgroup analyses confined to the FGAs, LAI formulations were characterized by greater relapse prevention than were oral formulations (10 studies; RR, 0.82; 95% CI, 0.65 to 0.97;  $p=0.02$ ). Herein, Kishimoto *et al.*<sup>11</sup> explained that the findings could be associated with

a publication bias and/or changes in relapse definitions, and the superiority of LAIs to oral antipsychotics with respect to relapse prevention could not be clearly concluded. Moreover, whereas LAI antipsychotics are usually prescribed to schizophrenia patients with non-compliance and greater illness severity in clinical psychiatry, LAI antipsychotics might also be prescribed to those with compliance and less illness severity. Herein, the RCTs for LAI and oral antipsychotics could present no significant differences in the efficacy in relapse prevention.<sup>72)</sup> However, our findings showed that LAI SGAs had greater efficacy in terms of relapse prevention and were associated with higher rates of compliance in the relapse prevention than were oral SGAs, in patients with schizophrenia. The superior efficacy of LAI antipsychotics to oral antipsychotics was often shown in studies lasting more than 1 year, rather than in studies lasting less than 1 year. Leucht *et al.*<sup>8)</sup> conducted a meta-analysis including only the LAI RCTs lasting more than 1 year and concluded that LAI antipsychotics result in greater relapse prevention than do oral antipsychotics in schizophrenia patients. In our systematic review and meta-analysis, most of the selected RCTs were continued for longer than 1 year. Moreover, differences in the study findings could be caused by variation in the definitions used to characterize relapse and hospitalization.

Kish *et al.*<sup>13)</sup> found no significant differences in all-cause death or suicide death between schizophrenia patients treated with LAI antipsychotics and placebo or oral antipsychotics in a meta-analysis including 52 RCTs. However, the authors speculated that extrapyramidal syndromes were more prevalent in the group treated with LAI antipsychotics, although the evidence was not well-captured by the meta-analysis.<sup>9)</sup> There were no significant differences in extrapyramidal symptoms, prolactin increase, or other adverse events between the LAI and oral antipsychotics treatments in a meta-analysis of 18 RCTs, including data for risperidone, olanzapine, aripiprazole, zuclopenthixol, fluphenazine and haloperidol.<sup>17)</sup> In contrast to these findings, a meta-analysis showed that LAI SGAs were characterized by a greater risk of developing extrapyramidal side effects than were LAI FGAs (RR, 1.451;  $p=0.048$ ).<sup>23)</sup> Moreover, our systematic review and meta-analysis have a virtue of presenting the evidence for significantly increased extrapyramidal syndrome and prolactin-related adverse effects in the group treated with LAI

SGAs compared with the group treated with oral SGAs. Herein, with the high level of evidence, our findings suggest that anticholinergic medications and other countermeasures against dopamine D<sub>2</sub> antagonism-related effects might be more necessary with LAI SGAs than with oral SGAs.

Several limitations of our study should be considered: First, the study subjects were limited to adults with schizophrenia. Second, in subgroup analysis, differences in the length of the follow-up period may contribute to high heterogeneity. The differences in disease severity in study subjects can be another contributor to high heterogeneity. Third, despite differences associated with the different pharmacological ingredients used in the intervention and control groups, we did not have a sufficient number of studies to enable a quantitative analysis of these differences. Fourth, cognitive symptoms were not included as a component of the efficacy outcomes, since the domain was not evaluated in previous clinical trials.

Despite these limitations, this systematic review and meta-analysis was able to demonstrate that LAI SGAs showed improved efficacy with respect to relapse rate, time to relapse, and hospital days, but also higher rates of dopamine D<sub>2</sub> antagonism-related adverse effects, when compared with oral SGAs, with moderate to high levels of evidence. The superior efficacy of LAI SGAs to oral SGAs in our meta-analysis may be associated with the fact that most of the selected trials chosen for analysis continued for more than 1 year.

#### ■ Acknowledgments

This study was supported by a grant from the National Evidence-based Healthcare Collaborating Agency (NC15-004).

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