Long-Acting Injectable Versus Oral Antipsychotics in Schizophrenia: A Systematic Review and Meta-Analysis of Mirror-Image Studies

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ABSTRACT

Objective: Recent, large, randomized controlled trials (RCTs) showed no benefit of long-acting injectable (LAI) antipsychotics over oral antipsychotics in preventing relapse in schizophrenia, nor did a recent meta-analysis incorporating these studies. However, RCTs might enroll a disproportionate number of patients with better treatment adherence and lower illness severity. Mirror-image studies, which compare periods of oral antipsychotic versus LAI treatment in the same patients, might therefore better reflect the real-world impact of LAIs.

Data Sources: A systematic literature search without language restriction was conducted using MEDLINE/PubMed, Cochrane Library, Web of Science, PsycINFO, and CINAHL until May 31, 2012. Search terms included synonyms of (1) antipsychotic(s) AND (2) schizophrenia and related disorders AND (3) depot, (long-acting) injection(s), microsphere, decanoate, palmitate, enanthate.

Study Selection: Of 5,483 identified citations, 607 articles were fully inspected, and 582 were ineligible. Finally, 25 mirror-image studies from 28 countries that followed 5,940 patients with schizophrenia for ≥ 12 months (≥ 6 months each on oral antipsychotic and LAI treatment) met the inclusion criteria and were analyzed.

Data Extraction: Coprimary outcomes were hospitalization risk and number of hospitalizations. Secondary outcomes included hospitalization days and length of stay.

Data Synthesis: LAIs showed strong superiority over oral antipsychotics in preventing hospitalization (16 studies, N = 4,066; risk ratio = 0.43; 95% CI, 0.35–0.53; $P < .001$) and in decreasing the number of hospitalizations (15 studies, 6,342 person-years; rate ratio = 0.38; 95% CI, 0.28–0.51; $P < .001$). This strong advantage was also observed for secondary outcomes and in multiple clinically relevant subpopulations and treatment groups.

Conclusions: Results from mirror-image studies in patients eligible for clinical use of LAIs showed strong superiority of LAIs compared to oral antipsychotics in preventing hospitalization. The results were in contrast to the recent meta-analysis of RCTs, which showed no superiority of LAIs. Given the possible biases in mirror-image studies, such as expectation bias, natural illness course, and time effect, a cautious interpretation is required. Nevertheless, the population in mirror-image studies better reflects the population receiving LAIs in clinical practice.

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As psychopathology and social functioning can worsen with repeated psychotic episodes in patients with schizophrenia,[1,2] relapse prevention is critical. High nonadherence rates in schizophrenia can limit the efficacy of pharmacotherapy[3,4]; therefore, the use of long-acting injectable (LAI) antipsychotics is considered to be an important treatment option.[5] However, new, large randomized controlled trials (RCTs) did not show significant superiority of LAIs over oral antipsychotics.[6,7] Moreover, this failure to find superiority of LAIs over oral antipsychotics was confirmed in our latest meta-analysis[8] of RCTs, which incorporated these new studies. We did not find a significant difference between LAIs and oral antipsychotics in preventing relapse (21 studies, N = 4,950; risk ratio [RR] = 0.93; 95% CI, 0.80–1.08; $P = .35$), in preventing hospitalization (10 studies; RR = 0.89; 95% CI, 0.78–1.02; $P = .09$), or in secondary outcomes, which were also related to relapse.

However, RCTs might enroll a disproportionate number of patients with better treatment adherence and lower illness severity. In addition, it is important to consider that participation in a clinical trial can alter the ecology of treatment delivery and experience; for example, patients receive reminders, reimbursement, free medication, and assessments. Therefore, the standard RCT might not be the best strategy to examine the effectiveness of LAIs.

Mirror-image studies, which compare a period of oral antipsychotic treatment with a subsequent period of LAI treatment for the same patients, might better reflect the relative impact of LAIs versus oral antipsychotics in the targeted population and in naturalistic settings and circumstances. There are reviews of mirror-image studies of either first-generation antipsychotic (FGA) or second-generation antipsychotic (SGA) LAIs.[9–11] However, as far as we know, no meta-analysis incorporating both FGA and SGA LAIs without language restriction has been performed. We therefore conducted a meta-analysis of mirror-image studies of all LAIs that compared the period of oral antipsychotic treatment with the subsequent period of LAI treatment.

METHOD

The meta-analysis was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[12] which is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

Clinical Points

- Recent randomized controlled trials showed no benefit of long-acting injectables (LAIs) over oral antipsychotics in preventing relapse in schizophrenia.
- The reported meta-analysis based on 25 mirror-image studies that compared periods of treatment with oral antipsychotics versus LAIs in the same patients showed strong superiority of LAIs over oral antipsychotics in preventing hospitalization.
- Mirror-image studies might better reflect the real-world impact of LAIs; however, one should consider the biases of different study designs when evaluating the comparative effectiveness of LAIs.

Search

Two independent investigators (T.K., M.N.) conducted the literature search. We conducted a search without language restrictions using MEDLINE/PubMed, Cochrane library, Web of Science, PsycINFO, and CINAHL (last search: May 31, 2012) for the studies meeting the inclusion criteria mentioned below. To avoid publication bias, we also included unpublished studies, such as those contained in conference proceedings and clinical trial registries (http://clinicaltrials.gov/). Search terms included synonyms of (1) antipsychotic(s) AND (2) schizophrenia and related disorders AND (3) depot, (long acting) injection(s), microsphere, decanoate, palmitate, enanthate. The electronic search was supplemented by hand search of reference lists of relevant publications. There were multiple reports that were derived from the same study or that seemed to involve overlapping patient populations with other reports (eg, nationwide cohort studies with different publication years but overlapping study year[s]). In such cases, we selected the newer and/or larger report. However, whenever specific outcomes were reported in separate reports, we used each of the reports for each separate outcome.

Inclusion Criteria

We included mirror-image studies comparing the period before and after initiation of LAI antipsychotic treatment in adults with schizophrenia or schizoaffective disorder. We included studies that followed patients ≥ 12 months (≥ 6 months each with oral antipsychotic and LAI) and that provided information about hospitalization or relapse-related data. We excluded case reports and case series with ≤ 30 patients. There were studies that compared 2 or more LAIs in a mirror-image design, such as switching from FGA LAIs to risperidone LAI. Because the purpose of our study was to examine the comparative effectiveness of LAIs to oral antipsychotics, we extracted only the data for patients who switched from oral antipsychotic to LAI or vice versa. If this was not possible, we excluded the study from the analysis. We excluded penfluridol, a once-weekly oral antipsychotic, considering it neither an LAI nor an oral antipsychotic.

Data Extraction and Outcomes

Data were extracted independently by ≥ 2 reviewers (T.K., M.N., C.U.C.). Authors and companies were contacted to provide missing information and unpublished data. Any disagreements were resolved by discussion. Foreign papers were translated by bilingual speakers, and data extraction was double-checked by at least 1 investigator (T.K., M.N.) using Google Translate (http://translate.google.com/).

Coprimary outcomes were (1) hospitalization risk, defined as a proportion of patients experiencing 1 or more hospitalizations, and (2) the total number of hospitalizations during the study period, expressed as the hospitalization rate, ie, the number of hospitalizations per person-year. Secondary outcomes included total hospitalization days and length of stay (ie, mean duration of 1 hospitalization).

Data Analysis

Because mirror-image studies compare outcomes for each patient under 2 conditions, they sometimes allow us to reduce the error term in the analysis by taking account of the correlation between outcomes under the 2 conditions. The nature of the data (the fact that many patients had zero events) made that option impossible here, and we therefore treated the correlation as zero. This is a conservative approach, in that it exaggerates the magnitude of the standard error.

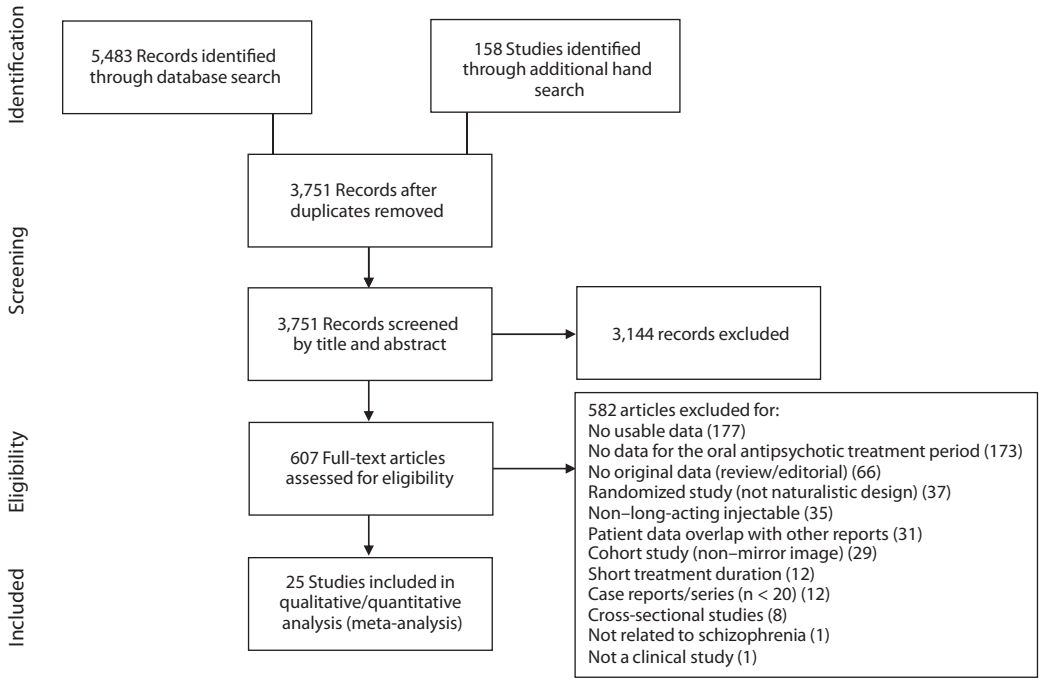
Risk of hospitalization was computed as the number of patients hospitalized divided by the number of patients at risk. The risk ratio was then given by the ratio of risks for LAI versus oral antipsychotic. Rate of hospitalizations was computed as the number of hospitalizations divided by the person-years at risk. The rate ratio was then given by the ratio of rates for LAI versus oral antipsychotic.

Reporting of relapse-related outcomes differed widely. Some studies reported the number of hospitalizations before and after introduction of the LAI for each patient. In such cases, we used the data for both the risk ratio calculation and the rate ratio calculation. Some of the studies reported only the proportion of patients who had at least 1 hospitalization and stopped the follow-up when patients had their first relapse. In such cases, we used these data only for the risk ratio calculation. Other studies reported only the total number of hospitalizations during the period before and after the introduction of the LAI. The follow-up length was fixed among patients in some studies, but varied among patients in others. Notably, however, the length of the observation period was always the same before and after initiation of the LAI in each individual patient across all studies. Due to these differences in follow-up duration, we calculated the rate (the number of hospitalizations per year) in order to standardize the unit of observation time.

For days hospitalized, we computed the standardized mean difference between groups (Hedges' *g*). Similarly, for mean length of hospitalization, we computed the standardized mean difference between groups (Hedges' *g*).

The meta-analyses were performed using a random-effects model.[13] The summary effect and 95% confidence

Figure 1. Flowchart of Literature Search



intervals (CIs) were reported for each outcome. With regard to the heterogeneity, τ^2, I^2, Q, and P values are reported.

While the primary analysis was based on the full set of studies, we also conducted analyses on subgroups of studies in order to identify potential methodological biases or subpopulations in which outcomes differed. These included subgroups based on (1) medication group (FGA LAI vs risperidone LAI [only risperidone LAI data were available among SGA LAIs]), (2) publication year (older RCTs [published before 2000] vs newer RCTs [published in 2000 or later]), (3) study sample size ($N > 100$, $N \leq 100$), (4) region (North America, western Europe), (5) pharmaceutical sponsorship, and (6) data acquisition method in LAI phase (including LAI dropouts in the analysis vs excluding LAI dropouts in the analysis).

Data were entered into a funnel graph (trial effect against trial size) to investigate the possible presence of publication bias.[14] If there was a significant risk of publication bias, we employed the "trim-and-fill" method[15] to assess the possible impact of the bias. Data were double-entered into and analyzed with Comprehensive Meta-Analysis Version 2 (BioStat; Englewood, New Jersey).

RESULTS

Search and Study Characteristics

The literature search using the aforementioned electronic databases yielded a total of 5,483 citations. Of 5,483 identified citations, 607 articles were fully inspected, and 582 were removed from analysis due to following reasons: no usable data (177 articles), no data for the oral antipsychotic treatment period prior to LAI treatment (173 articles), no original data (66 articles), randomized study (37 articles), non-LAI (35 articles), patient data overlap with other reports (31 articles), cohort study (non–mirror-image) (29 articles), short treatment duration (12 articles), case report/series (12 articles), and other reasons (10 articles) (Figure 1).

Finally, 25 mirror-image studies from 28 countries that followed 5,940 patients with schizophrenia for ≥ 12 months (≥ 6 months each on oral antipsychotics and LAIs) met the inclusion criteria and were analyzed. The mean (SD) study duration was 20.9 (15.9) months. As reports were all naturalistic observational studies that compared the period of time that patients were on oral antipsychotic treatment versus on LAI treatment, the medication choice, especially for the oral antipsychotic phase, was arbitrary. Reflecting this, in all studies but 1 (96.0%), any medications were allowed or medications were not reported during the oral antipsychotic phase. In 1 study (4.0%), olanzapine was used during the oral antipsychotic phase. On the other hand, the numbers of studies with each LAI were as follows: risperidone, 10 (40%); fluphenazine, 8 (32%); mixed, or any FGA, 2 (8%); clopenthixol, perphenazine, and flupenthixol (each), 1 (4%); risperidone or FGA, 1 (4%). Thus, risperidone LAI was the only SGA LAI with mirror-image study data.

In all studies, patients were switched only from oral antipsychotic to LAI, not the other way around. Moreover, data during the oral antipsychotic phase were collected retrospectively in all studies. However, in the LAI phase, 5 studies (20.0%) followed up patients prospectively. Altogether, 15 studies (60.0%) collected the data during the LAI phase when patients were on treatment with the LAI by selecting patients who continued LAI for a specific duration or collected data until the patients stopped the LAI; that is, LAI dropouts were excluded from (or not included in) the analysis. However, 9

Table 1. Study Characteristics

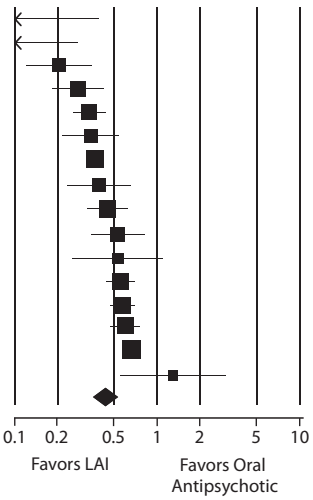
Study/Country	N[a]	Follow-up Duration, Oral Antipsychotic/LAI (mo)	Inclusion Criteria	Age (y)[b]	LAI Medication	Oral Antipsychotic Medication
Chang et al, 2012[16]/Taiwan	184	12/12	Schizophrenia (*ICD-9*), started RLAI, followed ≥ 1 y before and after RLAI initiation, treated regularly with RLAI	Range, 36–55[c]	RLAI	CLO, RIS, other SGA, oral FGA
Rosa et al, 2012[17]/France, Kuwait, Portugal, Saudi Arabia	98	6/6	Schizophrenia/schizoaffective disorder (*DSM-IV*), nonacute, previously treated with OLA (stable dose) and willing to switch to RLAI, not known as RIS nonresponder	0.2 (14.0)[d]	RLAI	OLA
Crivera et al, 2011[18]/United States	435	12/12	Schizophrenia (*DSM-IV*), appropriate for RLAI initiation	41.9 (12.6)	RLAI	NR
Ren et al, 2011[19]/United States	924	12/12	Schizophrenia (*ICD-9*), started RLAI, had ≥ 4 RLAI injections following initiation	51 (11)	RLAI	NR
Peng et al, 2011[20]/United States	147	6/6	Schizophrenia (*ICD-9*), started any depot, but no depot injection in the 6 mo before baseline, ≥ 2 outpatient visits or ≥ 1 hospitalization within 180 d	42.6 (14.7)	RLAI, HAL, FPZ	NR
Carswell et al, 2010[21]/New Zealand	443	12/12	Schizophrenia (*DSM-IV*), nonadherent to oral antipsychotic (or preferred RLAI), intensive treatment in the year prior to switching to RLAI	35.9 (12.4)	RLAI	NR
Girardi et al, 2010[22]/Italy	88	6/6 (24)[e]	Schizophrenia/schizoaffective disorder (*DSM-IV*), clinically inadequate response to ≥ 2 oral antipsychotics within 3 mo, BPRS total score ≥ 65	41.2 (10.6)	RLAI	OLA, CLO, QUE, HAL, ARI, RIS
Su et al, 2009[23,f]/Taiwan	108	12/12	Schizophrenia (*ICD-9*), regularly treated with RLAI for ≥ 1 y, ≥ 1 y data in pre-RLAI periods, had < 90-d hospital stay	42.0 (10.4)	RLAI	RIS, other SGA, FGA, FGA + RIS, FGA + other, SGA, none
Lam et al, 2009[24,g]/15 countries[h]	2,300[i]	12/12	Schizophrenia, participated in RLAI clinical trials	Mean = 38.4	RLAI	Oral antipsychotic
Fuller et al, 2009[25]/United States	106	Mean (SD), 10.2 (6.4)/ 10.2 (6.4)	Schizophrenia/schizoaffective disorder (*ICD-9*) at any time of the study period (January 2003–January 2006), with continuous enrollment throughout the study period, ≥ 4 injections of RLAI	51.9 (10.2)	RLAI	ARI, OLA, QUE, RIS, ZIP
Beauclair et al, 2005[26,g]/Canada	63	39.4/40.3	Schizophrenia, participated in RLAI clinical trials	NR	RLAI	NR
Bourin et al, 1998[27]/France	48	Mean (SD), 62.4 (33.6)/ 69.6 (38.4)	Schizophrenia (*ICD-10*), hospitalized	NR	FGA	NR
Svestka et al, 1984[28]/Czech	34	10.3/10.3	Schizophrenia, in remission	Mean = 37.4	Clopenthixol decanoate	NR
Waldmann and Neumann, 1984[29]/Germany	65	31.2/31.2	Schizophrenia/schizoaffective disorder, outpatients and patients in day hospital who were receiving FPZ decanoate	NR	FPZ	NR
Michel et al, 1981[30]/Chile	112	Range, 12–17/12–17	Schizophrenia, on depot when study was conducted	Range, 25–44[j]	FPZ	NR
Tan et al, 1981[31]/Singapore	127	24/24	Schizophrenia, duration of illness ≤ 8 y, ≥ 24 mo treatment before and after institution of FPZ depot	32.5 (8.8)	FPZ	NR
Arató and Erdós, 1979[32]/Hungary	51	44/26	Schizophrenia/schizoaffective disorder, ≥ 1 y on depot, ≥ 2 hospitalizations in the past	34	FGA mix	NR
Devito et al, 1978[33]/United States	122	12/12	Schizophrenia spectrum disorders, treated in the same inpatient program and referred for outpatient treatment in the FPZ program	Range, 18–39[k]	FPZ	NR
Polonowita and James, 1976[34]/ New Zealand	43	13/13	Schizophrenia (*ICD-8*), started FPZ depot	NR	FPZ decanoate	NR
Lindholm, 1975[35]/Sweden	24	Mean, 26.9/26.9	Schizophrenia, administered perphenazine enanthate for > 1 y	Mean = 44.9	Perphenazine enanthate	NR
Gottfries and Green, 1974[36]/ Sweden	58	NR[l]	Schizophrenia, discharged, treated with flupenthixol decanoate during observational period	NR	Flupenthixol decanoate	NR
Morritt, 1974[37]/United Kingdom	33	12/12	Schizophrenia, administered FPZ decanoate and with 1 y record pre- and post-FPZ depot initiation	NR	FPZ decanoate	NR
Johnson and Freeman, 1972[38]/ United Kingdom	126[l]	12/12[l]	Schizophrenia, administered FPZ depot and with follow-up record of 1 or 2 y[m]	NR	FPZ enanthate or decanoate	NR
Denham and Adamson, 1971[39]/ United Kingdom	103	Mean, 24.8/24.8	Schizophrenia, receiving FPZ depot, ≥ 12 m follow-up record after injection, with completely documented previous history	Mean = 38.5	FPZ	NR
Malm, 1971[40]/Denmark	44	36/36	Schizophrenia, chronic, known to have difficulty with adherence to oral medication	NR	FGA mix	NR

[a]Original study sample size. [b]Values expressed as mean (SD) unless otherwise noted. [c]Majority (60.3%) were 36–55 years old. [d]Based on patients who received at least 4 doses of RLAI (n = 96). [e]Analyzed pre- vs post-LAI phase (6 months each), but study had 18-month extension follow-up phase. [f]Analysis used only hospital days due to the patient overlap with Chang et al.[16] [g]Unpublished data. [h]Australia, Belgium, Brazil, Canada, Czech, Denmark, Greece, Korea, Mexico, Netherland, Norway, Russia, Slovakia, Spain, and Sweden. [i]Analyzed 1,748 patients who were taking oral atypical antipsychotics before RLAI. [j]Majority (65.2%) were 25–44 years old. [k]Majority (57.4%) were 18–39 years old. [l]Mean (SD) observation period for 36 patients who had relapse(s) was 43.2 (10.8) months. [m]Analyzed patients with 1-year follow-up.

Abbreviations: ARI = aripiprazole, BPRS = Brief Psychiatric Rating Scale, CLO = clozapine, FGA = first-generation antipsychotic, FPZ = fluphenazine, HAL = haloperidol, LAI = long-acting injectable, NR = not reported, OLA = olanzapine, QUE = quetiapine, RIS = risperidone, RLAI = risperidone long-acting injectable, SGA = second-generation antipsychotic, ZIP = ziprasidone.

Figure 2. Hospitalization Risk

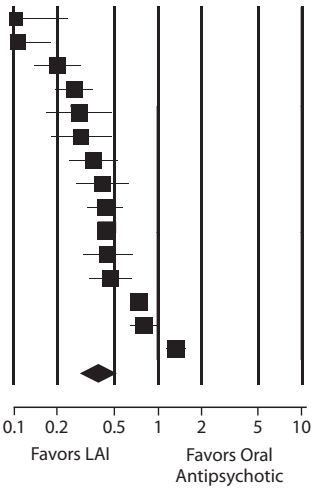
Study	Risk Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value
Girardi et al, 2010[22]	0.024	0.001	0.397	−2.609	.0091
Beauclair et al, 2005[26]	0.092	0.030	0.282	−4.166	.0000
Arató and Erdós, 1979[32]	0.204	0.119	0.350	−5.761	.0000
Devito et al, 1978[33]	0.281	0.183	0.430	−5.844	.0000
Denham and Adamson, 1971[39]	0.333	0.254	0.438	−7.884	.0000
Morritt, 1974[37]	0.343	0.214	0.550	−4.440	.0000
Lam et al, 2009[24]	0.369	0.327	0.415	−16.569	.0000
Lindholm, 1975[35]	0.391	0.232	0.660	−3.515	.0004
Peng et al, 2011[20]	0.452	0.321	0.636	−4.554	.0000
Gottfries and Green, 1974[36]	0.529	0.341	0.822	−2.831	.0046
Rosa et al, 2012[17]	0.529	0.251	1.116	−1.672	.0944
Chang et al, 2012[16]	0.557	0.437	0.711	−4.697	.0000
Johnson and Freeman, 1972[38]	0.570	0.461	0.704	−5.203	.0000
Crivera et al, 2011[18]	0.597	0.463	0.768	−4.003	.0001
Ren et al, 2011[19]	0.663	0.611	0.720	−9.746	.0000
Svestka et al, 1984[28]	1.286	0.541	3.056	0.569	.5694
	0.430	0.350	0.527	−8.074	.0000



Abbreviation: LAI = long-acting injectable.

Figure 3. Number of Hospitalizations

Study	Rate Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value
Beauclair et al, 2005[26]	0.103	0.044	0.239	−5.298	.0000
Arató and Erdós, 1979[32]	0.106	0.062	0.182	−8.140	.0000
Waldmann and Neumann, 1984[29]	0.201	0.137	0.296	−8.143	.0000
Denham and Adamson, 1971[39]	0.262	0.192	0.357	−8.437	.0000
Morritt, 1974[37]	0.283	0.165	0.485	−4.590	.0000
Malm, 1971[40]	0.294	0.179	0.484	−4.811	.0000
Devito et al, 1978[33]	0.355	0.239	0.528	−5.113	.0000
Polonowita and James, 1976[34]	0.414	0.269	0.639	−3.990	.0001
Chang et al, 2012[16]	0.430	0.318	0.580	−5.519	.0000
Carswell et al, 2010[21]	0.441	0.381	0.511	−10.983	.0000
Lindholm, 1975[35]	0.447	0.299	0.670	−3.899	.0001
Peng et al, 2011[20]	0.469	0.331	0.666	−4.232	.0000
Ren et al, 2011[19]	0.742	0.682	0.808	−6.898	.0000
Tan et al, 1981[31]	0.800	0.641	0.999	−1.968	.0491
Bourin et al, 1998[27]	1.333	1.125	1.579	3.326	.0009
	0.381	0.283	0.512	−6.397	.0000



Abbreviation: LAI = long-acting injectable.

studies (36%) collected data even after patients discontinued the LAI; that is, LAI dropouts were included in the analysis. Nevertheless, this distinction was ambiguous and was not clearly mentioned in some studies. Study characteristics are summarized in Table 1 (see Supplementary eTable 1 at PSYCHIATRIST.COM for more detailed information).

Primary Outcomes: Hospitalization Risk, Total Number of Hospitalizations

LAIs showed strong superiority over oral antipsychotics in preventing hospitalization (16 studies, N = 4,066; risk ratio = 0.43; 95% CI, 0.35–0.53; $P < .001$; heterogeneity: $\tau^2 = 0.117$, $I^2 = 87.6\%$, $Q = 121$, $df = 15$, $P < .001$). In fact, 14 of the 16 studies showed statistically significant superiority of LAIs over oral antipsychotics (Figure 2).

LAIs also showed strong superiority over oral antipsychotics in decreasing the number of hospitalizations (15 studies, 6,342 person-years; rate ratio = 0.38; 95% CI, 0.28–0.51; $P < .001$; heterogeneity: $\tau^2 = 0.301$, $I^2 = 95.0\%$, $Q = 280$, $df = 14$, $P < .001$). All studies except 1 showed significant superiority of LAIs over oral antipsychotics (Figure 3).

Secondary Outcomes: Hospitalization Days, Length of Stay

LAIs showed significant superiority in decreasing the days patients were hospitalized (7 studies; Hedges' $g = 0.77$; 95%

Table 2. Subgroup Analyses

Outcome	No. of Studies	Effect Size	95% CI	P^a	Heterogeneity τ^2	I^2	Q	df	P^a
Hospitalization risk		Risk Ratio							
FGA LAI = old studies (1999 or earlier)	8	0.40	0.30–0.54	**<.001**	0.13	76.1	29.3	7	**<.001**
Risperidone LAI	7	0.46	0.33–0.64	**<.001**	0.36	92.4	78.9	6	**<.001**
New studies (2000 or later)	8	0.46	0.34–0.62	**<.001**	0.12	91.2	80.0	7	**<.001**
Sample size > 100	7	0.49	0.39–0.63	**<.001**	0.093	92.3	77.9	6	**<.001**
Sample size ≤ 100	8	0.35	0.23–0.51	**<.001**	0.20	70.6	27.2	8	**<.001**
North American studies	5	0.43	0.30–0.62	**<.001**	0.13	86.8	30.3	4	**<.001**
Western European studies	6	0.42	0.31–0.56	**<.001**	0.081	68.1	15.7	5	**.008**
Industrial sponsorship	4	0.43	0.27–0.66	**<.001**	0.17	94.8	57.7	3	**<.001**
No industrial sponsorship	10	0.38	0.23–0.62	**<.001**	0.59	95.8	213.3	9	**<.001**
Including LAI dropouts	6	0.44	0.28–0.67	**<.001**	0.18	94.0	83.2	5	**<.001**
Excluding LAI dropouts	10	0.42	0.34–0.53	**<.001**	0.076	71.8	31.9	9	**<.001**
No. of hospitalizations		Rate Ratio							
FGA LAI = old studies (1999 or earlier)	10	0.36	0.22–0.61	**<.001**	0.66	96.8	216.1	9	**<.001**
Risperidone LAI	4	0.42	0.27–0.65	**<.001**	0.17	95.1	61.3	3	**<.001**
New studies (2000 or later)	5	0.43	0.29–0.63	**<.001**	0.15	93.7	63.8	4	**<.001**
Sample size > 100	6	0.50	0.36–0.68	**<.001**	0.37	93.8	80.8	5	**<.001**
Sample size ≤ 100	9	0.30	0.16–0.58	**<.001**	0.96	96.0	199.3	8	**<.001**
North American studies	4	0.38	0.21–0.68	**.001**	0.31	92.1	37.9	3	**<.001**
Western European studies	6	0.38	0.17–0.82	**.014**	0.92	96.9	159.4	5	**<.001**
Industrial sponsorship	6	0.46	0.32–0.64	**<.001**	0.14	93.4	75.2	5	**<.001**
No industrial sponsorship	9	0.42	0.31–0.56	**<.001**	0.13	77.7	35.9	8	**<.001**
Including LAI dropouts	5	0.42	0.29–0.63	**<.001**	0.16	93.5	61.3	4	**<.001**
Excluding LAI dropouts	10	0.36	0.22–0.60	**<.001**	0.62	95.9	217.9	9	**<.001**

[a]Boldface indicates statistical significance.
Abbreviations: FGA = first-generation antipsychotics, LAI = long-acting injectable.

CI, 0.22–1.33; $P = .0063$; heterogeneity: $\tau^2 = 0.527$, $I^2 = 97.9\%$, $Q = 289$, $df = 6$, $P < .0001$) (Supplementary eFigure 1). The length of the hospitalization was rarely reported. However, on the basis of only 2 studies, LAIs showed significant superiority in decreasing the duration of the hospitalization (Hedges' $g = 0.26$; 95% CI, 0.07–0.46; $P = .009$; heterogeneity: $\tau^2 = 0.014$, $I^2 = 65.5\%$, $Q = 2.9$, $df = 1$, $P = .089$) (Supplementary eFigure 2).

Subgroup Analyses

The superiority of LAIs over oral antipsychotics remained in all clinically relevant subpopulations and treatment groups: (1) medication group (FGA LAI vs risperidone LAI); (2) publication year (published before 2000 vs after 2000); (3) study sample size; (4) region (North America, western Europe); (5) pharmaceutical sponsorship; and (6) data acquisition design in LAI phase (Table 2).

Publication Bias

There was an indication that the effect size is larger in the smaller studies. For risk of hospitalization (Supplementary eFigure 3), Egger's regression test yielded a P value of .073. Similarly, for total number of hospitalizations (Supplementary eFigure 4), Egger's regression test yielded a P value of .0055. To address the possibility that the observed findings could be partly due to publication bias, we employed Duval and Tweedie's trim-and-fill method[15] to estimate the true effect based on observed studies plus (imputed) "missing" studies. When we employed this procedure, the overall conclusion remained the same. LAIs remained superior, even when we adjusted for the possibility that studies with smaller effects were not published (adjusted hospitalization risk: risk ratio = 0.52; 95% CI, 0.49–0.55; adjusted number of hospitalizations: rate ratio = 0.41; 95% CI, 0.30–0.54).

DISCUSSION

To the best of our knowledge, this is the first meta-analysis comparing LAIs versus oral antipsychotics based on mirror-image studies incorporating both FGA and SGA LAIs without language restriction. In our analysis, LAIs showed strong superiority over oral antipsychotics. Effect sizes for preventing hospitalization (risk ratio = 0.43) or decreasing the number of hospitalizations (rate ratio = 0.38) were very large. These results are in strong contrast with those from our recent meta-analysis[8] on RCTs, which did not find significant differences between LAIs and oral antipsychotics in preventing relapse, hospitalization, and other relapse-related outcomes.

Although pharmacokinetics can be different between LAIs and oral antipsychotics, pharmacologic characteristics of LAIs and oral antipsychotics are considered to be fundamentally the same. Therefore, it is fair to say that the superiority of LAIs is primarily conferred by assured medication delivery. It is well established that nonadherence is highly prevalent in the schizophrenia population.[3,4,41] Because of this, one would hope that LAIs prevent relapse better than oral antipsychotics. The likely reason why we did not see the benefit of using LAIs compared to oral antipsychotics in RCTs is that patients enrolled in RCTs tend to differ systematically from patients in naturalistic settings.[10] In RCTs, patients who are willing to listen to a lengthy explanation of the trial and give consent and who show up for appointments are likely to be recruited. Conversely, those who miss appointments and are less cooperative are likely to be excluded from the study

recruitment procedure. Thus, systematic differences include less severe impairments in adherence and cognitive function and less severe comorbidity patterns, as well as greater motivation for treatment, familial support, educational background, and clinical stability in samples enrolled into RCTs.[8] In short, patients in RCTs may not be representative of the patient group for whom clinicians would choose LAIs.

Moreover, it is very important to consider that participation itself in RCTs can alter the ecology of treatment delivery and experience. Such study participation effects include reminders, reimbursement, provision of transportation, and assessment of efficacy, safety, and even adherence. Patients are monitored much more frequently and closely in RCTs than in usual care settings, where the duration and frequency of visits can be as low as 15–30 minutes every 1–3 months with multiple medication refills being written in 1 brief medication management visit. Thus, patients in RCTs are likely to receive much more and different types of attention than patients in routine clinical practice, and all of these differences may work to the disadvantage of LAIs. By contrast, for a generalizable assessment of the comparative effectiveness of LAIs compared to oral antipsychotics, RCTs should be conducted in real-world settings employing real-world procedures and including patients with a recent history or a pattern of nonadherence and sufficient response to antipsychotic treatment. This is why in this meta-analysis we focused on mirror-image studies, which include populations that are more comparable to those receiving LAIs in usual clinical practice.[10] It is important to recognize that, in mirror-image studies, LAIs showed such strong superiority, given the lack of superiority in RCTs.

An interesting finding from the previous meta-analysis[8] of RCTs was that when older studies (exclusively consisting of FGA LAIs) and newer studies (predominantly consisting of SGA LAIs) were analyzed separately, LAIs were significantly superior to oral antipsychotics in older studies (or FGA LAI studies), whereas the difference was not significant in newer studies (or SGA LAI studies).[8] The possible reasons for this disparity include different comparators (old studies used FGA oral antipsychotics, whereas new studies used SGA oral antipsychotics, which may be better tolerated and prevent relapse better[42]), publication bias (old negative studies might not have been published), more stringent procedures in newer studies to participate in clinical trials (selecting more adherent patients), and change of relapse definition (new studies may be using lower thresholds for relapse, which can increase false-positive rates).[8] However, such differences were not found in this analysis based on mirror-image studies; LAI superiority was so strong that LAIs showed significant superiority over oral antipsychotics not only in the full population, but also in every subgroup. This included both FGA LAI and risperidone LAI, the only SGA LAI formulation with analyzable data, which were each superior to oral antipsychotics and with similar effect sizes. On the basis of these findings, one might ask why SGA LAIs are not being used more widely. The answer is beyond the scope of this article, but it might include relatively short injection intervals (for risperidone LAI), the risk of the postinjection delirium sedation syndrome (olanzapine LAI), higher cost, and a general bias against LAIs, including use as a last resort after many relapses and rehospitalizations instead of use for preventing relapses early in the illness course.

Although 23 (92.0%) of the 25 analyzed studies showed significant superiority of LAIs over oral antipsychotics, in 2 studies,[27,28] results were in the opposite direction. In 1 (6.7%) of 15 studies, the number of hospitalizations was significantly lower with oral antipsychotics ($P = .0009$).[27] In 1 (6.3%) of 16 studies, hospitalization risk was nonsignificantly lower with oral antipsychotics ($P = .57$).[28] However, both of these studies were very small (N = 48 and N = 34), raising questions about the representativeness of the sample and precision of the results. Moreover, while most studies included patients who were nonadherent, chronically unstable, or recently discharged, 1 of these 2 outlier studies[28] included only patients who were in remission, decreasing the chance of showing LAI superiority. Finally, the other study[27] actually reported that hospitalizations due to noncompliance decreased significantly with LAIs (79% to 33%, $P < .001$). However, hospitalizations due to life events (16.5% to 52%, $P < .001$) and therapeutic escape (4.1% to 13.5%, $P < .001$) increased even more with LAIs, resulting in an overall advantage of oral antipsychotics. This discrepancy shows that hospitalizations are multifactorial and that findings can be influenced by life events that may have no relationship to the prescribed medications, especially in small samples.

Notwithstanding these findings, it is also very important to understand the limitations of mirror-image studies.[9] First, because these mirror-image studies utilize the timing when the oral medication is switched to an LAI, expectation bias can have an impact on the main outcome, that is, hospitalization, for it is reasonable to believe that patients' poor response to oral antipsychotics led to the initiation of LAIs. Another specific expectation bias with the use of LAIs is that, because it is an LAI, the clinician and family know that the patient is still on medication. They might decline the opportunity to admit patients, even if there is symptom exacerbation, considering that they would not see a full-blown relapse. Conversely, it is also possible that clinicians would be more likely to admit a patient on LAI treatment who shows some worsening, since the worsening occurred despite known medication delivery. Moreover, it is important to consider the natural course of the illness, that is, regression to the mean. Patients are likely to return to their usual status after a while even if the medication remains unchanged. Using a control group continuing to receive the same oral medication could help resolve this problem. However, without randomization, such studies would contain biases regarding patient characteristics related to the decision of starting an LAI or continuing oral antipsychotic treatment. In addition, all of the studies that met inclusion criteria involved the switch from oral antipsychotics to LAIs. Very few studies reported the data when patients switched from LAI to oral antipsychotic, and none of those reports met inclusion criteria. To eliminate expectation bias,

it would have been ideal to have studies with data going in both directions.

Second, most of the studies extracted data only when patients were on the LAI; in other words, studies either included only patients who stayed on LAIs for a specified amount of time, or followed up patients until they stopped medication (or until study termination) and compared the results to the data when patients were on oral antipsychotics for the equivalent duration. This selection bias could have worked in favor of LAIs. However, at the same time, patients were able to change oral medication during the oral antipsychotic phase, whereas patients had no choice other than 1 LAI during the LAI phase in all studies. Moreover, when we analyzed only studies including LAI dropouts in a subgroup analysis, LAIs still showed significant superiority over oral antipsychotics.

Third, mirror-image studies can be biased by independent events, such as health policy change and reduction in bed numbers or insurance coverage. Nevertheless, there is no ideal approach to examine the efficacy of LAIs, and a mirror-image design most likely includes patients who are more reflective of populations who receive LAIs in clinical practice than RCTs.

Besides the biases of the mirror-image study design mentioned above, several other limitations should be taken into consideration. As our aim was to compare the effectiveness of LAIs with that of oral antipsychotics in preventing relapse, we used hospitalization as the proxy of relapse. This is an inherent difficulty in mirror-image studies, since they usually explore the data retrospectively, using large databases. Some studies used patients' charts, but even using such sources, which may contain more detailed information, hospitalization was the only outcome commonly found across studies. Furthermore, the threshold for hospitalization can vary, largely reflecting the medical system in specific countries or during the time of the study. However, no universal objective relapse definition has been established, and clinical trials have been applying their own definitions according to their aims or settings.[43] At the same time, most of the studies used hospitalization as one domain of relapse, and therefore we consider it to have been practical and reasonable to use hospitalization as a proxy for relapse. Another limitation is that patients' disease severity was not reported in many studies. As the inclusion criteria for the studies show, the patient populations included in the analyzed studies were chronically ill. However, it was impossible to know their level of stability, insight, severity of negative symptoms, and cognitive deficits, which of course might influence the effectiveness of LAIs. Furthermore, information on adverse effects that also impact on real-world effectiveness of LAIs and oral antipsychotics was missing. Thus, all of the above can limit the interpretation of the results in mirror-image studies. Nevertheless, the major limiting factor of RCTs is overcome, in that patients eligible for LAIs in clinical care are actually studied.

In summary, our large meta-analysis based on mirror-image studies comparing oral antipsychotics and LAI treatment phases showed strong superiority of LAIs over oral antipsychotics in preventing hospitalization. The results are in contrast with the recent meta-analysis of RCTs, which showed no superiority of LAIs. However, given the possible biases in mirror-image studies, such as expectation bias, natural course of the illness, and time effect, a cautious interpretation of these results is required. Nevertheless, the population in mirror-image studies better reflects the population receiving LAIs in clinical practice. In the future, large, simple RCTs may benefit from more closely replicating routine clinical circumstances. Two-way mirror-image studies (oral to LAI, LAI to oral) might be another option to examine the comparative effectiveness of LAIs to oral antipsychotics.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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Author contributions: **Dr Kishimoto** contributed to designing the study, literature search, quality assessment of studies, data extraction/entering, statistical analysis, and writing the report. **Mr Nitta** contributed to literature search, quality assessment of studies, data extraction/entering, and writing the report. **Dr Borenstein** contributed to designing the study, statistical analysis, and writing the report. **Dr Kane** contributed to designing the study and writing the report. **Dr Correll** contributed to designing the study, quality assessment of studies, statistical analysis, and writing the report.

Potential conflicts of interest: **Dr Kishimoto** has received consultant fees from Dainippon Sumitomo, Novartis, and Otsuka; speakers honoraria from Banyu, Eli Lilly, Dainippon Sumitomo, Janssen, Novartis, Otsuka, and Pfizer; and grant support from the Byoutaitaisyakenkyukai Fellowship (Fellowship of Astellas Foundation of Research on Metabolic Disorders) and Eli Lilly Fellowship for Clinical Psychopharmacology. **Mr Nitta** is an employee of Dainippon Sumitomo. **Dr Borenstein** is founder of Biostat, has received grants from National Institutes of Health and IES to develop software for meta-analysis, and has a commercial interest in the software Comprehensive Meta-Analysis. **Dr Kane** has been a consultant to Alkermes, Amgen, AstraZeneca, Janssen, Pfizer, Eli Lilly, Bristol-Myers Squibb, Dainippon Sumitomo/Sepracor/Sunovion, Johnson & Johnson, Otsuka, Pierre Fabre, Vanda, Proteus, Takeda, Targacept, IntraCellular Therapies, Merck, Lundbeck, Novartis, Roche, Rules Based Medicine, and Sunovion; has received honoraria for lectures from Otsuka, Eli Lilly, Esai, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck, and Janssen; is a shareholder of MedAvante; and has received grant support from the National Institute of Mental Health. **Dr Correll** has been a consultant and/or advisor to or has received honoraria from Actelion, Alexza, AstraZeneca, Biotis, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Desitin, Eli Lilly, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Ortho-McNeill/Janssen/J&J, MedAvante, Merck, Novartis, Otsuka, Pfizer, ProPhase, Roche, Sepracor/Sunovion, Takeda, Teva, and Vanda and has received grant support from the Feinstein Institute for Medical Research, National Institute of Mental Health, NARSAD, and Ortho-McNeil/Janssen/J&J.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Long-Acting Injectable Versus Oral Antipsychotics in Schizophrenia: A Systematic Review and Meta-Analysis of Mirror-Image Studies

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List of Supplementary Material for the article

1. eTable 1 Detailed Study Characteristics
2. eFigure 1 Hospitalization Days
3. eFigure 2 Length of Stay
4. eFigure 3 Funnel Plot for Hospitalization Risk
5. eFigure 4 Funnel Plot for Number of Hospitalizations

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Supplementary eTable 1. Detailed Study Characteristics

Study/ Country	n[a)]	Data Source	LAI phase	Follow up Duration OAP/LAI (months)	Inclusion Criteria	Reported Outcome	Mean±SD Age (years)	% Male	Chronicity Information	Medication	
										LAI (n)[b)] / OAP (n)[b)]	Mean±SD Dose (mg)
Chang et al. 2012/Taiwan	184	Medical claims data, nationwide	Retrospective, dropouts excluded	12/12	SCZ (ICD-9), started RLAI, followed ≥1Y before and after RLAI initiation, treated regularly with RLAI	# Hp # Outpatient visits # ER visit % Hp[c)] Hp days # relapse Cost	36-55[d)]	50.5	DOI ≥6Y in 77.2%	RLAI (184)	total 177/3M
										CLO (7) RIS (80) Other SGA (50) Oral FGA (91)	NR
Rosa et al. 2012/France, Kuwait, Portugal, Saudi Arabia	98	Multinational	Prospective, dropouts excluded	6/6	SCZ/SCZAD (DSM-IV), non-acute, previously treated with OLA (stable dose) and willing to switch to RLAI, not known as RIS non-responder	# experienced Hp # experienced Hp due to psychotic disease # experienced relapse Hp days Psychopathology Social functioning Safety measures	40.2±14.0[e)]	77.1[e)]	Mean DOI: 13.5Y[e)]	RLAI (79)[f)]	32.6±7.1/2W
										OLA (79)[f)]	16.2±5.6
Crivera et al. 2011/US	435	Multicenter	Prospective, dropouts included	12/12[g)]	SCZ(DSM-IV), appropriate for RLAI initiation	# Hp # psychiatric Hp # ER visit % psychiatric Hp	41.9±12.6	66.7	Mean±SD DOI: 17.6± 12.1Y[j)]	RLAI (435, 343[g)])	25/2W[h)]
										NR (435, 343[g)])	NR
Ren et al. 2011/US	924	VA, multicenter	Retrospective, dropouts included	12/12	SCZ (ICD-9), started RLAI, and had ≥4 RLAI injections	# psychiatric Hp % psychiatric Hp % ≥2 psychiatric Hp Hp days Length of stay	51±11	94	NR	RLAI (924)	38.9±13.0/2W
										NR (924)	NR
Peng et al. 2011/US	147	Commercial claims data, multicenter	Retrospective, dropouts included	6/6	SCZ (ICD-9), started any depot, but without depot injection in the 6M before baseline, ≥2 outpatient visits or ≥1 Hp within 180 days	# Hp % Hp % psychiatric Hp % Hp for SCZ Hp days Psychiatric Hp days Hp days for SCZ	42.6±14.7	53.7	NR	RLAI (38) HAL (69) FPZ (40)	NR
										NR (147)	NR
Carswell et al. 2010/New Zealand	443	Multicenter (5 centers)	Retrospective, dropouts included	12/12	SCZ (DSM-IV), non-adherent to OAP (or preferred RLAI), intensive treatment in the year prior to switching to RLAI	# Hp Hp days Days of compulsory treatment order Cost	35.9±12.4	64.3	Mean±SD DOI: 11.7± 9.9Y	RLAI (427[i)])	41.5/2W[j)]
										NR (427[i)])	NR

Study/ Country	n[a)]	Data Source	LAI phase	Follow up Duration OAP/LAI (month)	Inclusion Criteria	Reported Outcome	Mean±SD Age (y.o.)	% Male	Chronicity Information	Medication	
										LAI (n)[b)] / OAP (n)[b)]	Mean±SD Dose (mg)
Girardi et al. 2010/Italy	88	Multicenter	Prospective, no dropouts during the 6M phase	6/6 (24)[k)]	SCZ/SCZAD (DSM-IV), with clinically inadequate response to ≥2 oral APs within 3M, BPRS-T≥65	% Hp Response rate Psychopathology Safety	41.2±10.6	64.8	Mean±SD DOI: 18±5.0Y Mean±SD # of Hp: 8.26±2.79	RLAI (88)	47.4±10.1/2W
										OLA (29) CLO (26) QUE (21) HAL (13) ARI (9) RIS (2)	NR
Su et al. 2009[l)]/Taiwan	108	Medical claims data, nationwide	Retrospective, dropouts excluded	12/12	SCZ (ICD-9), regularly treated with RLAI for ≥1Y, ≥1Y data in pre-RLAI periods, had <90D hospital stay	# Hp # ER visit HP days # relapse	42.0±10.4	50	NR	RLAI (108)	175.4±54.5/3M
										RIS (17) Other SGA (41) FGA (27) FGA+RIS (10) FGA+other SGA (5) None (8)	NR
Lam et al. 2009[m)]/15 countries [n)]	2300	Multinational	Prospective, dropouts included	12/12	SCZ who participated in RLAI clinical trials	% Hp All cause discontinuation Psychopathology	38.4[o)]	NR	Mean DOI: 10.3Y[o)]	RLAI (1748[o)])	NR
										OAP (1748[o)])	NR
Fuller et al. 2009/US	106	VA (Ohio), multicenter (5 centers)	Retrospective,dropout included	10.2± 6.4/10.2±6.4 (mean±SD)	SCZ/SCZAD (ICD-9) at any time of the study period (1/2003-1/2006), with continuous enrolment throughout the study period, ≥4 injections of RLAI	# psychiatric Hp [p)] % psychiatric Hp [p)] % ≥2 psychiatric Hp Psychiatric Hp days Psychiatric Hp days/month # psychiatric-related outpatient visits Compliance Cost	51.9±10.2	93	NR	RLAI (106)	35.5/2W (end)
										ARI (7) OLA (19) QUE (30) RIS (57) ZIP (8)	26.3±4.9 15.1±7.1 423.5±275.5 3.8±1.9 107.7±45.1
Beauclair et al.[p)] 2005/Canada	63	Multicenter	Retrospective,dropout included	39.4/ 40.3	SCZ who participated in RLAI clinical trials	# Hp % Hp % experienced ≥2 Hp Hp days All cause discontinuation Concomitant anticholinergic/anxiolytic/sedative	NR	NR	NR	RLAI (63)	NR
										NR (63)	NR
Bourin et al. 1998/France	48	Single center	Retrospective, dropouts excluded	62.4±33.6/69.6±38.4 (mean±SD)	SCZ (ICD-10), hospitalized	# Hp Hp days	NR	50	NR	FGA (44)[q)]	NR
										OAP (48)	NR

Study/ Country	n[a)]	Data Source	LAI phase	Follow up Duration OAP/LAI (months)	Inclusion Criteria	Reported Outcome	Mean±SD Age (years)	% Male	Chronicity Information	Medication	
										LAI (n)[b)] OAP (n)[b)]	Mean±SD Dose (mg)
Svestka et al. 1984/Czech	34	Single center	Prospective, dropouts included	10.3/10.3	SCZ, in remission	% Hp	37.4	23.5	Mean DOI: 9.2Y # Hps in lifetime (range): 1-12	clopenthixol decanoate (34)	169.5/3.7W
										NR	NR
Waldmann et al. 1984/Germany	65	Single center	Retrospective, dropouts excluded	31.2/31.2	SCZ/SCZAD, outpatients and patients in day hospital who were receiving FPZ decanoate	# Hp	NR	27.7	Duration of treatment: 1-9Y	FPZ (65)	17.7/3W
										NR (65)	NR
Michel et al. 1981/Chile	112	Single center	Retrospective, dropouts excluded	12-17/12-17 (range)	SCZ, on depot when study was conducted	Hp days	25-44 [r)]	67.9	NR	FPZ	NR
										NR	NR
Tan et al. 1981/Singapore	127	Multicenter (6 centers)	Retrospective, dropouts excluded	24/24	SCZ, duration of illness ≤8Y, ≥24M treatment before and after the institution of FPZ depot	# Hp Hp days Compliance	32.5±8.8	61.4	6-8[s)]	FPZ (127)	25/M[t)]
										NR (127)	NR
Arato 1979/Hungary	51	Single center	Retrospective,dropouts excluded	44/26	SCZ/SCZAD, ≥1Y on depot, ≥2 Hp in the past	# Hp Number of patients who experienced Hp	34	100	Mean DOI: 7.2Y	Mixed FGA	FPZ (12.5-25 mg/4W)[u)], flupenthixol 20mg/3W)[u)]
										NR	NR
Devito et al. 1978/USA	122[v)]	Single center	Retrospective, dropouts excluded	12/12	SCZ spectrum disorders, treated in the same inpatient program and referred for outpatient treatment in the FPZ program	# Hp % Hp Length of stay # Hp per patient	18-39[w)]	50.8	NR	FPZ (61[v)])	37.5mg/3-4W
										NR (61[v)])	NR
Polonowita and James 1976/New Zealand	43	Single center	Retrospective, dropouts included	13/13	SCZ (ICD-8), started FPZ depot.	# Hp Hp days	NR	67.4	NR	FPZ decanoate (43)	NR
										NR (43)	NR
Lindholm 1975/Sweden	24	Multicenter (2 centers)	Retrospective, dropouts excluded	26.9/26.9	SCZ, administered perphenazine enanthate for >1Y	# Hp % Hp Hp days Concomitant antiparkinson medication	44.9	25.0	Mean DOI: 6.8Y	perphenazine enanthate (24)	107 mg
										NR (24)	NR

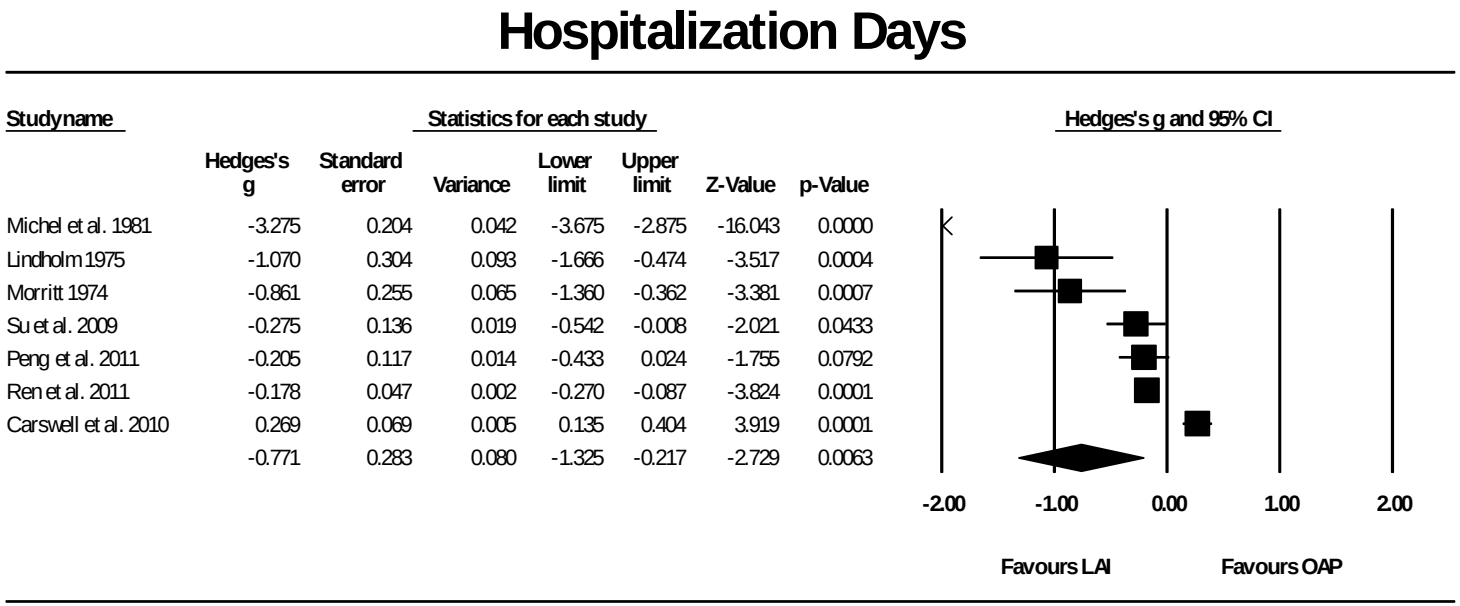
Study/ Country	n[a)]	Data Source	LAI phase	Follow up Duration OAP/LAI (months)	Inclusion Criteria	Reported Outcome	Mean±SD Age (years)	% Male	Chronicity Information	Medication	
										LAI (n)[b)] OAP (n)[b)]	Mean±SD Dose (mg)
Gottfries and Green 1974/Sweden	58	Single center	Retrospective, dropouts excluded	NR[x)]	SCZ, discharged, treated with flupenthixol decanoate during observational period	# relapse requiring Hp % Hp Hp days Length of stay All cause discontinuation	NR	NR	Patients started LAI during Hp and later were transferred to ambulant treatment.	flupenthixol decanoate (58)	40/2W as a general rule, range (20mg-60mg)
										NR (58)	NR
Morritt 1974/UK	33	Single center	Retrospective, dropouts excluded	12/12	SCZ, administered FPZ decanoate and with1 year record pre/post FPZ depot	# Hp % Hp Hp days	NR	42.4	NR	FPZ decanoate (33)	NR
										NR (33)	NR
Johnson and Freeman 1972/UK	126[y)]	Single center	Retrospective, dropouts excluded	12/12[y)]	SCZ, administered FPZ depot and withfollow-up record of 1 or 2Y[y)]	% Hp Hp Days	NR	NR	NR	FPZ enanthate or decanoate (126[y)])	12.5/5W – 25/10D
										NR (126[y)])	NR
Denham and Adamson 1971/UK	103	Single center	Retrospective, dropouts excluded	24.8/24.8 (mean)	SCZ, receiving FPZ depot, ≥12M follow-up record after injection, with completely documented previous history	# Hp % Hp Hp days # Hp due to specific reasons Hp days due to specific reasons	38.5	55.3	Chronic	FPZ (103)	FPZ enanthate (6.25-50 mg/2W) or decanoate (12.5-37.5 mg/2W)
										NR (103)	NR
Malm 1971/Denmark	44	Single center	Retrospective, dropouts excluded	36/36	SCZ, chronic, known to have difficulty with adherence to AP oral medication	# Hp Hp days	NR	100	Chronic	FGA mix (44)	NR
										NR (44)	NR

a) Original study sample size
b) Number of patients analyzed
c) Obtained directly from author
d) Majority (60.3%) were between 36-55 years old
e) Based on patients who received at least 4 doses of RLAI (n=96)
f) Patients who received efficacy assessments and completed 6M of treatment were included in analysis.
g) Analysis for hospitalization risk was conducted on subpopulation who received >2 RLAI injections with 12M observation.
h) Majority (73.8%) started with a dose of 25mg/2W
i) Patients who were transferred to other health services, died, or spent more than 12 months as an inpatient were excluded from the analysis.
j) Dose at 12M
k) Analyzed pre- vs. post-LAI phase (6M each), but study had 18M extension follow up phase.
l) Only hospital days was used for the analysis due to the patient overlap with Chang et al.
m) Unpublished data
n) Australia, Belgium, Brazil, Canada, Czech, Denmark, Greece, Korea, Mexico, Netherland, Norway, Russia, Slovakia, Spain and Sweden

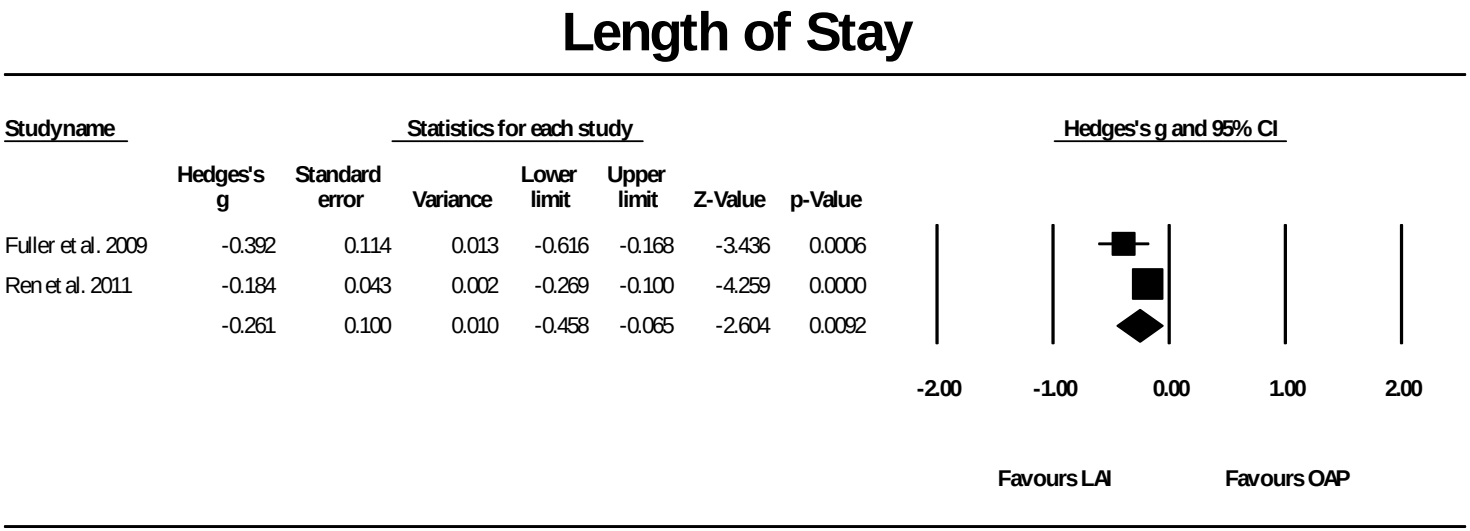
o) Analyzed 1748 patients who were taking oral atypical antipsychotics before RLAI
p) Not analyzed due to potential overlap with Ren et al.
q) 44 patients were analyzed in LAI phase.
r) Majority (65.2%) were between 25-44 years old.
s) Illness durations was 6-8Y for the majority (65.3%) of patients
t) Dose for majority of the patients (96.1%)
u) Doses for majority of the patients
v) Majority (57.4%) were between 18-39 years old.
w) Half of the participants were assessed in a mirror-image setting.
x) Mean±SD observation period for 36 patients who had relapse(s) was 43.2(10.8) months.
y) Patients with 1 year of follow up period were analyzed in this meta-analysis.

Abbreviations: AP=antipsychotic, ARI=aripiprazole, BPRS-T=brief psychiatric rating scale, CLO=clozapine, D=days, DOI=duration of illness, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders - fourth edition, ER=emergency room, FGA=first generation antipsychotic, FPZ=fluphenazine, HAL=haloperidol, Hp=hospital, hospitalization, ICD=International Classification of Diseases, LAI=long acting injectable, M=months, NR=not reported, OAP=oral antipsychotic, OLA=planzapine, QUE=quetiapine, RIS=risperidone, RLAI=risperidone long acting injection, SCZ=schizophrenia, SCZAD=schizoaffective disorder, SGA=second generation antipsychotic, VA=Veterans Affairs, W=week, Y=year, ZIP=ziprasidone

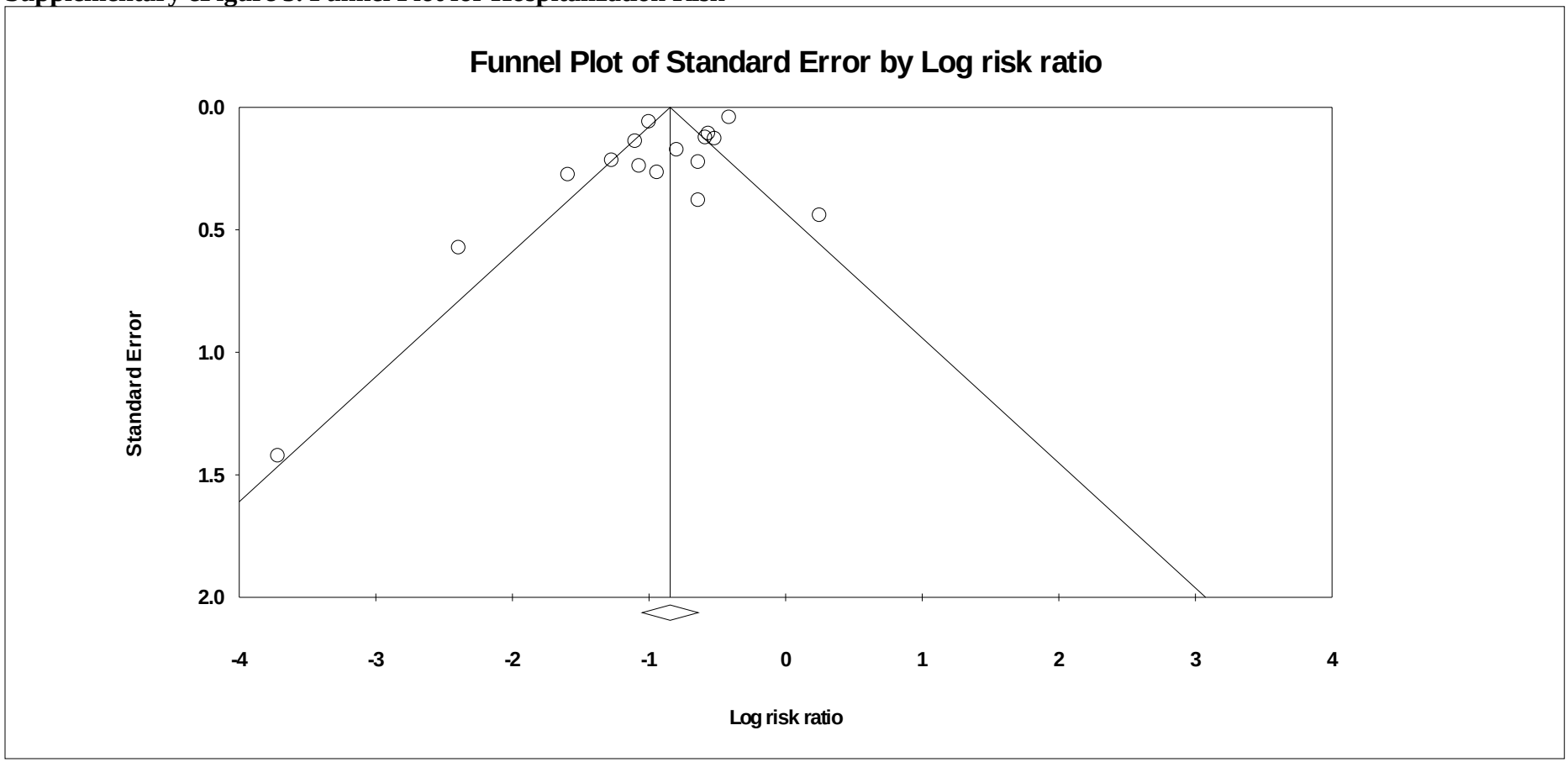
Supplementary eFigure 1. Hospitalization Days



Suppelmentary eFigure 2. Length of Stay



Supplementary eFigure 3. Funnel Plot for Hospitalization Risk



Supplementary eFigure 4. Funnel Plot for Number of Hospitalization