

# Effectiveness of Long-Acting Injectable vs Oral Antipsychotics in Patients With Schizophrenia: A Meta-analysis of Prospective and Retrospective Cohort Studies

Taishiro Kishimoto<sup>1-4,9</sup>, Katsuhiko Hagi<sup>2,5,9</sup>, Masahiro Nitta<sup>2,5</sup>, Stefan Leucht<sup>6</sup>, Mark Olfson<sup>7</sup>, John M. Kane<sup>2-4,8</sup>, and Christoph U. Correll<sup>\*,2-4,8</sup>

<sup>1</sup>Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan; <sup>2</sup>Department of Psychiatry, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY; <sup>3</sup>Department of Psychiatry and Molecular Medicine, Hofstra Northwell School of Medicine, Hempstead, NY; <sup>4</sup>Center of Psychiatric Neuroscience, The Feinstein Institute for Medical Research, Manhasset, NY; <sup>5</sup>Sumitomo Dainippon Pharma Co., Ltd., Medical Affairs, Tokyo, Japan; <sup>6</sup>Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar der Technischen Universität München, München, Germany; <sup>7</sup>New York State Psychiatric Institute/Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, NY; <sup>8</sup>Department of Psychiatry and Behavioral Medicine, Albert Einstein College of Medicine, Bronx, NY

<sup>9</sup>These two authors contributed equally to this article.

\*To whom correspondence should be addressed; The Zucker Hillside Hospital, 75-59 263rd Street, Glen Oaks, NY 11004, US; tel: 718-470-4812, fax: 718-343-1659, e-mail: [ccorrell@northwell.edu](mailto:ccorrell@northwell.edu)

Compared with oral antipsychotics (OAPs), long-acting injectable antipsychotics (LAIs) should improve medication adherence and reduce relapses in schizophrenia. However, meta-analyses of randomized trials and mirror-image studies yielded inconsistent results. Nonrandomized cohort studies with parallel comparisons of LAIs and OAPs offer a third design to examine this issue. We meta-analyzed cohort studies with  $\geq 24$  weeks duration and hospitalization data. Primary outcome was hospitalization rate, ie, number of hospitalizations per person-year. Secondary outcomes included hospitalization risk, ie, proportion of patients experiencing  $\geq 1$  hospitalizations, all-cause discontinuation, and total hospitalization days. Patient severity and/or chronicity at baseline was also meta-analyzed and explored as a potential effect size moderator. Altogether, 42 studies ( $n = 101\ 624$ ; follow-up =  $18.6 \pm 10.0$  mo) were meta-analyzed. LAIs were superior to OAPs regarding hospitalization rate (studies = 15, person-years = 68 009, rate ratio = 0.85, 95% CI = 0.78–0.93,  $P < .001$ ) and all-cause discontinuations (studies = 10,  $n = 37\ 293$ , risk ratio = 0.78, 95% CI = 0.67–0.91,  $P = .001$ ), but not regarding hospitalization risk (studies = 33,  $n = 51\ 733$ , risk ratio = 0.92, 95% CI = 0.84–1.00,  $P = .06$ ), and hospitalization days (studies = 11,  $n = 21\ 328$ , Hedges'  $g = -0.05$ , 95% CI =  $-0.16$  to  $0.06$ ,  $P = .39$ ). Illness severity/chronicity was significantly greater in patients prescribed LAIs vs OAPs when all available information was pooled together (studies = 23,  $n = 61\ 806$ , Hedges'  $g = 0.15$ , 95% CI = 0.03–0.26,  $P = .01$ ), but not when examined separately. In summary, this meta-analysis of cohort studies, which included patients that are

broadly representative of clinical practice, indicates that LAIs are superior to OAPs. The lack of significant superiority of LAIs for hospitalization risk and hospital days needs to be interpreted in the context of naturalistic treatment selection with subsequently greater illness severity/chronicity in LAI-treated patients.

*Key words:* maintenance therapy/hospitalization/depot/psychosis/treatment discontinuation/moderators

## Introduction

Because psychopathology and social functioning can worsen with repeated psychotic episodes in patients with schizophrenia,<sup>1,2</sup> relapse prevention is a critical goal. There is strong evidence of antipsychotic efficacy for relapse prevention in chronic and first-episode patients.<sup>3,4</sup> Relapse risk is 2–6 times higher without antipsychotics.<sup>3-6</sup> However, because non-adherence, which occurs in up to 50% of patients, limits the clinical efficacy of pharmacotherapy,<sup>7,8</sup> long-acting injectable antipsychotics (LAIs) are an important option.<sup>9</sup> LAIs are often recommended for individuals with known or expected non-adherence to oral antipsychotics (OAPs).

There are inconsistencies in the literature comparing the effectiveness of LAIs and OAPs for schizophrenia. Several large randomized controlled trials (RCTs) have not shown significant superiority of LAIs over OAPs.<sup>10-13</sup> However, significant advantages were identified in a few studies that targeted populations with early stage

illness<sup>14,15</sup> or a special population that required not only relapse prevention, but also reduction in risk of criminal justice involvement.<sup>16</sup> A recent meta-analysis of RCTs did not find a significant difference between LAIs and OAPs in preventing relapse or hospitalization or in secondary outcomes related to relapse.<sup>17</sup> However, RCTs might enroll a disproportionate number of patients with better treatment adherence and lower illness severity.<sup>18</sup> In addition, participation in clinical trials can alter the ecology of treatment delivery and experience. For example, patients may receive appointment reminders, reimbursements, free medication, and adherence assessments.<sup>18</sup> Therefore, the standard RCT might not be the best strategy to examine the effectiveness of LAIs compared to OAPs.<sup>19</sup> Conversely, a subsequent meta-analysis of mirror-image studies, in which hospitalization risk/rate during a period of OAP treatment was compared with a subsequent period of LAI treatment in the same patients, demonstrated significant superiority of LAIs over OAPs.<sup>20</sup> Effect sizes were large for preventing hospitalization (risk ratio = 0.43) and decreasing the number of hospitalizations (rate ratio = 0.38). However, mirror image studies are vulnerable to critical methodological limitations including expectation bias and regression to the mean.<sup>18</sup>

Given inconsistent results and different biases inherent in RCTs and mirror image studies, nonrandomized, but parallel comparison cohort studies of LAIs and OAPs are a third design to explore the comparative effectiveness of LAIs and OAPs. We, therefore, conducted a meta-analysis of cohort studies that provided information about hospitalization or relapse-related data.

## Methods

The meta-analysis followed MOOSE guidelines for reporting meta-analyses of observational studies.<sup>21</sup>

### Study Selection

We selected cohort studies with hospitalization of LAIs and OAPs in adults with schizophrenia and related disorders. Cohort studies, by definition involve a design where samples are followed prospectively (though some cohort studies examine data retrospectively) and subsequent status/outcome evaluations are conducted to determine differences between a priori defined groupings. In our case, we collected studies that followed patients who initiated LAIs or OAPs and provided hospitalization data. We included both prospective and retrospective cohort studies. The former refers to studies in which 2 groups were started and followed prospectively, while the latter refers to studies in which the investigator collected data from past records, but the 2 cohorts were assessed longitudinally in a parallel manner from the point of cohort inception.

### Data Sources

We conducted a search without language restrictions, using MEDLINE/PubMed, Cochrane library, PsycINFO, and CINAHL from database inception (last search: December 3, 2016), for cohort studies of patients with schizophrenia and related disorders with a prospective observation period of  $\geq 24$  weeks. We also searched for unpublished studies, such as 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, monohydrate. Hand searches of reference lists of relevant publications were also conducted. When multiple reports referred to the same study or overlapping patient populations (eg, nationwide cohort studies with different publication years, but overlapping study year[s]), we included the newer or more extensive report.

### Data Extraction

Data were extracted independently by  $\geq 2$  reviewers (T.K., K.H., M.N., C.U.C.) experienced in conducting literature searches and data extraction. Authors and companies were contacted to provide missing information and unpublished data. Disagreements were resolved by consensus. Foreign language papers were translated by bilingual speakers, and data extraction was double checked by at least 2 investigator (T.K., K.H., M.N.) using Google Translate (<http://translate.google.com/>).

Primary outcome was set as hospitalization rate. Secondary outcomes included hospitalization risk, all-cause discontinuation and total hospitalization days. We also compared severity and/or chronicity of the patients on LAIs vs OAPs, as in cohort studies, it was expected that as compared to patients on OAPs, patients on LAIs are likely to be have more severe or persistent conditions.

### Data Synthesis

All data were double-entered into and meta-analyzed with Comprehensive Meta-Analysis Version 3 (BioStat) using a random effects model, as heterogeneity among studies was expected.<sup>22</sup> For categorical variables, we computed rate ratio and/or risk ratio, with their 95% CIs, as the effect size, with values  $< 1$  indicating superiority of LAIs and values  $> 1$  indicating superiority of OAPs. Hospitalization rate was computed as the number of hospitalizations divided by person-years at risk. The rate ratios were calculated as the ratio of rates for LAIs vs OAPs. Hospitalization risk was computed as the number of patients who had  $\geq 1$  hospitalization divided by the number of patients at risk. The risk ratio was then calculated as the ratio of risk for LAIs vs OAPs. Numbers-needed-to-treat (NNTs) with 95% CIs

were calculated for categorical outcomes by dividing 1 by the risk difference.

Reporting of hospitalization-related outcomes differed widely and rate ratio was calculated as described below. Some studies reported the mean number of hospitalizations during the study period. In such cases, we calculated the number of hospitalizations by multiplying the mean number of hospitalizations and the number of patients. Similarly, we calculated patient-year by multiplying the duration of the study and the patients' number. Some studies stopped the follow-up when patients had their first hospitalization with information of the length of time from baseline to hospitalization. In such cases, we counted the number of hospitalization and added up the follow-up length. Regarding risk ratio, there was no standardization of the observation time. For example, when a study reported only the proportion of patients who had  $\geq 1$  hospitalization during the study period, without reporting when the relapse occurred, we were only able to calculate risk ratio. In cases where we could extract both rate and risk, we used the data for rate ratio and risk ratio outcomes. To derive the effect size of patients' illness severity/chronicity, we meta-analytically compared relevant clinical characteristics of patients on LAIs and OAPs. These included prior number of hospitalizations, prior hospitalization days, illness duration, and proportion of hospitalized patients in the last year. These parameters were examined separately and pooled. When reporting the pooled comparative severity/chronicity parameters, we used the variable reported by the most studies following the hierarchical order of frequency described above to avoid study overlaps and to reduce heterogeneity. For continuous variables related to prior hospitalization and illness duration at study entry, we computed Hedges'  $g$  with 95% CIs as the effect size, with values  $< 0$  indicating superiority of LAIs or indicating that LAI patients were less severely/chronically ill, and with values  $> 0$  indicating inferiority of LAIs or that LAI patients were more severely/chronically ill. Heterogeneity was only inspected when there were  $\geq 2$  studies in an analysis. With regard to the heterogeneity,  $\tau^2$ ,  $I^2$ ,  $Q$ , and  $P$  values are reported.<sup>23</sup>

We also conducted subgroup analyses in order to identify potential methodological biases or subpopulations in which primary outcome differed. Subgroup analyses were based on (1) country, (2) region (North-America, Western Europe, Asia or others), (3) publication year (published before 2000, from 2000 to 2009, 2010 or later), (4) pharmaceutical sponsorship, (5) data source (single institution, multiple institutions, large database studies, including nationwide registration and insurance databases), (6) LAI medication group (FGA, SGA, mix), (7) OAP medication group (FGA, SGA, mixed), (8) informed consent (Obtained/Not obtained), (9) study design (prospective vs retrospective), (10) statistical adjustment of differences in baseline patient characteristics (Yes/No), (11) study sample size ( $N = < 100$ , 100–499, 500–999,  $\geq 1000$ ), (12) clozapine

patients (Included/Not included), (13) analysis method (intention to treat (ITT) vs observed cases (OC)), (14) study quality score; Newcastle-Ottawa scale<sup>24</sup> (high [score  $\geq 8$ ] vs low [score  $< 8$ ]), (15) same medication allocation (FGA-LAI vs FGA-OAP, SGA-LAI vs SGA-OAP), and (16) follow-up duration (median split, ie,  $> 12$  mo vs  $\leq 12$  mo).

The Newcastle-Ottawa quality scale captures representativeness of the exposed cohort; selection of the unexposed cohort; ascertainment of exposure; outcome of interest not present at start of study; control for important factor/additional factor; assessment of outcome; follow-up long enough for outcomes to occur; and adequacy of follow-up.

Egger's regression test<sup>25</sup> followed by Duval and Tweedie's trim and fill method<sup>26</sup> were used to assess publication bias. In this large, exploratory set of analyses, no adjustments were made to the  $P$ -values for the multiple comparisons; therefore, the  $P$  values should be interpreted with caution.

## Results

### *Search and Study Characteristics*

The literature search yielded 9498 citations. We identified 42 cohort studies with 101 624 participants diagnosed with schizophrenia followed for  $\geq 6$  months (supplementary figure 1). Study, patient, illness and treatment characteristics are summarized in table 1 (for additional details, see supplementary table 1).<sup>27–68</sup> Altogether, 27 studies had a retrospective database design ( $n = 70\ 165$ ) and 15 studies were prospective ( $n = 31\ 459$ ). The number of patients per study ranged from 50 to 14 610 (median = 522), and the mean study duration was  $18.6 \pm 10.0$  (range = 6–48, median = 12) months (duration:  $\leq 1$  y = 23 studies,  $\geq 2$  y = 15 studies). There were 14 studies with FGA LAIs (33.3%); 9 with mixed FGA and SGA LAIs (21.4%); 10 with risperidone LAI (23.8%); 6 with paliperidone LAI (14.3%); 1 with haloperidol LAI (2.4%); and 1 with risperidone and paliperidone LAIs (2.4%). There were 29 studies with FGA and SGA OAPs, (70.7%); 6 with any SGA OAP (12.2%); 3 with risperidone OAP (7.3%); 1 with any FGA OAP (2.4%); 1 with clozapine (2.4%); and 1 with haloperidol OAP (2.4%). The search yielded 15 studies that reported number of hospitalizations and 33 reported hospitalization risk. Six studies reported both outcomes (supplementary figure 1).

### *Primary Outcome: Hospitalization Rate*

Pooled together, the hospitalization rate was significantly lower with LAIs compared to with OAPs (studies = 15, person-years = 68 009, rate ratio = 0.85, 95% CI = 0.78–0.93,  $P < .001$ ; NNT = 6, 95% CI = 4–17, based on 11 studies with raw rate information). Significant heterogeneity

**Table 1.** Study, Patient, Illness and Treatment Characteristics

Study/Country	n <sup>a</sup>	Design/Data Source	F/U Duration (M)	Inclusion Criteria	Mean Age (SD) (y.o.)	Information Regarding Severity/Chronicity	Medication	
							LAI (n) <sup>b</sup>	OAP (n) <sup>b</sup>
Babiker, <sup>27</sup> '87/ Canada	1235	Retro/MHSB and SPDP	24	SCZ Pts (ICD-9) who were discharged, not affective disorder.	Total 41.1 (15.8)	First admission 30.4%, Maintenance Therapy 69.6%	FGA LAI (368) FGA (508)	(26)
Barrio et al <sup>28</sup> '13/ Spain	52	Retro /Single center	24	Recent-onset SCZ (<2Y) who started RLAI, continued the medication and were followed up for ≥2Y (LAI group). Consecutively selected SCZ, matched by age and sex who started OAP after their first psychotic episode, were followed up for ≥2Y with appropriate adherence.	RLAI 26.9 (6.7) Any OAP 27.4 (7.5)	NR	(26) <sup>c</sup>	
Baser et al <sup>29</sup> '15/ United States	670	Retro/Multi center	12	Aged ≥18 and <65 on the index date; Continuous health plan enrollment for 24M prior to the index date (baseline period) and for 12M after the index date; At least one pharmacy claim for an OAP or LAI in the baseline period; No LAI use between the first 2 claims for the index therapy, no claims for PP in the 24M baseline period. Individuals in the OAP cohort were also required to have no claims for their index OAP product for 6M prior to the index date and no claims for PP in the 12M follow-up period.	PP 51.3 (9.9) OAP 51.2 (10.3)	Prior # Hp: 2.1 (3.3) Prior # Hp days: 30.7 (56.2)	(335)	
Bellido et al <sup>30</sup> '08/ Spain	60	Pro/Single center	12	OP of SCZ or SCZAD (ICD-10 and DSM-IV), no Hp in the previous 6M, no other mental disease	Total 34.5 (8.9)	DOI ≥15Y for 68.3% of pts, Prior # Hp <5 for 76.7% of pts	Any LAI (35) Any OAP (25)	
Bitter et al <sup>31</sup> '13/ Hungary	9567	Retro /NHIF	12	SCZ (ICD-10), started a new AP monotherapy, no prescription of the same medication within the previous 6 M, no other AP prescription after 30 days from inclusion.	RLAI 45.6 OAP 48.2	NR	(1095) RIS (2480), OLA (1633), QUE (1587), AMI (920), CLO (790), ARI (601), ZIP (461)	
Calabresi and Marchetti <sup>32</sup> '83/ Italy	56	Retro /Single center	12	Chronic OP with SCZ on long term treatment, not first episode patients, not borderline personality disorder	FLU LAI 39.0 Any OAP 37.5	Chronic patients	(18)	
Chan et al <sup>33</sup> '15/ Taiwan	379	Retro /Single center	12	At least 18 years of age, recruited at the same regional hospital, E-Da Hospital, Schizophrenia (DSM IV-TR)	RLAI 33.8 OAP 39.4	# of Hps in the last year 29/43 # of Hps in the last year 108/336	(43)	

Table 1. Continued

Study/Country	n <sup>a</sup>	Design/Data Source	F/U Duration (M)	Inclusion Criteria	Mean Age (SD) (y.o.)	Information Regarding Severity/Chronicity	Medication
Chue et al <sup>34</sup> '05/ Canada	137	Retro /Multi center	NR	SCZ who initiated on RLAI or a new oral atypical AP	RLAI 45.3 OAP 39.1	NR	LAI (n) <sup>b</sup> OAP (n) <sup>b</sup> (63) RIS (36), OLA (31), QUE (5), Other OAP (2) RIS (79), ZUC (7), FLU (6)
Ciudad et al <sup>35</sup> '12/ Spain	597	Pro / Multi center	12	OP, SCZ (DSM-IV) who required any modification in the treatment based on the risk of non-adherence, not already on LAI medication	Total 40.1 (11.1)	DOI years (SD): 15.2 (10.0) Onset of disease: 24.9 years old Prior # Hp ≤ 4 for 58.3%	OAP (505) FLU (59), HAL (59) RIS (149), OLA (103), CLO (41)
Conley et al <sup>36</sup> '03/ United States	411	Pro / Multi center	12	SCZ(DSM-IV), started AP and discharged on the same medication	FLU 39.9 (9.4), HAL 35.1 (8.9) RIS 38.0 (14.5), OLA 39.7 (13.7), CLO 36.9 (9.4) FGA LAI 49 (12)	Prior # Hp: 1.0 (1.2) Prior # Hp: 1.3 (1.6)	OAP (505) FLU (59), HAL (59) RIS (149), OLA (103), CLO (41)
Conlon et al <sup>37</sup> '02/ Ireland	69	Pro / Multi center	24	SCZ(DSM-IV) who had been using the same FGA depot for ≥ 3M prior to the study.	RIS 51 (11)	DOI years: 24 (8.0), >10 years of depot use: 59% DOI years: 24 (9.5), >10 years of depot use: 76%	(36) (33)
Grimaldi-Bensouda et al <sup>38</sup> '12/ France	1859 <sup>d</sup>	Pro / Multi center	12	SCZ (DSM-IV), ambulatory or hospitalized for <92 consecutive days.	RLAI 36.7 (10.7) Non-RLAI 38.6 (11.2) Total 41.4	Prior # Hp days: 60.8 Prior # Hp days: 45.2	(489) (1370) <sup>d</sup>
Gutwinski et al <sup>39</sup> '07/ Germany	233	Retro/Multi center	36	Aged ≥16 and <81 on the index date; SCZ pts were identified at the time of rehospitalization, and duration of relapse free interval was determined.		NR	FGA (77) SGA (156)
Haro et al <sup>40</sup> '07/ International	7728	Pro/Multi center	36	SCZ who were initiating or changing AP (as monotherapy), who presented within the normal course of OP care	FGA LAI 42.1 (12.2) OAP 39.7	DOI years: 12.3 (10.4), % of first treatment: 6.0 DOI years: 10.6 (10.8), % of first treatment: 12.4	(348) OLA (4247), RIS (1549), QUE (583), CLO (274), AMI (256), FGA (471) (47) FGA (17), SGA (59) NR
Hoiberg and Nielsen <sup>41</sup> '06/ Norway	123	Retro /Single center	12	SCZ (ICD-10)	FGA LAI 41.6 OAP 38.2	Prior # Hp: 16.3 Prior # Hp: 8.1	FGA (17), SGA (59) NR
Huang et al <sup>42</sup> '13/ Taiwan	14 610	Pro/Taiwan NHRI	12	SCZ or SCZAD (ICD-9-CM code 295). Pts admitted frequently were retrieved for analysis. Frequent admission was defined as Hp for SCZ treatment at least twice in an acute psychiatric ward within 2 consecutive years.	Total 38.4 (12.8)	NR	NR

Table 1. Continued

Study/Country	n <sup>a</sup>	Design/Data Source	F/U Duration (M)	Inclusion Criteria	Mean Age (SD) (y.o.)	Information Regarding Severity/Chronicity	Medication	
							LAI (n) <sup>b</sup>	OAP (n) <sup>b</sup>
Ibach and Schreiner <sup>43</sup> '08/ NR	230	Pro/Multi center	12	Recently diagnosed SCZ (ICD-10), presence of symptomatology for ≥1Y and <5Y	RLAI 34.4 OAP 34.3	DOI years: 2.8 (1.8) DOI years: 2.4 (1.5)	(113) ARI (25), OLA (20), QUE (21), ZIP (19), RIS (18), AMI (14) (810)	
Ju et al <sup>44</sup> '14/ Taiwan	1755	Retro /PIMC	12	Pts who joined the psychiatric home care program within 60 days after hospital discharge between 2004 and 2009 were initially included in this study.	Any LAI 41.1 (10.1) Any OAP 41.8 (12.1)	NR	(945)	
Kelin et al <sup>45</sup> '11/ International	406	Pro/Multi center	12	OP, SCZ (DSM-IV) who had ≥2 clinical worsening requiring Hp or increased level of care in 24M before study, at risk of nonadherence, required a switch of their primary OAP, not treatment resistant	LAI 35.8 (12.1)	Prior # Hp: 1.1 (1.2)	HAL (8), ZUC (5), PIP (5), Other FGA (3), RLAI (22)	
Kim et al <sup>46</sup> '08/ South Korea	50	Pro/Single center	24	AP-naïve OP with first-episode SCZ or SCZAD (DSM-IV), stable for ≥4W before the baseline in an OP setting.	RLAI 32.5 (10.6) RIS 31.0 (10.1)	DOI years: 1.5 (1.5), Stable for ≥4W DOI years: 2.2 (3.1), Stable for ≥4W	HAL (10), TRI (10), Other FGA (18), OLA (93), AMI (55), RIS (48), ARI (47), Other SGA (82) (22)	
Lafeuille et al <sup>47</sup> '13/ United States	3828	Retro /PREMIER	30	Adult SCZ, who received OAP during Hp and who received OAP or LAI at the time of second Hp (relapse).	LAI 42.1 Any OAP 42.4	Prior # Hp days: 16.3 (19.4) Prior # Hp days: 16.0 (22.3)	RLAI or PP (1032) (2796)	
Liu et al <sup>48</sup> '15/ Taiwan	92	Retro /Single center	36	Pts who also have not previously received more than 3 consecutive LAI doses, and who continued to receive OAP medications throughout index admission.	LAI 37.8 (10.5)	Prior # Hp: 3.0 (1.9)	RLAI (15), Flupentixol decanoate (20) FLU (12) (45)	
Marchiaro et al <sup>49</sup> '05/ Italy	60	Retro /Single center	24	OP with SCZ who completed 2Y treatment on OAP or LAI.	OAP 37.4 (12.4) LAI 40.7 (8.57)	Prior # Hp: 3.5 (2.6) Prior # Hp: 6.63 (3.76) DOI years: 15.8 (9.16)	HAL (14), FLU (10), ZUC (6)	
Marcus et al <sup>50</sup> '15/ United States	3768	Retro/Medicade	6	OPs with SCZ who were aged ≥18 years, who had no use of CLO prior to Hp, and who had received an OAP or LAI within 30 days of hospital discharge.	OAP 39.4 (10.79) LAI 37.5 (13.8)	Prior # Hp: 6.50 (5.39) DOI years: 15.9 (9.48) Prior # Hp days: 12.8 (12.0)	RIS (13), OLA (12), QUE (5) FLU (45), HAL (112), RIS (81), PAL (102) (3428)	

Table 1. Continued

Study/Country	n <sup>a</sup>	Design/Data Source	F/U Duration (M)	Inclusion Criteria	Mean Age (SD) (y.o.)	Information Regarding Severity/Chronicity	Medication	
							LAI (n) <sup>b</sup>	OAP (n) <sup>b</sup>
Moore et al <sup>51</sup> '98/ United States	118	Retro/Multi center	24	All pts discharged with prescription of depot HAL, depot FLU or oral RIS.	NR	NR	FLU (29), HAL (14) RIS (75)	
Offord et al <sup>52</sup> '13 United States	3669	Retro/Multi center	12	Pts with Dx of ICD-9-CM code 295.X, who initiated LAI or OAP and had ≥ 12M continuous medical and prescription drug coverage prior to and after the initiation. Pts commercially insured or Medicare insured.	LAI 48.6 (18.2)  OAP 43.1 (20.2)	Prior # Hp: 0.97 (1.17), Prior # Hp days: 12.1 (17.3) Prior # Hp: 0.35 (0.62), Prior # Hp days: 3.21 (6.52)	FLU, HAL or RIS (541)  RIS, OLA, QUE, ARI, PAL, CLO, HAL, PER, or FLU (3128)	
Olivares et al <sup>53</sup> '09/ Spain	1622	Pro/Multi center	24	Pts who initiated treatment with or changed AP to RLAI or OAP.	RLAI 38.4 (11.2) OAP 37.0 (10.8)	DOI years: 12.6 (9.5) DOI years: 10.9 (9.7)	(1345) (277)	
Pesa et al <sup>54</sup> '15/ United States	5183	Retro/Medicade	12	Pts newly started on PP or OAP as of the index date. Pts were required to have continuous enrollment 6M before and 12M after the index date, be at least 18 y.o. at index date	LAI 38.8 (12.3)  OAP 41.6 (12.9)	# of Hps in the last year LAI: 363/984 # of Hps in the last year OAP: 1796/4199	PP (984)  OAP (4199)	
Pinto et al <sup>55</sup> '00/ Portugal	183	Retro/Single center	36	At least 2 Y of illness admitted to the Hp	FGA LAI 37.5 (11.6) OAP 38.5 (11.4) FGA LAI 36.5	DOI years > 2Y	(98)	
Remington and Khranov <sup>56</sup> '01/ Canada	66	Retro/Single center	18	SCZ (DSM-IV) stabilized for 3-6M on one of the followings: an oral or depot FGA, CLO or RIS, then maintained on the same treatment for ≥18M	OAP 32.4  Total 38.2 (11.1)	Prior # Hp: 11.1 (9.3), DOI years: 13.7 (8.1) Prior # Hp: 7.0 (8.9), DOI years: 9.7 (8.1) Prior # Hp: 2.7 (2.2), DOI of 57.2% was > 10 years	FGA (18) <sup>f</sup> , CLO (15), RIS (15) SGA (723), FGA (109)	
San et al <sup>57</sup> '13/ Spain	1646	Pro/Multi center	12	All consecutive SCZ or SCZAD (DSM-IV) admitted to and discharged from short-stay or acute-care psychiatric units. DOI ≥2Y. Having medical history data for the previous 3Y.		Pts were admitted to and discharged from short-stay or acute-care psychiatric units.	FGA (45), SGA (567)	
Schreiner et al <sup>58</sup> '14/ International	1084	Pro/Multi center	12	≥18 y.o. with a diagnosis of SCZ for whom ≥ 6M of retrospective clinical records Eligible Pts were required to have newly initiated or switched to RLAI or an OAP within 2W prior to study enrollment.	RLAI 42.5 (12.9) OAP 41.9 (13.3)	DOI years: 11.5 (10.2) DOI years: 11.0 (10.4)	(561) OAP total (522); RIS (126) PAL (94), ARI (84), QUE (59), OLA (54), ZIP (31), FGA (28)	

Table 1. Continued

Study/Country	n <sup>a</sup>	Design/Data Source	F/U Duration (M)	Inclusion Criteria	Mean Age (SD) (y.o.)	Information Regarding Severity/Chronicity	Medication	
							LAI (n) <sup>b</sup>	OAP (n) <sup>b</sup>
Tavcar et al <sup>69</sup> '00/ Slovenia	447	Pro/Single center	12	SCZ or SCZAD (ICD-10) discharged with AP	FGA LAI 38.6 (10.8)	Prior # Hp: 5.7 (5.6) DOI years: 10.4 (9.0) % first time Hp: 19.6 % previously receiving LAI: 70.8	(332)	
Tiihonen et al <sup>60</sup> '11/ Finland	2588	Pro/FNHDR	24	All Finnish SCZ (ICD-10) who had their first Hp and had not collected AP within 6M before Hp	OAP FGA 40.1 (15.1) OAP SGA 40.6 (13.0)	Prior # Hp: 6.6 (6.5) DOI years: 11.7 (10.2) % first time Hp: 21.6 % previously receiving LAI: 19.2	FGA (82), SGA (43)	
Valevski et al <sup>61</sup> '12/ Israel	720	Retro/Single center	12	SCZ admitted consecutively, not readmitted ≤5 days following discharge, not treated with a combination of FGA and SGA	LAI 31.3 (11.9)	Prior # Hp: 2.4 (4.3) DOI years: 7.3 (9.1)	RLAI (119) <sup>§</sup> , PER (109) <sup>§</sup> , ZUC (52) <sup>§</sup> , HAL (18) <sup>§</sup> , OLA (904) <sup>§</sup> , RIS (581) <sup>§</sup> , CLO (412) <sup>§</sup> , QUE (217) <sup>§</sup> , PER (63) <sup>§</sup> , HAL (13) <sup>§</sup> , ZUC (12) <sup>§</sup> , OtherOAP (82) <sup>§</sup> , PolyPharm (321) <sup>§</sup>	
Varner et al <sup>62</sup> '01/ United States	153	Retro/Single center	48	Acutely hospitalized psychotic pts (primarily with SCZ) who received depot or oral HAL prior to discharge	Total 35.9 (10.8)	Acutely hospitalized Prior # Hp: 3.0 (2.7)	FLU (118), HAL (87) ZUC (87), Other FGA (1) CLO (74)	
Voss et al <sup>63</sup> '15/ United States	218	Retro/Medicade	12	SCZ pts (ICD-9) switching from RLAI to PP or oral AP medication.	LAI 40.4 (13) OAP 42.2 (13)	Acutely hospitalized LAI Prior # Hp: 2.63 OAP Prior # Hp: 2.69	HAL (95)	
Werneck et al <sup>64</sup> '11/ Brazil	242	Retro/Single center	36	SCZ (ICD-10) discharged from the participating Hp	LAI 45 (12)  OAP 38	Prior # Hp: 3.4 (4.8) Prior # Hp days: 55 (46) DOI years: 20.0 (8.0) Prior # Hp: 2.3 (2.7) Prior # Hp days: 46 (37) DOI years: 16.6 (9.12)	HAL (16), PIP (3), ZUC (1)	
Xiao et al <sup>65</sup> '15/ United States	13 126	Retro/Medicade	Mean F/U LAI: 10.1 OAP: 10.9 2009.	Adult Pts with a SCZ diagnosis, who received PP or OAP since July 1, 2009.	PP 40.3 (12.7) OAP 45.3 (13.6)	NR	RIS (63), CLO (59), HAL (41), OLA (26), ZIP (13), AMI (10), TRI (6), CPZ (2), ARI (1), PEN (1) PP (952) OAP (12 174)	



Table 1. Continued

Study/Country	n <sup>a</sup>	Design/Data Source	F/U Duration (M)	Inclusion Criteria	Mean Age (SD) (y.o.)	Information Regarding Severity/Chronicity	Medication
							LAI (n) <sup>b</sup>
Xiao et al <sup>66</sup> '16/ United States	11 654	Retro/Medicade	12	Adult Pts (age ≥18years old) with a SCZAD diagnosis, who received PP or OAP since January 1, 2010.	PP 42.6 (31.8) OAP 43.0 (9.7)	Prior # Hp: 2.1 (9.1) Prior # Hp:1.9 (2.6)	PP (5589) OAP (6065)
Young-Xu et al <sup>67</sup> '16/ US	10 290	Retrospective/VHA	12	Adult Pts (age ≥18years old) who had at least 2 SCZ diagnoses during the observation period and at least 2 dispensings of PP or OAA within 90 days between January 1, 2010, and October 31, 2014.	PP 53.4 (17.2)	PP Prior # Hp: 2.2 (2.6)	PP (5052)
NCT 01894984 <sup>68</sup> China	640	Pro/NR	6	Total course of disease no more than 5Y. According to physician's discretion, participants need to be changed to RLAI and other atypical anti-psychotic drug	OAP 53.0 (9.8) RLAI 27.4 (9.44) OAP 32.2 (11.6)	OAP Prior # Hp: 2.2 (1.7) NR	OAP (5238) (396) (243)
<p>Region: North America (studies = 15, n = 54 526), Western Europe (studies = 13, n = 9148), Asia (studies = 6, n = 17 526), ROTW (studies = 4, n = 10 976), International (studies = 3, n = 9218), NR (study = 1, n = 230).</p> <p>Study Design: RETROSP (studies = 27, n = 70 165), PROSP (studies = 15, n = 31 459).</p> <p>Data source: Multi center (studies = 15, n = 20 479), Single center (studies = 14, n = 2683), Large database (studies = 12, n = 77 822), NR (studies = 1, n = 640).</p> <p>F/U duration: Mean = 18.6 ± 10.0M (range6-48), ≤1Y = 24studies, ≥2Y = 15studies, Patient-Years = 115 141.</p> <p>Mean age: 39.5 ± 5.2 y.o. The number of patients per study: Median=522 (range 50–14 610).</p> <p>LAI: Any FGA (studies = 14), FGA and SGA mixed (studies = 9), Risperidone (studies = 10), Paliperidone (study = 6), Haloperidol (study = 1), Risperidone and Paliperidone (study = 1), Unclear (study = 1).</p> <p>OAP: FGA and SGA mixed (studies = 29), Any SGA (studies = 6), Risperidone (studies = 3), Any FGA (studies = 1), Clozapine (study = 1), Haloperidol (study = 1), Unclear (study = 1).</p>							

Note: AMI, amisulpride; AP, antipsychotic; ARI, aripiprazole; CLO, clozapine; CPZ, chlorpromazine; DOI, duration of illness; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders – fourth edition; FGA, first generation antipsychotic; FLU, fluphenazine; FNHDR, the Finnish National Hospital Discharge Register; F/U, follow-up; HAL, haloperidol; Hp, hospital, hospitalization; ICD, International Classification of Diseases; LAI, long acting injectable; M, months; MHSB, the Mental Health Services Branch; NHIF, the National Health Insurance Fund; NHRI, National Health Research Institutes; NR, not reported; OAP, oral antipsychotic; OLA, olanzapine; OP, outpatient; PAL, paliperidone; PANSS, the Positive and Negative Syndrome Scale; PEN, penfluridol; PER, perphenazine; PIMC, Psychiatric Inpatient Medical Claims Data; PIP, piperazine; PP, paliperidone palmitate; PREMIER, the Premier Perspective Comparative Hospital Database; Pro, prospective cohort study; Pt, patient; QUE, quetiapine; RET, retrospective cohort study; RIS, risperidone; RLAI, risperidone long acting injection; ROTW, rest of the world; SCZ, schizophrenia; SCZPD, schizophreniform disorder; SPDP, the Saskatchewan Prescription Drug Plan; SCZAD, schizoaffective disorder; SGA, second generation antipsychotic; SUL, sulpiride; TRI, trifluoperazine; VHA, the Veterans Health Administration; W, weeks; Y, year; y.o., years old; ZIP, ziprasidone; ZUC, zuclopentixol; ZOT, zotepine.

<sup>a</sup>Original study sample size.

<sup>b</sup>Number of patients analyzed.

<sup>c</sup>Antipsychotics at baseline in the oral group included OLA 12, RIS 11, AMI 1, ARI 1, and QUE 1. At endpoint, antipsychotics in the oral group included OLA 2, RIS 6, CLO 11, ZIP 1, ARI 4, and PAL 2.

<sup>d</sup>Number of patients in original study was shown. Subpopulation was used for the analysis.

<sup>e</sup>Fluphenazine decanoate 4; flupenthixol decanoate 7; haloperidol decanoate 4; piperazine palmitate 3.

<sup>f</sup>Trifluoperazine 8, pimozide 4, loxapine 3, methotrimeprazine 1; perphenazine 1; thioridazine 1.

<sup>g</sup>Person-years.

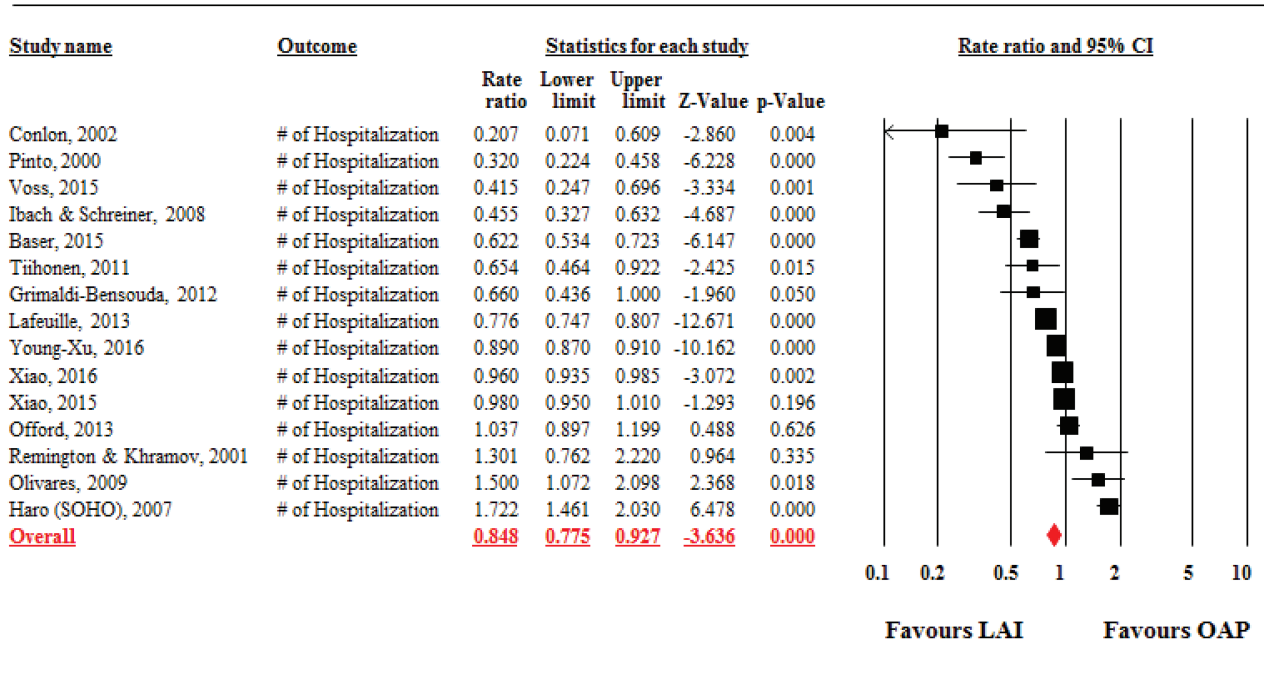


Fig. 1. Hospitalization Rate. Note: LAI, long-acting injectable antipsychotic; OAP, oral antipsychotic.

was observed across studies ( $\tau^2 = 0.02$ ,  $I^2 = 94.9\%$ ,  $Q = 272.6$ ,  $df = 14$ ,  $P < .001$ ; figure 1).

Secondary Outcomes: Hospitalization Risk, All-Cause Discontinuation, and Hospitalization Days

The hospitalization risk with LAIs was not superior to OAPs (studies = 33,  $n = 51\ 733$ , risk ratio = 0.92, 95% CI = 0.84–1.00,  $P = .06$ ). The risk ratio varied significantly across studies ( $\tau^2 = 0.03$ ,  $I^2 = 84.6\%$ ,  $Q = 207.4$ ,  $df = 32$ ,  $P < .001$ ; figure 2).

LAIs were associated with significantly lower risk of all-cause discontinuation than OAPs (studies = 10,  $n = 37\ 293$ , risk ratio = 0.78, 95% CI = 0.67–0.91,  $P = .001$ ; heterogeneity,  $\tau^2 = 0.04$ ,  $I^2 = 93.0\%$ ,  $Q = 128.6$ ,  $df = 9$ ,  $P < .001$ , NNT = 10, 95% CI = 6–25) (figure 3). LAIs did not separate from OAPs regarding number of hospitalization days (studies = 11,  $n = 21\ 328$ , Hedges’  $g = -0.05$ , 95% CI = -0.16 to 0.06,  $P = .39$ ; heterogeneity,  $\tau^2 = 0.02$ ,  $I^2 = 84.8\%$ ,  $Q = 65.9$ ,  $df = 10$ ,  $P < .001$ ; supplementary figure 2).

Subgroup Analyses

Superiority of LAIs over OAPs regarding hospitalization rate was confirmed in approximately half (24/50) of the subpopulations and treatment groups (supplementary table 2). Subgroups in which LAIs demonstrated significantly lower hospitalization rates than OAPs included study publication year  $\geq 2010$  ( $P < .001$ ), academic sponsorship ( $P = .021$ ), large database studies ( $P < .001$ ), and

no need for informed consent ( $P < .001$ ). Significant superiority of LAIs was also demonstrated in studies using retrospective databases ( $P < .001$ ), statistical adjustment for differences in baseline patient characteristics ( $P < .001$ ), intent-to-treat analyses ( $P < .001$ ), higher study quality score ( $P < .001$ ), and follow-up duration of 6–12 months ( $P < .001$ ). Regarding the LAI class, SGA-LAIs were statistically superior to OAPs (studies = 9,  $n = 47\ 114$ , rate ratio = 0.83, 95% CI = 0.76–0.90,  $P < .001$ ; heterogeneity,  $\tau^2 = 0.01$ ,  $I^2 = 95.2\%$ ,  $Q = 166.5$ ,  $df = 8$ ,  $P < .001$ ), although this was not observed for FGA-LAIs ( $P = .43$ ) and mixed LAI subgroups ( $P = .47$ ).

Patient Illness Severity/Chronicity

When comparing reported clinical characteristics between LAIs and OAPs regarding each severity/chronicity information, illness duration was longer in LAI-treated patients (studies = 11,  $n = 12\ 146$ , Hedge’s  $g = 0.10$ , 95% CI = 0.00–0.20,  $P = .046$ ; heterogeneity,  $\tau^2 = 0.010$ ,  $I^2 = 48.2\%$ ,  $Q = 19.3$ ,  $df = 10$ ,  $P = .036$ ), whereas LAIs groups had no significant difference in proportions of patients who had past hospitalization, in baseline hospitalization days and in prior number of hospitalization (studies = 3,  $n = 15\ 129$ , Hedge’s  $g = 0.37$ , 95% CI = -0.15 to 0.90,  $P = .164$ ; heterogeneity,  $\tau^2 = 0.202$ ,  $I^2 = 98.7\%$ ,  $Q = 148.5$ ,  $df = 2$ ,  $P < .001$ , studies = 7,  $n = 13\ 045$ , Hedge’s  $g = 0.20$ , 95% CI = -0.17 to 0.57,  $P = .282$ ; heterogeneity,  $\tau^2 = 0.235$ ,  $I^2 = 98.2\%$ ,  $Q = 329.7$ ,  $df = 6$ ,  $P < .001$ , and studies = 13,  $n = 28\ 529$ , Hedge’s  $g = 0.11$ , 95% CI = -0.05 to 0.28,  $P = .18$ ;

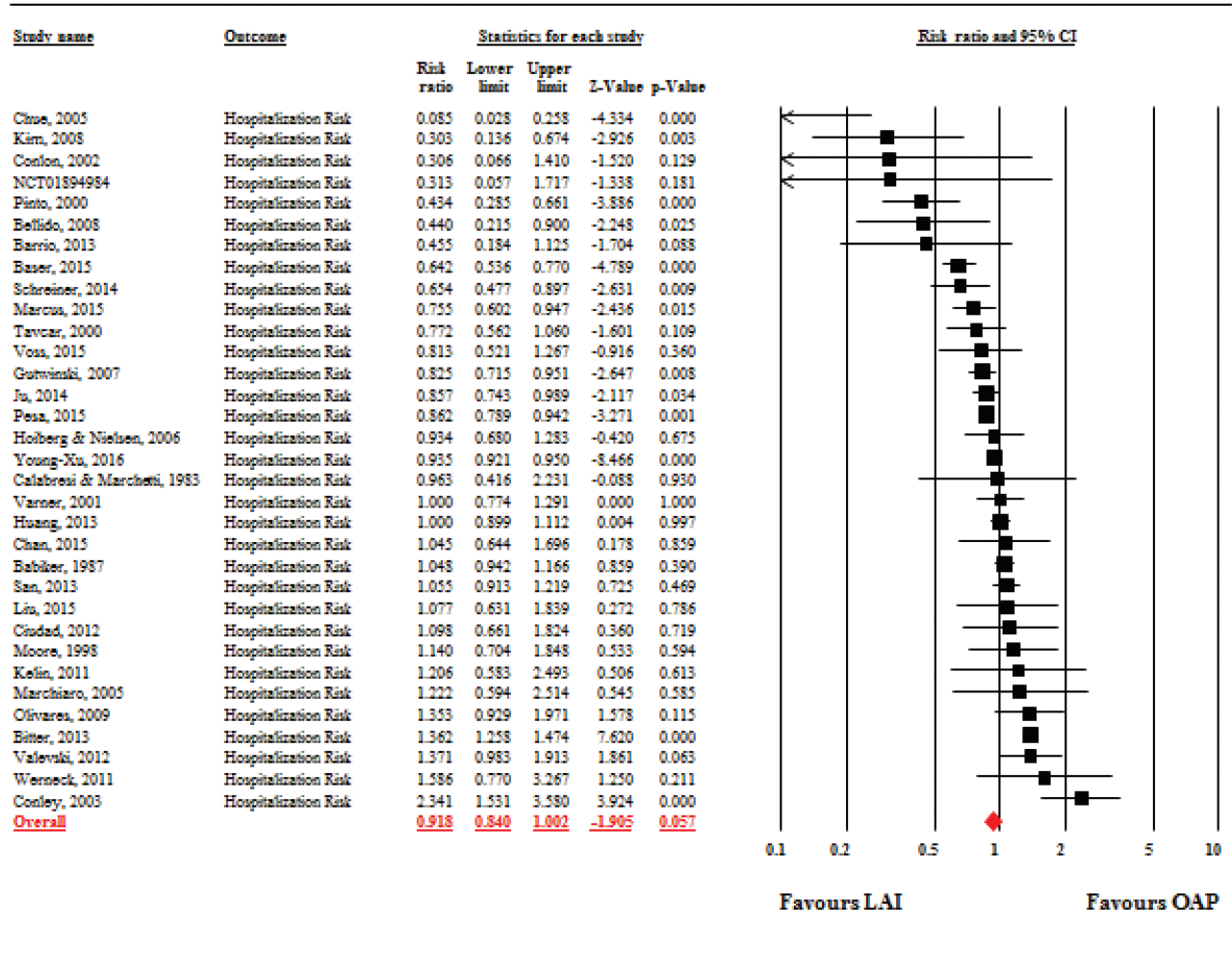


Fig. 2. Hospitalization Risk. Note: LAI, long-acting injectable antipsychotic; OAP, oral antipsychotic.

heterogeneity,  $\tau^2 = 0.072$ ,  $I^2 = 96.1\%$ ,  $Q = 306.0$ ,  $df = 12$ ,  $P < .001$ , respectively). When synthesizing these illness severity/chronicity information, patients receiving LAIs were more severely/chronically ill than patients receiving OAPs (studies = 23,  $n = 61\ 806$ , Hedges'  $g = 0.15$ , 95% CI = 0.03–0.26,  $P = .01$ ; heterogeneity,  $\tau^2 = 0.062$ ,  $I^2 = 95.8\%$ ,  $Q = 524.5$ ,  $df = 22$ ,  $P < .001$ ; figure 4).

#### Publication Bias

The funnel-plot to assess publication bias was asymmetrical (supplementary figure 3). Subsequently, we conducted the trim-and-fill method to adjust for potential publication biases. Imputing missing studies did not change the result (original rate ratio = 0.85, 95% CI = 0.78–0.93 vs adjusted rate ratio = 0.91, 95% CI = 0.83–0.99).

#### Discussion

We report a comprehensive meta-analysis of parallel group nonrandomized cohort studies comparing LAIs and OAPs for the treatment of schizophrenia. Previously

Kirson et al<sup>19</sup> conducted a similar meta-analysis of 13 studies examining the effects of study design on comparative effectiveness of LAIs only based on RCTs and cohort studies published after 2000. Because that prior analysis treated hospitalization, all-cause discontinuation, and relapse as one outcome and allowed data overlap, we believe that our analysis of 42 studies is both more inclusive and methodologically rigorous. Based on our results, LAIs were superior to OAPs in decreasing the hospitalization rate, in other words, number of hospitalizations per unit time. Moreover, patients on LAIs were less likely to discontinue treatment. Superiority of LAIs over OAPs was not observed in some of the secondary outcomes including risk of hospitalization risk (although trend-level significance was observed) and number of hospital days. However, it was noteworthy that as compared with patients on OAPs those on LAIs had clinical characteristics consistent with greater severity and chronicity.

We selected hospitalization rate as the primary outcome because unlike hospitalization risk, the rate adjusts for duration of follow-up. Because patients on LAIs were less likely to discontinue treatment than their

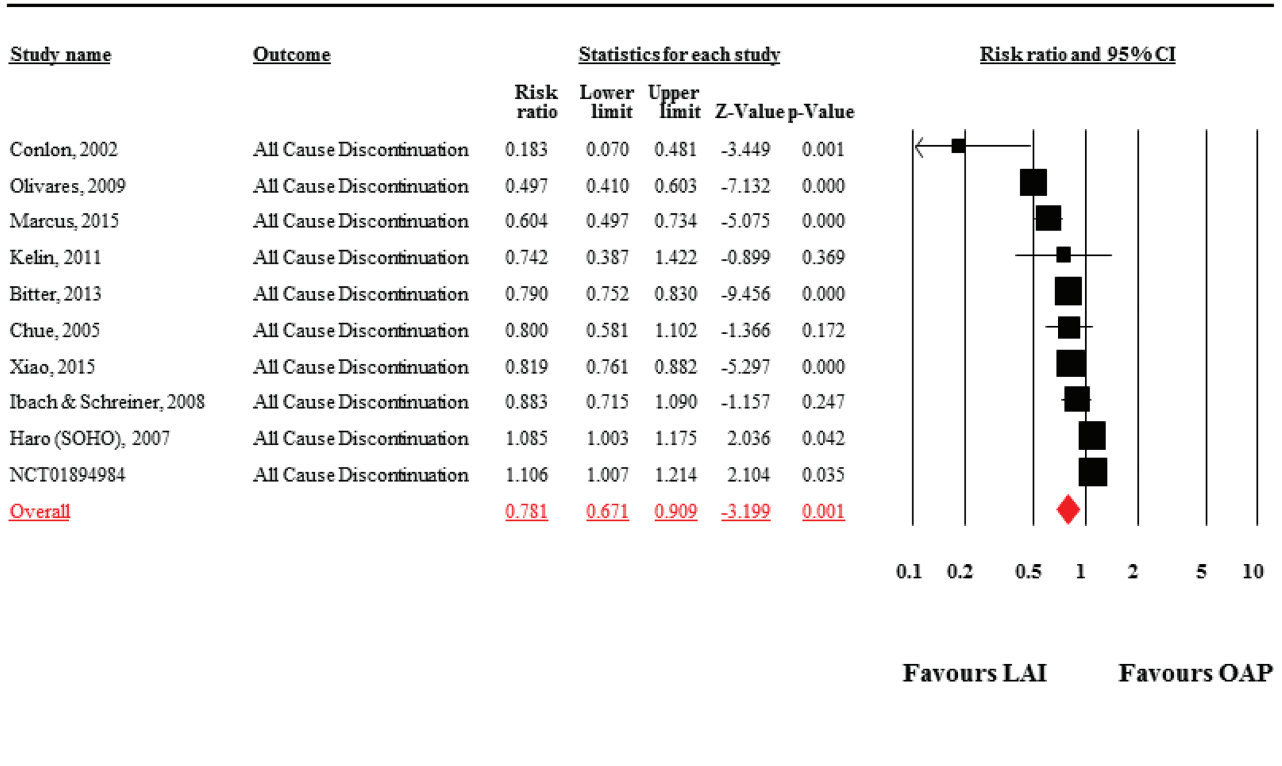


Fig. 3. All-cause discontinuation. Note: LAI, long-acting injectable antipsychotic; OAP, oral antipsychotic.

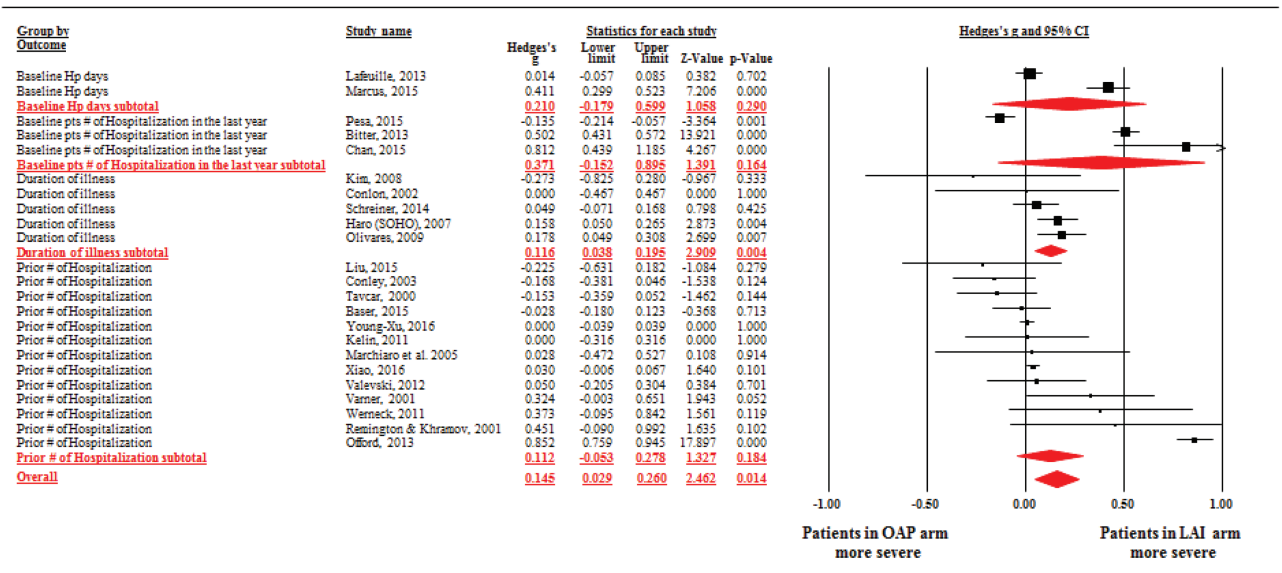


Fig. 4. Patient severity/chronicity—oral antipsychotic groups vs long-acting injectable groups. Note: LAI, long-acting injectable antipsychotic; OAP, oral antipsychotic.

counterparts on OAPs they were likely to be observed for a longer time. Failing to control for follow-up time could therefore have biased results in favor of OAPs. Moreover, unlike risk ratios, rate ratios do not have ceiling effects. As compared to risk ratios, therefore, rate ratios more precisely represent the differential treatment effects.

Given the advantage of LAIs over OAPs regarding hospitalization rate, it appears that LAIs are comparatively more effective in patients at risk for multiple hospitalizations.<sup>69</sup> However, we did not find a significant difference between LAIs and OAPs regarding the number of inpatient days. This finding is noteworthy, because the number

of inpatient days made an important contribution to overall treatment costs days. However, as discussed further below, since patients on LAIs seemed more severely ill, having similar numbers of inpatient days as the OAP patients may represent a positive outcome for LAIs.

Cohort studies and mirror image studies include patients whose medication choice is determined in real-world clinical settings without study-related alterations in treatment ecology. In contrast with mirror image studies, cohort studies have no predetermined order effect and time effects occur concurrently, as both LAI and OAP groups are followed in parallel. Nevertheless, like mirror image studies, cohort studies are prone to expectation biases, as there is no blinding. This might introduce bias if treatment decisions (eg, whether to hospitalize or not) are influenced by knowledge of route of antipsychotic administration. Furthermore, a particular disadvantage of cohort studies, as observed in the meta-analysis, is a systematic channeling bias in that patients who are more severely ill or prone to poor illness insight and non-adherence are more likely to be selected by clinicians to receive LAIs, whereas patients who are perceived to be at lower risk for relapse and hospitalization are more likely treated with OAPs.

SGA-LAIs, but not FGA-LAIs, were superior to OAPs with respect to hospitalization rate. This finding might be due to better tolerability of SGA-LAIs than FGA-LAIs. However, a recent Danish study reported that FGA-LAIs and risperidone-LAI do not differ with regard to time to hospitalization, all-cause discontinuation, and duration of hospitalization.<sup>70</sup> A head-to-head RCT comparing haloperidol and paliperidone once monthly also found no differences regarding all-cause treatment failure and other relapse and hospitalization related outcomes.<sup>71</sup> Moreover, superiority of SGA-LAIs over OAPs is the opposite of the subgroup analyses in our meta-analysis of RCTs<sup>17</sup> where FGA-LAIs, but not SGA-LAIs separated significantly from OAPs. Thus, based on these inconsistencies, more high-quality head-to-head trials in representative patients are needed that compare FGA-LAIs and SGA-LAIs with OAPs, such as the currently ongoing European Long-acting Antipsychotics in Schizophrenia Trial (EULAST).<sup>72</sup>

Results of the present meta-analysis were highly heterogeneous. We conducted multiple sensitivity/meta-regression analyses in order to identify potential treatment effect moderators. In addition to the superiority of SGA-LAIs, several significant moderators of superiority of LAIs but not of OAPs were identified. For variables associated with significantly lower hospitalization rates, the identified moderators strengthened the finding of superiority of LAIs, as they each related to either a more generalizable patient sample or more naturalistic data ascertainment and a lower likelihood of bias including academic sponsorship, statistical adjustment for differences in baseline patient characteristics, intent-to-treat analyses, and higher Newcastle-Ottawa scale score.

These considerations above highlight the complexities and difficulties of evaluating the comparative effectiveness of a treatment that consists of the same molecular entity in different formulations where non-adherence is the targeted mediating factor of favorable outcomes. As argued before,<sup>18</sup> since RCTs, mirror-image studies and cohort studies have different strengths and weaknesses, the best design may actually be a large pragmatic trial that retains random assignment but minimizes barriers for participation and alters clinical care as little as possible. Such considerations are supported by a recent analysis of explanatory vs pragmatic features of RCTs comparing LAIs and OAPs which found that studies with more pragmatic features were more likely to identify advantages of LAIs over OAPs.<sup>73</sup> Unlike other recent RCTs, 3 recent studies, which focused on patients in early stages of their illness as well as at particularly high risk for non-adherence, found LAIs to be superior to OAPs regarding relapse, treatment failure or rehospitalization.<sup>14-16</sup> Along with 2 ongoing pragmatic trials in first-episode and early-phase schizophrenia patients,<sup>72,74</sup> these new studies advance our understanding of this complex comparative effectiveness issue.

### *Limitations*

A key shortcoming of this meta-analysis is that the cohort studies were nonrandomized and therefore prone to a selection bias regarding the clinician's choice of treatment with either LAIs or OAPs. Although some studies adjusted for such baseline differences, only 6 out of 42 studies did so, and some other studies did so for hazard ratio or odds ratio, which we could not use for the meta-analytic synthesis in this study due to insufficient data.

Second, for all outcomes that we examined, results were significantly heterogeneous, meaning that effects varied significantly across the meta-analyzed studies which suggests that the studies differed regarding design, population, and treatment variables. By conducting sensitivity analyses, we identified several moderators that strengthened or weakened group differences between LAIs and OAPs. Although based on the data it is not possible to determine the most important moderator, as most of the significant moderators drove the effect in favor of LAIs and related to greater generalizability and higher quality of the results. As a side note, patient characteristics that may have led to LAI superiority in recent RCTs, ie, recent onset schizophrenia and/or incarcerated patients, were not reported in the selected studies. Therefore, we were unable to examine their effects in subgroup analyses. Third, the indicators that we used as proxies for illness severity/chronicity, such as number of past hospitalizations, inpatient days in the past year, and proportion of patients admitted in the last year, may not necessarily capture the true

severity/chronicity of the patients, although there were limited options in the reported data. We also note that illness severity and chronicity are not necessarily directly related to each other, as in some cases longer illness duration and chronicity may reduce the risk of hospitalization. Fourth, the secondary outcome, hospitalization days may not be a meaningful outcome to assess the comparative effectiveness of LAIs vs OAPs because it can be influenced by variables, such as patient insurance, legal, or housing status. Moreover, despite their clinical importance, quality of life and functional status were not included in our meta-analysis because none of the studies reported these outcomes. Fifth, the number of studies for rate ratio calculation ( $N = 15$ ) was relatively small compared to risk ratio ( $N = 33$ ). Nevertheless, as discussed previously, we believe that rate ratio is superior to risk ratio in terms of accounting for follow-up length and avoiding the ceiling effect of limiting the outcome to one possible hospitalization per patient, although reducing the risk of multiple hospitalizations is even more relevant. Future cohort studies should include hospitalization rate as an outcome. Finally, data on treatment adherence, psychopathology and adverse effects were too sparse to allow for meaningful meta-analysis. Such outcomes should be reported in future cohort studies. Given these limitations, future cohort studies should include detailed assessments of pre-baseline illness severity, chronicity and insight, as well as medication attitude and adherence and adjust for any between-group imbalances.

In summary, in a meta-analysis of cohort studies, LAIs were superior to OAPs regarding reducing hospitalization rate and treatment discontinuation, whereas LAIs were not superior to OAPs regarding hospitalization risk and hospitalization days. These results occurred even though patients on LAIs were more severely and/or chronically ill than were patients on OAPs. Whether or not advantages over OAPs are larger with SGA-LAIs requires further investigation, but will be relevant given the cost differences between SGA-LAIs and FGA-LAIs.

### Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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