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# Long-Acting Injectable vs Oral Antipsychotics for Relapse Prevention in Schizophrenia: A Meta-Analysis of Randomized Trials

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Results from this study were presented at the Schizophrenia International Research Society 3rd biennial meeting, April 14–18, Florence, Italy, and the NCDEU 52nd Annual meeting, May 29-June 1, 2012 Arizona, USA.

***Background:*** **While long-acting injectable antipsychotics (LAIs) are hoped to reduce high relapse rates in schizophrenia, recent randomized controlled trials (RCTs) challenged the benefits of LAIs over oral antipsychotics (OAPs).** ***Methods:*** **Systematic review/meta-analysis of RCTs that lasted ≥6 months comparing LAIs and OAPs. Primary outcome was study-defined relapse at the longest time point; secondary outcomes included relapse at 3, 6, 12, 18, and 24 months, all-cause discontinuation, discontinuation due to adverse events, drug inefficacy (ie, relapse + discontinuation due to inefficacy), hospitalization, and nonadherence.** ***Results:*** **Across 21 RCTs (*n* = 5176), LAIs were similar to OAPs for relapse prevention at the longest time point (studies = 21, *n* = 4950, relative risk [RR] = 0.93, 95% confidence interval [CI]: 0.80–1.08, *P* = .35). The finding was confirmed restricting the analysis to outpatient studies lasting ≥1 year (studies = 12, RR = 0.93, 95% CI:0.71–1.07, *P* = .31). However, studies using first-generation antipsychotic (FGA)-LAIs (studies = 10, RR = 0.82, 95% CI:0.69–0.97, *P* = .02) and those published ≤1991 (consisting exclusively of all 8 fluphenazine-LAI studies; RR = 0.79, 95% CI: 0.65–0.96, *P* = 0.02) were superior to OAPs regarding the primary outcome. Pooled LAIs also did not separate from OAPs regarding any secondary outcomes. Again, studies using FGA-LAIs and those published ≤1991 were associated with LAI superiority over OAPs, eg, hospitalization and drug inefficacy.** ***Conclusions:*** **In RCTs, which are less representative of real-world patients than naturalistic studies, pooled LAIs did not reduce relapse compared with OAPs in schizophrenia patients. The exceptions were FGA-LAIs, mostly consisting of fluphenazine-LAI studies, which were all conducted through 1991. Because this finding is vulnerable to a cohort bias, studies comparing FGA-LAI vs second-generation antipsychotics-LAI and LAI vs OAP RCTs in real-world patients are needed.**

*Key words:* antipsychotics/adherence/depot/long-acting injection/meta-analysis/relapse/schizophrenia/treatment discontinuation

## Introduction

Because psychopathology and social functioning can worsen with repeated psychotic episodes in patients with schizophrenia,[1,2] relapse prevention is critical. There is strong evidence of antipsychotic efficacy for relapse prevention in chronic and first-episode patients,[3,4] in that the risk of relapse is 2–6 times higher without medication.[3–6] However, because nonadherence rates as high as 50% can limit the efficacy of pharmacotherapy,[7,8] the use of long-acting injectable antipsychotics (LAIs) is an important option.[9] In practice, patients and clinicians are sometimes reluctant to use LAIs because of stigma, needle pain, time constraints, side effect concerns, and cost.[10] Given these drawbacks to the use of LAIs, convincing data showing the superiority of LAI over oral antipsychotics (OAPs) is needed to support the use of LAIs. The first LAI was introduced in the 1960s. Since then, at least 5 first-generation antipsychotics (FGAs)-LAIs and 3 second-generation antipsychotics (SGA)-LAIs have become available. Our previous meta-analysis found

that LAIs were associated with significantly lower relapse rates than OAPs.[11] However, new, large, controlled trials showed no benefit of LAIs.[12–15] We performed a meta-analysis that incorporated the new randomized controlled trials (RCTs) and also applied broader inclusion criteria. The new analyses are based on twice as many studies and 3 times as many patients as compared with the earlier ones.

## Method

The meta-analysis was performed following PRISMA guidelines.[16]

### *Search*

We conducted a search without language restrictions, using MEDLINE/PubMed, Cochrane library, PsycINFO and CINAHL (last search: 06/2012), for RCTs of relapse prevention or maintenance treatment in schizophrenia and related disorders lasting ≥6 months. To avoid publication bias, we also included unpublished studies, such as conference proceedings and clinical trial registries (http://clinicaltrials.gov/). Search terms included synonyms of (1) antipsychotic(s); (2) schizophrenia and related disorders, (3) randomized; and (4) depot, (long-acting) injection(s), microsphere, decanoate, palmitate, enanthate. The electronic search was supplemented by hand search of reference lists of relevant publications. At least 2 independent investigators (TK, AR, CL) conducted the literature search.

### *Inclusion Criteria*

We included randomized, head-to-head comparisons of LAI vs OAP for relapse prevention or maintenance treatment in schizophrenia. Patients in studies had to be ≥17 years old and have diagnoses of schizophrenia or schizoaffective disorder according to study diagnoses, but we included studies having other diagnoses, such as schizophreniform disorder, if schizophrenia or schizoaffective disorder were the vast majority of the study population. We included studies with a duration of at least 24 weeks and that provided information about relapse-related information, such as study-defined relapse or rehospitalization. We excluded penfluridol, a once-weekly OAP, considering it neither a LAI nor OAP.

### *Data Extraction and Outcomes*

Data were extracted independently by ≥2 reviewers (TK, AR, CL, SL, CC). Authors and companies were contacted to provide missing information and unpublished data. Any disagreements were resolved by discussion.

The primary outcome was study-defined relapse at the latest point of follow-up. Where possible, the relapse rate was based on survival curves (which estimate relapse and take account of dropouts), but in other cases, relapse was based on the initial number of patients at risk. In those cases where the paper did not define relapse, we used the next most-appropriate outcome, typically hospitalization or psychotic exacerbation (table 1).

Secondary outcomes included relapse at 3, 6, 12, 18, and 24 months, all-cause discontinuation, discontinuation due to adverse events, drug inefficacy (defined as relapse + discontinuation due to inefficacy; or defined as relapse when the overlap with discontinuation due to inefficacy was unclear), hospitalization, and nonadherence (defined as discontinuation due to nonadherence or study-defined nonadherence; see online supplementary figure 10).

### *Data Analysis*

We used 2 population sets: (1) the "randomized" or "intent-to-treat" (IIT) population, where patients who dropped out due to group assignment are included in the analysis and (2) the "safety and/or efficacy" population, which includes only those patients who took ≥1 dose and received at least one postbaseline assessment. In contrast to our previous report where the randomized sample was primary, in this analysis the safety/efficacy population was primary, while the randomized population was examined in secondary analyses. All outcomes were dichotomous. The comparison of LAI vs OAP was performed (1) for each LAI individually (fluphenazine, risperidone, etc) and (2) across all pooled LAIs. In each analysis, we computed the pooled RR with its 95% confidence interval (CI) using the random-effects model.[17] Number-needed-to-treat (NNT) was calculated where appropriate. With regard to the heterogeneity, $\tau^2$, $I^2$, $Q$, and $P$-values are reported.

In addition to the primary and secondary outcome analyses, we conducted a series of subgroup/sensitivity analyses. In order to assess the robustness of the primary outcome, we repeated the analyses using relapse rates based on the initial sample size (where available, as well as exclusively), whereas the primary analysis employed relapse rates based on survival curves (where available, as well as exclusively). While the primary analysis was based on the full set of studies, we also conducted analyses on subgroups (identified a priori) of studies in order to identify potential methodological biases or different populations. These included subgroups based on (1) medication group (FGA-LAI vs SGA-LAI), (2) publication year (older RCTs [published ≤1991] vs newer RCTs [published ≥2005]); there was a 14 year gap between the last study published in 1991 and the next study published in 2005, (3) treatment concealment (double-blind double-dummy vs rater-masked vs open label), (4) in-/outpatient status (outpatients at baseline or shortly after initiation of antipsychotic treatment vs mixed patient status [in-/outpatients mixed or inpatients throughout the study]), (5) study duration (≥1 year vs <1 year), and (6) medication allocation (same vs different antipsychotics in LAI and OAP arm). Finally, we also reexamined the results with the same inclusion criteria applied in the previous, more restricted meta-analysis,[11] ie, outpatient studies lasting ≥1 year.

**Table 1.** Description of Included Studies

| Study/Country | *n*[a] | Study Design | Duration (wks) | Inclusion Criteria | Definition of Relapse-Related Outcome | Mean Age (Range) (y.o.) | % Male | % Hp at Baseline | Information Regarding Chronicity (# Hp, Duration of illness etc.) | Medication | Randomized # | Safety/ Efficacy # | Mean Dose (Range) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| First-generation antipsychotic LAIs | | | | | | | | | | | | | |
| Fulphenazine depot | | | | | | | | | | | | | |
| Crawford and Forrest[45] 74/UK | 31 | DBDD | 40 | Stable and cooperative OPs with SCZ who are adherent to medication and attending the clinic | Withdrawal[b]: termination of the trial due to significant Sx that warranted unblinding the treatment in order to inform future Pt management | NR (20–65) | 29 | 0 | NR | FPZ decanoate | 14 | 14 | NR (Same dose as before the trial) |
| | | | | | | | | | | Triflu-operazine | 17 | 15 | 10 mg/d (fixed) |
| Del Giudice et al.[25] 75/USA | 88 | DBDD/ RM[c] | 69 | IPs with SCZ who responded to oral FPZ and were discharged | Re-Hp[b] | NR (20–50) | 100 | 0 | 48.8% had 5–10 Hps in the past | FPZ Enanthate | 27 | 27 | 25 mg/2 wks (fixed) |
| | | | | | | | | | | FPZ | 61 | 61 | 21.7 mg (5–80 mg) |
| Rifkin et al.[27] 77/USA | 73[d] | DBDD | 52 | Stable OPs[e] on FPZ depot or oral for 4 wks, no more than minor side effects, cooperative and compliant | Relapse: clinical deterioration with marked social impairment | 23.7 (17–38) | 67 | 0 | Mean # of Hps in the past: 1.79 | FPZ decanoate | 23 | 23 | NR (0.5–2 ml/ 2–wks) |
| | | | | | | | | | | FPZ | 28 | 28 | NR (5–20 mg) |
| Falloon et al.[26] 78/UK | 53 | DBDD | 52 | SCZ Pts returning to the community following Hp of an acute schizophrenic episode | Relapse: reappearance or exacerbation of schizophrenic features that led to withdrawal from the trial, regardless of re-Hp | 39 (17–60) | 45 | 0 | 81% had ≥2 Hps in the past | FPZ decanoate | NR | 20 | 25 mg/2 wks[f] (flexible) |
| | | | | | | | | | | Pimozide | NR | 24 | 8 mg/d[f] (flexible) |

**Table 1.** Continued

| Study/Country | $n^a$ | Study Design | Duration (wks) | Inclusion Criteria | Definition of Relapse-Related Outcome | Mean Age (Range) (y.o.) | % Male | % Hp at Baseline | Information Regarding Chronicity (# Hp, Duration of illness etc.) | Medication | Randomized # | Safety/ Efficacy # | Mean Dose (Range) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hogarty et al.[46] 79/USA | 105 | DBDD | 104 | Pts with SCZ who received major neuroleptic treatment during the Hp and was discharged | Relapse: unequivocal clinical deterioration of such magnitude that Hp appeared imminent after all reasonable attempts to maintain Pts with study medication failed or suicide | 34.2 (18–55) | 46 | 0 | 88% had ≥1 Hp in the past | FPZ decanoate | 55 | 55 | 34 mg/2 wks (12.5–125 mg/2 wks) |
| | | | | | | | | | | FPZ | 50 | 50 | 9.9 mg/d (2.5–40 mg/d) |
| Schooler et al.[43] 80/USA | 290 | DBDD | 52 | Pts with SCZ discharged after acute phase treatment and being treated in community | Relapse: deterioration that could not managed satisfactory after adjustment of dosage within protocol limits | 29 (18–55) | 59 | 100/0[g] | 100% newly Hp | FPZ decanoate | 143 | 107[h] | 34.2 mg/3 wks (12.5–100 mg/3 wks) |
| | | | | | | | | | | FPZ | 147 | 107[h] | 24.8 mg/d (2.5-60 mg/d) |
| Barnes et al.[47] 83/UK | 36 | DBDD | 52 | OPs with SCZ (PSE) regularly receiving depot FPZ for ≥6 months, and willing to participate the trial | Relapse: marked exacerbation of psychotic features requiring increase medication and re-Hp | 49.5 (NR) | 50 | 0 | ≥77.8% have social performance limitations | FPZ decanoate | 19 | 19 | NR (same dose as before the trial) |
| | | | | | | | | | | Pimozide | 17 | 17 | NR (dose equivalent before the trial) |
| Kaneno et al.[48] 91/Japan | 263 | DBDD | 24 | Chronic Pts with SCZ who need long-term treatment | Treatment discontinuation due to worsening of psychiatric Sx[b] | NR (NR)[i] | 65 | NR | Duration of illness was ≥10 years in 81% | FPZ decanoate | 130 | 127 | 12.6–50 mg/4 wks[f] (−75 mg/4 wks) |
| | | | | | | | | | | HAL | 133 | 132 | 3.1–12.0 mg/d[f] (−18 mg/d) |

**Table 1.** Continued

| Study/Country | *n*[a] | Study Design | Duration (wks) | Inclusion Criteria | Definition of Relapse-Related Outcome | Mean Age (Range) (y.o.) | % Male | % Hp at Baseline | Information Regarding Chronicity (# Hp, Duration of illness etc.) | Medication | Randomized # | Safety/ Efficacy # | Mean Dose (Range) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Haloperidol depot | | | | | | | | | | | | | |
| Glick et al.[49] 05/ USA | 35 | OL | 48 | OPs with SCZ or SzAD[j] (DSM-IV) who require long-term therapy | Pts who were no longer exacerbation free[b] | 42.3 (NR) | 80 | 0 | Mean duration of illness: 16.5 years | HAL decanoate | 14 | 10/9 | 170 mg/4 wks (200 mg/4 wks[k]) |
| | | | | | | | | | | QUE | 21 | 19/16 | 493 mg/d (500 mg/d[k]) |
| Zuclopenthixol depot | | | | | | | | | | | | | |
| Arango et al.[24] 06/ Spain | 46 | RM | 52 | Pts with SCZ (DSM-IV) who had a violent episode in the previous year, with a score of at least 3 on the physical aggression subscale of the modified Overt Aggression Scale | Hp[b] | 34.0 (NR) | 83 | 0 | NR | Zuclopenthixol depot | 26 | 26 | 233 mg/2 wks (NR) |
| | | | | | | | | | | Zuclopenthixol | 20 | 20 | 35 mg/d (NR) |
| Second-generation antipsychotic-LAIs | | | | | | | | | | | | | |
| Olanzapine-LAI | | | | | | | | | | | | | |
| Kane et al.[13] 10/ International | 1065[l] | DBDD | 24 | Clinically stable Pts with SCZ (DSM-IV) defined as having OP status for ≥4 wks, with a BPRS-P ≤4 on the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content | Psychotic exacerbation[b]: (1) an increase of any BPRS-P to a score of >4, with an absolute increase ≥2 for the specific item, (2) increase of any BPRS-P to a score >4, with an absolute increase ≥4 on the positive subscale, (3) Hp as the result of worsening of positive psychotic Sx | 38.9 (18–75) | 65 | 0 | Mean duration of illness: 13.3 years. 36.9% had ≥2 psychotic episodes or exacerbations in last 24 months | OLA-LAI | 599 | 599 | 150 mg/2 wks, 405 mg/4 wks, 300 mg/2 wks (fixed) |
| | | | | | | | | | | OLA | 322 | 322 | 14.3 mg/d (10, 15, 20 mg/d) |

**Table 1.** Continued

| Study/Country | *n*[a] | Study Design | Duration (wks) | Inclusion Criteria | Definition of Relapse-Related Outcome | Mean Age (Range) (y.o.) | % Male | % Hp at Baseline | Information Regarding Chronicity (# Hp, Duration of illness etc.) | Medication | Randomized # | Safety/ Efficacy # | Mean Dose (Range) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Detke et al.[50] 11/International | 524 | OL | 104 | OPs with SCZ (DSM-IV) who had no acute Hp in the 8 wks prior to visit 1, PANSS-T < 70, CGI-S ≤ 4 at visit 1 and 2, but had ≥2 episode of clinical worsening in the past 2 years | Relapse: (1) Hp, (2) >25% increase in PANSS-T, including ≥25% increase including ≥10 points increase (3) ≥1 increase in CGI-S CGI-S of ≥4, (4) deliberate self-injury or injury to others, (5) discontinuation from study because of worsening of Sx | 40.9 (18–65) | 67 | 0 | Mean duration of illness: 14.7 years. Mean # of psychotic episode in last 24 months: 2.7 | OLA LAI<br>OLA | 264<br>260 | 264<br>260 | 386.6 mg/4 wks (15–405 mg/4 wks)<br>12.7 mg/d (5–20 mg/d) |
| Risperidone-LAI Keks et al.[51] 07/International | 629[m] | OL | 53 | IP/OPs with SCZ or SzAD[n] (DSM-IV) who had acute exacerbation (Hp or requiring medical intervention) in the past 2 months, and had an additional acute exacerbation in the past 2 years, PANSS-T ≥50, BMI ≤40 | Significant deterioration [b)]: 1) Hp for Sx exacerbation, 2) need for an increased level of care and ≥2 points increase in CGI-S over 2 wks, 3) self-injury, suicidal/ homicidal ideation or violent behavior | 35.2 (≥18) | 57 | 44 | Mean duration of illness: 8.6 years | RIS-LAI<br>OLA | 253<br>310 | 247<br>300 | 40.7 mg/2 wks (25, 50 mg/2 wks)<br>14.6 mg/d (5–20 mg/d) |

**Table 1.** Continued

| Study/Country | *n*[a] | Study Design | Duration (wks) | Inclusion Criteria | Definition of Relapse-Related Outcome | Mean Age (Range) (y.o.) | % Male | % Hp at Baseline | Information Regarding Chronicity (# Hp, Duration of illness etc.) | Medication | Randomized # | Safety/ Efficacy # | Mean Dose (Range) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bai et al.[23] 07/Taiwan | 50 | RM | 48 | Symptomatically stable SCZ (DSM-IV)and have been on oral RIS for ≥3 months, PANSS-T <80, PANSS conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content are all <4, CGI-I screening visit and baseline were same | Relapse: definition not given | 46.4 (18–65) | 50 | 100[o] | Mean duration of Hop stay: 127.9 months | RIS LAI | 25 | 23[p] | Equivalent to oral 5.0 mg/d (25, 37.5, 50 mg/2 wks)[q] |
| | | | | | | | | | | RIS | 25 | 25 | 4.0 mg/d (Same dose as before the trial) |
| Potapov et al.[52] 08/Russia | 41 | OL | 52 | Ops with SCZ (ICD-10) whose PANSS-T ≥60 | Relapse: ≥5 increase in CGI-S and ≥20% in PANSS-T compared with previous assessment | 34.9 (18–65) | 58 | 0 | NR | RIS LAI | 20 | 20 | 41.7 mg/2 wks (NR) |
| | | | | | | | | | | OLA | 21 | 20 | 15.9 mg/d (NR) |
| Kamijima et al.[38] NCT00240708[37] 09/Japan | 205 | OL | 24 | IP/OPs with SCZ (DSM-IV) who are taking RIS ≤6 mg/d with no change in dose for 28 days, PANSS-T ≥60–<120 | Treatment discontinuation due to worsening of psychiatric Sx[b] | 42.7 (≥20) | 62 | 28 | Mean duration of illness: 14.9 years | RIS LAI | 153 | 147 | 32.3 mg/2 wks (25, 37.5, 50 mg/2 wks) |
| | | | | | | | | | | RIS | 52 | 51 | 3.4 mg/d (2–6 mg/d) |

**Table 1.** Continued

| Study/Country | *n*[a] | Study Design | Duration (wks) | Inclusion Criteria | Definition of Relapse-Related Outcome | Mean Age (Range) (y.o.) | % Male | % Hp at Baseline | Information Regarding Chronicity (# Hp, Duration of illness etc.) | Medication | Randomized # | Safety/ Efficacy # | Mean Dose (Range) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gaebel et al.[53] 10, de Arce Cordon et al. 12/ International | 710[r] | OL | 104 | Symptomatically stable IP/OPs with SCZ or SzAD[s] (DSM-IV) using stable dose of RIS ≤ 6 mg/d, OLA ≤ 20 mg/d, or FGA ≤ 10 mg/d HAL equivalent for ≥4 weeks and living in the same residence for ≥30 days, who were candidates for switching Tx. | Relapse: (1) psychiatric Hp, (2) increase in level of care and ≥25% PANSS-T increase, including ≥10 points increase, (3) deliberate self-injury, (4) clinically significant suicidal/homicidal ideation, (5) violent behavior resulting in significant injury to another person or property, (6) significant clinical deterioration defined as a CGI-C ≥6, (7) exceeding registered drug dose | 41.6 (≥18) | 58 | NR | Mean duration of illness: 10.0 years. Mean # of Hps in the past: 5.3 | RIS LAI | 355 | 329/327 | 33.6 mg/2 wks (up to 50 mg/2 wks) |
| | | | | | | | | | | QUE, ARI | 401[r] | 382/371[r)] | QUE: 413.4 mg/d (up to 750 mg/d), ARI: 15.1 mg/d (10–30 mg/d) |

**Table 1.** Continued

| Study/Country | $n^a$ | Study Design | Duration (wks) | Inclusion Criteria | Definition of Relapse-Related Outcome | Mean Age (Range) (y.o.) | % Male | % Hp at Baseline | Information Regarding Chronicity (# Hp, Duration of illness etc.) | Medication | Randomized # | Safety/ Efficacy # | Mean Dose (Range) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Macfadden et al.[14] 10/International | 355 | RM | 104 | Pts with SCZ (DSM-IV) who experienced at least 2 psychotic relapses in the past 2 years, and have been stabilized for ≥2 months | Relapse: determined by masked monitoring board; (1) worsening of psychiatric Sx (Hp or significant increases in level of psychiatric care), (2) an increase of ≥25% PANSS-T, including ≥10 points increase from baseline, and CGI-C ≥6 with CGI-S of ≥4, (3) deliberate self-injury, clinically significant suicidal/homicidal ideation, or violent behavior, (4) drug discontinuation or addition of another AP for >1 wk because of lack of efficacy, (6) increase in dosage beyond the recommended dosage | 37.9 (>18) | 60 | 0 | Mean duration of illness: 9.9 years | RIS LAI | 179 | 179/177 | 41.8 mg/2 wks (25–50 mg/2 wks) |
| | | | | | | | | | — | ARI | 176 | 176/172 | 19.9 mg/d (10–30 mg/d) |

**Table 1.** Continued

| Study/Country | *n*[a] | Study Design | Duration (wks) | Inclusion Criteria | Definition of Relapse-Related Outcome | Mean Age (Range) (y.o.) | % Male | % Hp at Baseline | Information Regarding Chronicity (# Hp, Duration of illness etc.) | Medication | Randomized # | Safety/ Efficacy # | Mean Dose (Range) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NCT00246259[44] 11/Canada | 85 | OL | 104 | IPs or OPs with SCZ, SzAD or schizophreniform dsorder[t] (DSM-IV) with early onset (≤3 years), PANSS-T ≥60 and ≤120, currently on monotherapy atypical AP below RIS = 6, OLA = 20, QUE = 800 mg/d or treatment naïve. Pts stable within 18 wks entered the maintenance phase | Relapse: (1) psychiatric Hp; (2) psychiatric care increase and 25% increase in PANSS-T, including ≥10 points increase; (3) self-injury, suicidal, homicidal ideation, violence; and (4) CGI-C ≥6 | 22.7 (18–30) | 84 | NR | Mean duration of illness: 2.1 years | RIS LAI | 44 | 42/32[g] | NR (25–50 mg/2 wks)[u] |
| | | | | | | | | | | Oral SGA except CLO | 41 | 35/31 [g)] | NR (flexible dose) |
| Rosenheck et al.[12] 11/USA | 382 | RM | 104 | Pts with SCZ or SzAD who are at risk of Hp as evidenced by current psychiatric Hp, Hp in the previous 2 years, or increased use of mental health services to prevent relapse | Hp[b] | 51.0 (≥18) | 91 | 40 | Mean duration of illness: 23.4 years | RIS LAI | 190 | 187 | 40.9 mg/1.5 wks (25,37.5, 50 mg/2 wks) |
| | | | | | | | | | | Any OAP except CLO | 192 | 182 | NR (flexible) |
| Schooler et al.[15] 11/USA | 305 | RM | 74–130[v] | OPs with SCZ or SzAD (32%) who had exacerbation within 12 months, CGI ≥ 4, in community ≥4 wks, ≥1 month since the most recent exacerbation | Relapse: determined by masked committee; Hp for psychosis, increases in level of care required to avoid Hp, substantial clinical deterioration measured by BPRS psychosis cluster, deliberate self-injury or violent behavior | 38.2 (18–65) | 71 | NR[w] | Mean duration of illness: 15.9 years. Mean # of Hps in the past: 11.0 | RIS microsphere | 153 | 146 | 33.6 mg/2 wks (12.5–75 mg/2 wks) |
| | | | | | | | | | | Oral SGA | 152 | 150 | NR (flexible) |

*Notes*: AP, antipsychotics, BMI, body mass index; BPRS-P, brief psychiatric rating scale positive item; CGI-C, clinical global impression change score; CGI-S, clinical global impression severity score; CLO, clozapine; DBDD, double-blind double-dummy; Dx, diagnosis; FPZ, fulphenazine; HAL, haloperidol; Hp, hospitalization; IP, inpatient; LAI, long acting injection; NR, not reported; OAP, oral antipsychotic; OL, open label; OLA, Olanzapine; OP, outpatient; PANSS, positive and negative symptom scale total score; PSE, present state examination; Pt, patient; QUE, quetiapine; RIS, risperidone; RM, rater masked; SCZ, schizophrenia; SGA, second-generation antipsychotics; Sx, symptom; SzAD, schizoaffective disorder; Tx, therapy.

[a] Original study sample size.
[b] Study-defined relapse-related outcomes used in place of relapse.
[c] Raters were masked for 3 arms, but DBDD were applied to 2 arms.
[d] Pts allocated to placebo arm are not included in the analysis.
[e] 100% Schizophrenia by clinical diagnosis but included 15% nonschizophrenia when assessed by research psychiatrists.
[f] Most common dosing.
[g] 100% during intensive treatment phase, 0% in maintenance phase.
[h] Pts entered maintenance phase are used in the safety/efficacy population analysis.
[i] Age range was not reported but 90% of the Pts were between 30–59 years old.
[j] Rate not reported.
[k] Clinicians were instructed to target this dose.
[l] Very low dose (OLA-LAI 45 mg/4 wks) group is not included in the analysis.
[m] Pts allocated to RIS LAI 75 mg/2 wks were excluded due to protocol change.
[n] ScAD = 17.3%.
[o] All the patients were required to be hospitalized throughout the trial.
[p] Two Pts were discharged due to stable condition and removed from the trial.
[q] Depot dose based on prior oral dose.
[r] Including exploratory arm (ARI), randomized: $n = 45$, efficacy: $n = 44$.
[s] ScAD = 17.7%.
[t] ScAD = 6.5%, schizophreniform = 3.9%.
[u] Started from 25 mg, but was increased by increments of 12.5 mg up to 50 mg corresponding to the symptoms.
[v] Full study period ranged between 17–30 months depending on enrollment date.
[w] OP study including some Pts that were briefly hospitalized initially.

In post-hoc analyses, we compared the chlorpromazine (CPZ) equivalents between the LAI arm and OAP arm in the following study groups in order to identify potential confounders: all studies, using the same or different antipsychotic in the LAI and OAP groups, FGA- or SGA-LAI studies, and older or newer studies. We also compared mean CPZ equivalents within each of the OAP and LAI arms between FGA- vs SGA-LAI studies and between older vs newer studies. Antipsychotic doses were converted to CPZ equivalents using published guidelines.[18–20] For LAIs, we used the manufacturers' recommended equivalent for the depot to oral conversion for the same drug and then converted to oral CPZ equivalents.

Data were entered into a funnel graph (trial effect against trial size) to investigate the likelihood of overt publication bias.[21] Data were double entered into Review Manager 5.1.4 (Cochrane Collaboration, http://ims.cochrane.org/revman).

## Results

### *Search and Study Characteristic*

We identified 21 RCTs with 5176 participants (see online supplementary figure 1). One study[22] was excluded because it did not quantify the number of patients at risk but reported only completed cases.

The number of patients per study ranged from 31–921 (median: 105), and mean study duration was 66.4±32.2 (range: 24–130) weeks; duration: <1year: studies = 4, ≥1year: studies = 17). Nine studies had a double-blind, double-dummy design, 5 were rater-masked, and 7 were open. There were 10 FGA-LAI and 11 SGA-LAI studies. The number of studies with each individual LAI were fluphenazine = 8, haloperidol = 1, zuclopenthixol = 1, risperidone = 9, olanzapine = 2. The number of the studies with each OAP were fluphenazine = 4, pimozide = 2, haloperidol = 1, trifluoperazine = 1, zuclopenthixol = 1, olanzapine = 4, quetiaapine = 2, risperidone = 2, aripiprazole = 2, and previous medication/physicians' choice = 3. Eleven studies (52.4%) used different antipsychotics in the 2 arms. Thirteen studies (61.9%) included only outpatients, 2 (9.5%) included inpatients at baseline who were discharged shortly after study initiation,[12,15] 1 (4.8%) required patients to be hospitalized throughout the trial,[23] while 5 (23.8%) provided insufficient information. Relapse definitions varied. In 9 studies (42.9%), relapse was not defined. In 3 of these, we used hospitalization rate as relapse[12,24,25]; in the remaining 6, we utilized study-defined symptomatic worsening (table 1).

### *Relapse Rate at the Longest Study Time Point*

Analyzing individual LAIs, fluphenazine-LAI showed significant superiority over OAPs (studies = 8, $n$ = 826, RR = 0.79, 95% CI: 0.65–0.96, $P$ = .02, $I^2$ = 23%, NNT = 13), while the other LAIs were not significantly superior to OAPs (pooled RRs for each LAI ranged from 0.99–1.28). When pooled together, the risk for LAIs was similar to the risk for OAPs (studies = 21, $n$ = 4950, RR = 0.93, 95% CI: 0.80–1.08, $P$ = .35). The risk ratio varied across studies ($\tau^2$ = 0.05, $I^2$ = 58%, $Q$ = 47.31, df = 20, $P$ = .0005) (figure 1).

### *Relapse Rate at Specific Time Points*

Comparing relapse rates at different time points (3, 6, 12, 18, and 24 months), pooled LAIs did not separate from OAPs (see online supplementary figures 2, 3, 4, 5, 6). A single study of fluphenazine depot yielded trend-level superiority at 18 months (study = 1, $n$ = 105, RR = 0.66, 95% CI: 0.44–0.99, $P$ = .05) and significant superiority at 24 months (study = 1, $n$ = 105, RR = 0.56, 95% CI: 0.38–0.80, $P$ = .002); 2 studies of olanzapine-LAI yielded trend-level inferiority at 6 months (studies = 2, $n$ = 1445, RR = 1.27, 95% CI: 0.97–1.66, $P$ = .09).

### *All-Cause Discontinuation*

Neither individual LAI nor pooled LAIs separated from OAPs regarding all-cause discontinuation (pooled LAIs: studies = 21, $n$ = 4882, RR = 1.00, 95% CI: 0.89–1.13, $P$ = .99) (figure 2).

### *Discontinuation Due to Adverse Events*

Neither individual nor pooled LAIs separated from OAPs regarding discontinuation due to adverse events in the safety/efficacy (pooled LAIs: studies = 19, $n$ = 4662, RR = 1.10, 95% CI: 0.74–1.64, $P$ = .65) (see online supplementary figure 7).

### *Drug Inefficacy*

Among individual LAIs, only fluphenazine was superior to OAPs regarding drug inefficacy defined as relapse + discontinuation due to inefficacy (studies = 8, $n$ = 826, RR = 0.78, 95% CI: 0.66–0.91, $P$ = .002) in the safety/efficacy population. Conversely, olanzapine-LAI was inferior to OAP on this measure ($n$ = 1445, RR = 1.52, 95% CI: 1.12–2.07, $P$ = .007), but this was based on only 2 studies. Pooled LAIs did not separate from OAPs regarding drug inefficacy (see online supplementary figure 8).

### *Hospitalization*

Among individual LAIs, only fluphenazine-LAI was superior to OAPs in preventing hospitalization (studies = 4, $n$ = 197, RR = 0.82, 95% CI: 0.67–0.99, $P$ = .04). Pooled LAIs showed trend-level superiority over OAPs (studies = 10, RR = 0.89, 95% CI: 0.78–1.02, $P$ = .09) (see online supplementary figure 9).

### *Nonadherence*

Only 2 studies utilized pill counts or urine concentration.[26,27] One zuclopenthixol study yielded trend-level

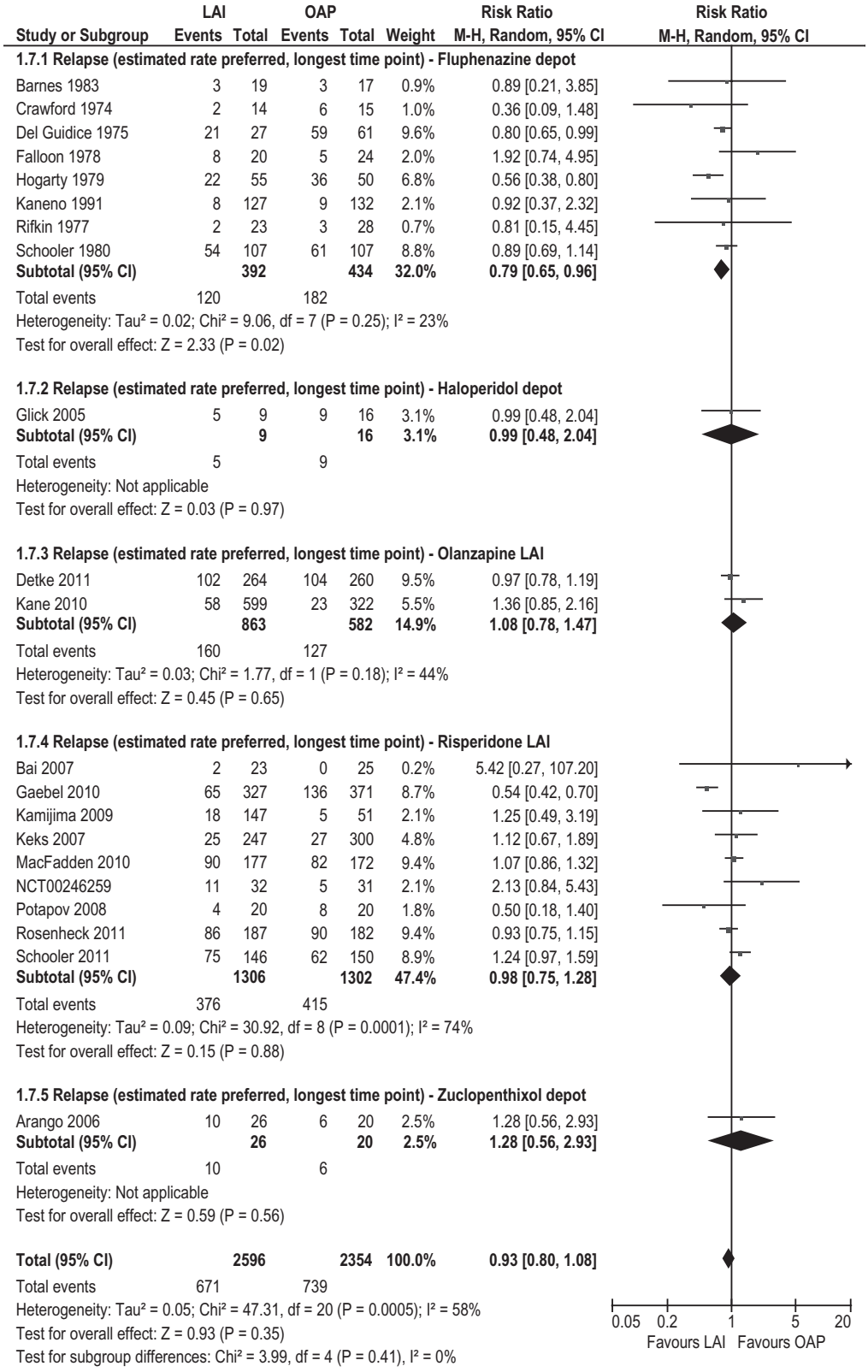


**Fig. 1.** Relapse rate-estimated rate preferred, longest time point (safety/efficacy population).

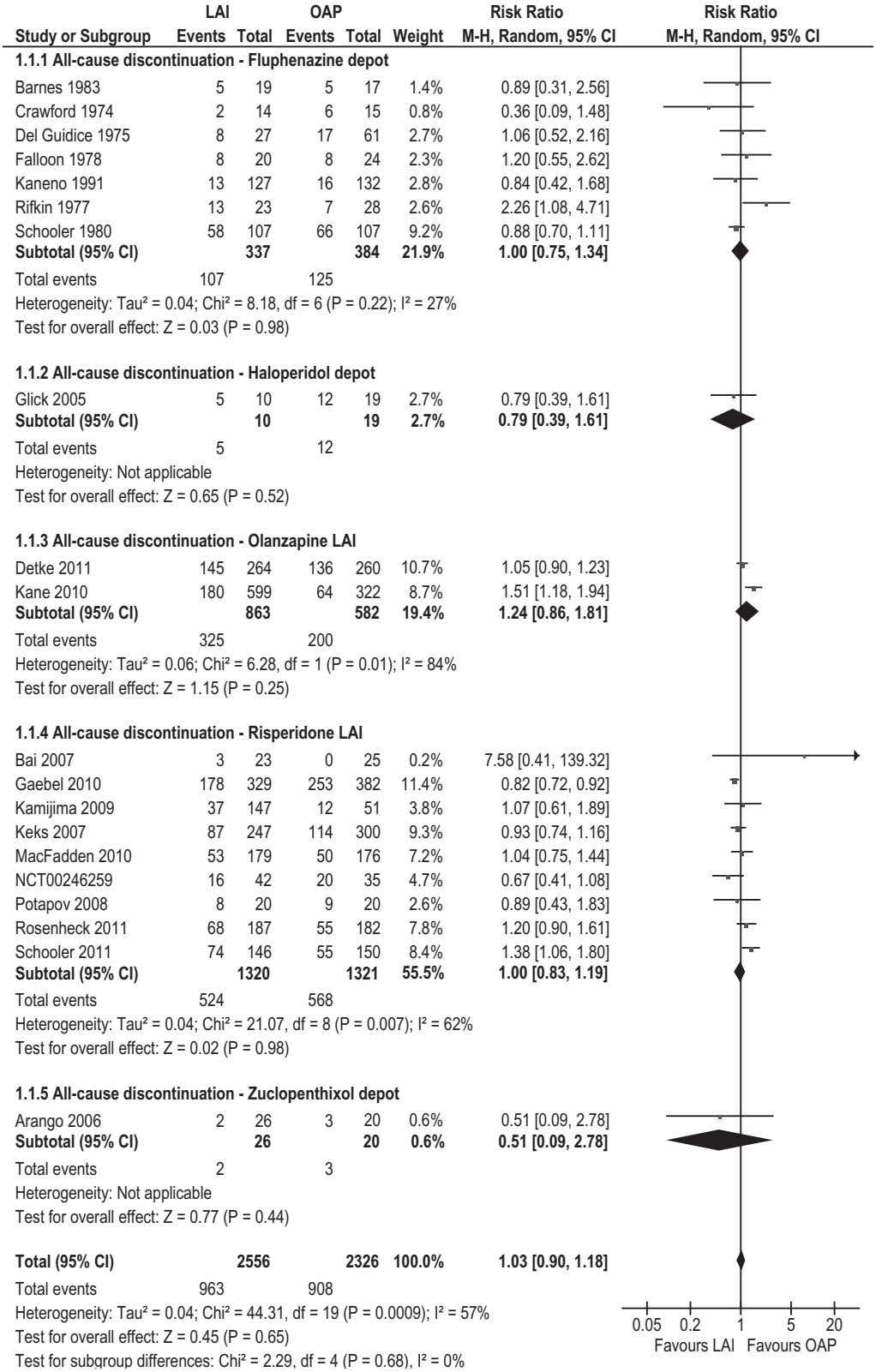


**Fig. 2.** All-cause discontinuation (safety/efficacy population).

superiority regarding adherence (study = 1, $n$ = 46, RR = 0.26, 95% CI: 0.06–1.14, $P$ = .07). Pooled LAIs did not separate from OAPs (studies = 10, $n$ = 2018, RR = 0.77, 95% CI: 0.49–1.22, $P$ = .22; see online supplementary figure 10).

### *Sensitivity and Subgroup Analyses: Primary Outcome*

Pooled LAIs did not separate from OAPs whether raw relapse rates were used preferentially over estimated relapse rates ($P$ = .49), or whether only estimated rates ($P$ = .25) or raw rates ($P$ = .48) were used.

Nonsuperiority of LAIs over OAP remained in all clinically relevant subpopulations and treatment groups, ie, treatment concealment (double-blind, double-dummy vs rater-masked vs open label), in-/outpatient status, study duration (≥1 year, or <1 year), using the same vs different medication in the LAI and OAP arm (table 2). When we repeated the analyses with more stringent inclusion criteria, which we had applied in our previous meta-analysis,[11] ie, outpatient study lasting ≥1 year, pooled LAIs again did not separate from OAPs (studies = 12, $n$ = 2162, RR = 0.93, 95% CI:0.71–1.07; table 2).

Analyzing FGA-LAIs and SGA-LAIs separately, FGA-LAIs were significantly superior to OAPs in preventing relapse (studies = 10, $n$ = 897, RR = 0.82, 95% CI: 0.69–0.97, $P$ = .02, NNT = 15). However, SGA-LAIs did not separate from OAPs (studies = 11, $n$ = 4053, RR = 1.00, 95% CI: 0.81–1.23, $P$ = 1.0; figure 3). Nevertheless, effect sizes for FGA-LAIs and SGA-LAIs were not significantly different from each other ($P$ = 0.14). Furthermore, the superiority of FGA-LAIs, was moderated by publication year. In RCTs published until 1991 (studies = 8, $n$ = 826, RR = 0.79, 95% CI: 0.65–0.96, $P$ = .02, $I^2$ = 23, $NNT$ = 13), consisting exclusively of all fluphenazine LAIs, LAIs were superior to OAPs. However, this was not the case in the newer RCTs published since 2005 (studies = 13, $n$ = 4124, RR = 1.01, 95% CI: 0.83–1.22, $P$ = .94), which included only 2/10 FGA-LAI studies; figure 3).

### *Subgroup Analyses: Secondary Outcome*

Limiting the sensitivity analyses to variables that showed a significant effect on the treatment comparison, superiority of FGA-LAIs over OAPs but not of SGA-LAIs over OAPs was also apparent regarding some secondary outcomes, such as drug inefficacy or hospitalization. However, again, the results were moderated by publication year (table 2).

### *CPZ Dose Within and Across Studies*

Only 13 of the 21 studies (61.9%) reported mean dose levels in both treatment arms. Converting antipsychotic doses to CPZ equivalents, we found no significant differences between LAI and OAP CPZ equivalents across all studies (studies = 13, $P$ = .11), within studies using the same antipsychotics in the LAI and OAP arms (studies = 8, $P$ = .95), FGA-LAI studies (studies = 5, $P$ = .63), SGA-LAI studies (studies = 8, $P$ = .15), and older studies (studies = 3, $P$ = 1.0). However, there was a trend-level difference for higher CPZ equivalents in OAP arms compared with LAI arms within studies using different antipsychotics (studies = 5, $P$ = .06) and in newer studies (studies = 10, $P$ = .06).

Comparing FGA- and SGA-LAI studies, there was a trend-level difference for higher CPZ equivalent doses in FGA-LAI studies in both LAI arms (15 treatment arms, $P$ = .08) and OAP arms (14 treatment arms, $P$ = .08). Moreover comparing older vs newer studies, CPZ equivalent doses were significantly higher both in the LAI arms (15 treatment arms, $P$ = .01) and in the OAP arms (14 treatment arms, $P$ = .03) of the older studies.

### *Randomized Population*

Using the randomized population, the results did not change, except for few minor variations: fluphenazine-LAI showed trend level superiority over OAP regarding relapse at 3 months ($P$ = .06) and at 12 months ($P$ = .08), hospitalization for pooled LAIs did not reach statistical significance ($P$ = 0.14), and double-blind double-dummy study design was associated with trend-level superiority of LAIs vs OAPs ($P$ = .09).

### *Publication Bias*

The symmetrical funnel-plot did not suggest overt publication bias (see online supplementary figure 11).

## Discussion

To our knowledge, this is the largest meta-analysis comparing LAI vs OAP efficacy for relapse prevention in schizophrenia. Compared with our prior meta-analysis,[11] we broadened the inclusion criteria by incorporating studies that enrolled inpatients and outpatients, and also by including studies lasting 6 months to <1 year. However, at the same time, we also examined the result within the studies meeting our previous inclusion criteria (outpatient study, lasting ≥1 year).

We found that pooled LAIs were not superior to OAPs in all of the examined relapse-related outcomes. The only exception was fluphenazine-LAI, which showed significant superiority over OAPs in several relapse-related outcomes. This lack of superiority of LAIs is in contrast to our previous meta-analysis,[11] which showed significant superiority of LAIs over OAPs in schizophrenia with a NNT = 10. However, this difference is not due to the use of broadened inclusion criteria for analyzed studies, as results were similar when the analyses were limited to the outpatient studies lasting ≥1 year. Rather, the nonsuperiority of LAIs vs OAPs

**Table 2.** Subgroup and Sensitivity Analysis in Safety/Efficacy Population

| Variables | # Trials | *n* | Relative Risk | | | $I^2$(%) | NNT |
|---|---|---|---|---|---|---|---|
| | | | RR | 95% CI | *P* | | |
| Relapse rate | | | | | | | |
| Relapse rate calculation | | | | | | | |
| Using preferentially raw over estimated rates | 21 | 4963 | 0.95 | 0.81, 1.11 | 0.49 | 55 | NA |
| Using only estimated rates | 12 | 3684 | 0.91 | 0.77, 1.07 | 0.25 | 71 | NA |
| Using only raw rates | 19 | 4605 | 0.94 | 0.78, 1.12 | 0.48 | 51 | NA |
| Medication class | | | | | | | |
| FGA-LAIs | 10 | 897 | 0.82 | 0.69, 0.97 | 0.02 | 15 | 15 |
| SGA-LAIs | 11 | 4053 | 1.00 | 0.81, 1.23 | 0.99 | 70 | NA |
| Publication year | | | | | | | |
| Older RCTs ≤1991 | 8 | 826 | 0.79 | 0.65, 0.96 | 0.02 | 23 | 12 |
| Newer RCTs ≥2005 | 13 | 4124 | 1.01 | 0.83, 1.22 | 0.94 | 64 | NA |
| Treatment concealment | | | | | | | |
| Double-blind double-dummy | 9 | 1717 | 0.86 | 0.68, 1.09 | 0.21 | 45 | NA |
| Rater-masked | 5 | 1108 | 1.07 | 0.93, 1.23 | 0.34 | 9 | NA |
| Open label | 7 | 2095 | 0.91 | 0.64, 1.28 | 0.58 | 70 | NA |
| In-/outpatient status at baseline | | | | | | | |
| Outpatient status | 15 | 3137 | 0.95 | 0.83, 1.08 | 0.41 | 45 | NA |
| Mixed patient status | 6 | 1813 | 1.05 | 0.61, 1.79 | 0.86 | 69 | NA |
| Study duration | | | | | | | |
| ≥1 year | 15 | 3470 | 0.91 | 0.77, 1.07 | 0.25 | 66 | NA |
| <1 year | 6 | 1480 | 1.14 | 0.82, 1.58 | 0.43 | 0 | NA |
| Medication allocation | | | | | | | |
| Same AP in LAI and OAP arm | 10 | 2544 | 0.92 | 0.78 1.09 | 0.35 | 47 | NA |
| Different AP in LAI and OAP arm | 11 | 2406 | 0.94 | 0.71, 1.26 | 0.70 | 68 | NA |
| Combination of categories | | | | | | | |
| Outpatient status + ≥1 year | 12 | 2162 | 0.93 | 0.81, 1.07 | 0.31 | 48 | NA |
| Drug inefficacy | | | | | | | |
| Medication class | | | | | | | |
| FGA-LAIs | 10 | 897 | 0.80 | 0.69, 0.93 | 0.004 | 0 | 17 |
| SGA-LAIs | 11 | 4072 | 1.07 | 0.85, 1.36 | 0.55 | 70 | NA |
| Publication year | | | | | | | |
| Older RCTs ≤1991 | 8 | 826 | 0.78 | 0.66, 0.91 | 0.002 | 0 | 15 |
| Newer RCTs ≥2005 | 13 | 4143 | 1.07 | 0.87, 1.33 | 0.51 | 64 | NA |
| Hospitalization | | | | | | | |
| Medication class | | | | | | | |
| FGA-LAIs | 5 | 243 | 0.84 | 0.69, 1.01 | 0.07 | 0 | NA |
| SGA-LAIs | 5 | 2098 | 0.91 | 0.74, 1.12 | 0.37 | 29 | NA |
| Publication year | | | | | | | |
| Older RCTs ≤1991 | 4 | 197 | 0.82 | 0.67, 0.99 | 0.04 | 0 | 9 |
| Newer RCTs ≥2005 | 6 | 2144 | 0.93 | 0.77, 1.12 | 0.43 | 19 | NA |

*Notes*: AP, antipsychotics; FGA, first-generation antipsychotics; LAI, long-acting injection; NA, not applicable; NNT, number needed to treat; OAP, oral antipsychotics; SGA, second-generation antipsychotics; RCTs, randomized controlled trial. *P*-values <.05 bolded to indicate statistical significance.

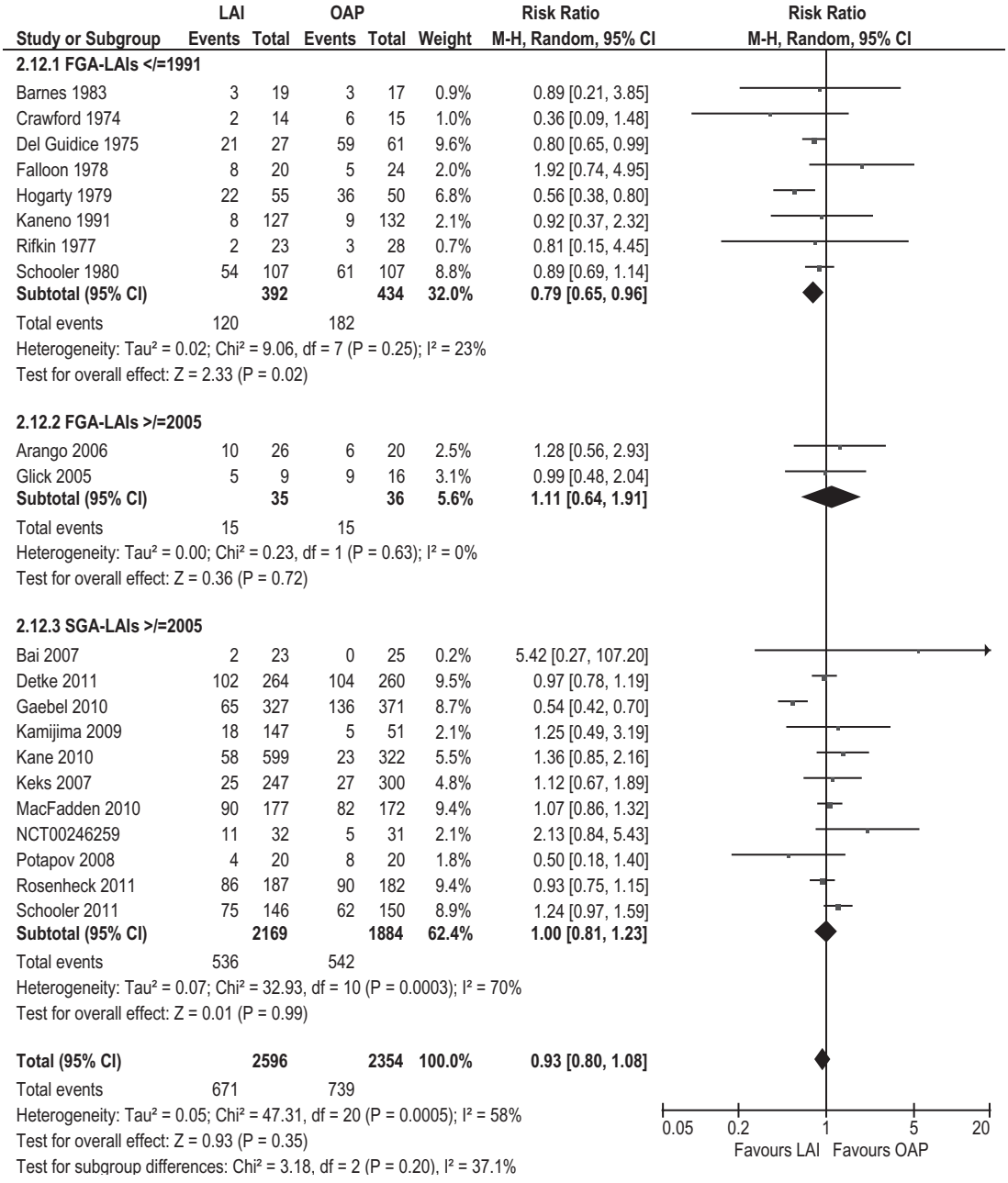


**Fig. 3.** Subgroup analysis comparing (1) FGA-LAI studies published ≤1991, (2) FGA-LAI studies published ≥2005, (3) SGA-LAI studies published ≥2005.

When FGA-LAIs (combining the top two groups) and second-generation antipsychotics (SGA)-LAIs (bottom group) were analyzed separately, FGA-LAIs were significantly superior to OAPs in preventing relapse (Studies = 10, $n$ = 897, RR = 0.82, 95% CI: 0.69–0.97, $P$ = 0.02, NNT = 15, heterogeneity: $\tau^2$ = 0.01, $I^2$ = 15%, $Q$ = 10.62, df = 9, $P$ = 0.30), but SGA-LAIs were not (Studies = 11, $n$ = 4053, RR = 1.00, 95% CI: 0.81–1.23, $P$ = 0.99, heterogeneity: $\tau^2$ = 0.07, $I^2$ = 70%, $Q$ = 32.93, df = 10, $P$ = 0.0003). When older randomized controlled trials (RCTs) (<1991) (top group) and the remaining newer RCTs (>2005) (combining the bottom two groups) were analyzed separately, LAIs had lower relapse rates in older RCTs (Studies = 8, $n$ = 826, RR = 0.79, 95% CI: 0.65–0.96, $P$ = 0.02, NNT = 13, heterogeneity: $\tau^2$ = 0.02, $I^2$ = 23%, $Q$ = 9.06, df = 7, $P$ = 0.25), but not in the remaining newer RCTs (Studies = 13, $n$ = 4950, RR = 1.01, 95% CI: 0.83–1.08, $P$ = 0.95, heterogeneity: $\tau^2$ = 0.06, $I^2$ = 64%, $Q$ = 33.39, df = 12, $P$ = 0.0008).

in the extended analyses of our study was due to a shift in the RR toward the null hypothesis rather than due to increased imprecision indicated by a widening of the CI. In fact, the CI of our primary result was slightly narrower than in the prior meta-analysis (RR = 0.93 [95% CI: 0.80–1.08] vs RR= 0 .70 (95% CI: 0.57–0.87]), suggesting that the point estimate was, if anything, somewhat more precise.

On the other hand, we found in subgroup analyses that FGA-LAIs studies or older RCTs showed significant superiority of LAIs over OAPs but that this was not the case in SGA-LAIs studies or newer RCTs. (In a byline,

we note that the distinction between FGAs and SGAs is a questionable one.)[28] However these findings require cautionary interpretation. Eight out of 10 FGA-LAI studies were published by 1991, and all 8 RCTs published by 1991 employed exclusively fluphenazine-LAI. Hence, these distinctions were nearly equal, and it is impossible to disentangle the potential reasons for different effect sizes. Moreover, the subgroup analysis comparing the effect sizes of FGA-LAIs and SGA-LAIs relative to OAPs did not yield a significant difference, suggesting that in this indirect comparison, there was no indication that FGA-LAIs are superior to SGA-LAIs. That being said, we consider the following explanations for the differential findings for FGA-LAIs (or older RCTs). One possibility is publication bias. Because the registration system of clinical trials has been introduced, companies are obliged to either publish all studies or make the data publically available, while in earlier years, studies showing less advantages for LAIs may not have been published. Another possibility is changing definitions of relapse. In order to mitigate potential adverse consequences of participating in clinical trials, recent studies tended to utilize lower thresholds for relapse, which can increase the rate of false positives. From the definitions encountered in these analyses, this tendency was not obvious (see table 1). However, it is hard to rule out this possibility, as some older studies used vague definitions rather than quantitative measures, such as predefined changes in PANSS score. In addition to various definitions, thresholds used to determine relapse can also have a big impact. For example, hospitalization as threshold is susceptible to health insurance system variations, social supports, or clinician's judgment and can differ by geographical regions or over time. Furthermore, the OAPs used in FGA-LAI studies published until 1991 were FGAs, while OAPs used in SGA-LAI studies published since 2005 were generally SGAs. One can argue that patients allocated to FGA-OAPs might have a greater chance of relapse, either due to poorer adherence or differences in neuropharmacologic properties compared with SGA-OAPs. This could be consistent with our recent meta-analysis comparing oral SGAs and FGAs, which showed a small but significant superiority of SGAs in preventing relapse, but due to limited information, we could not determine whether nonadherence was a factor.[29] We examined this possibility in the current analyses as well, but we did not find significant group differences. However, adherence is rarely assessed directly, and the evaluations involving these outcomes are very crude, which is a major limitation of the available RCTs. LAIs are thought to be better via improved adherence, not via intrinsically better efficacy. Therefore, it is unclear whether LAIs were not superior because compliance with OAPs was good enough in the context of RCTs.

Regarding CPZ equivalent doses, there were some significant or trend-level differences within and across studies. CPZ equivalents trended toward being higher in OAP arms compared with LAI arms within studies using different antipsychotics, which may have disadvantaged the LAI arms. However, in the studies that used the same medications in the LAI and OAP arm and used also similar CPZ equivalent doses in both arms, there was also no difference in terms of preventing relapse. In SGA-LAI studies, or newer studies, CPZ equivalent doses in the OAP arms also trended to be higher than in the LAI arms. In addition, CPZ equivalent dosages used in FGA-LAI studies and in older studies were at a trend level and significantly higher than in SGA-LAI studies and in newer studies, respectively. These findings are consistent with a trend toward using lower antipsychotic doses since the more widespread use of SGAs. Whether or not this difference is relevant for the superiority of FGA–LAIs and older studies that used higher doses in both the LAI and OAP arms than SGA-LAI and newer studies that used lower doses in both arms is unclear. However, it is possible that higher LAI doses were more effective in showing superiority over OAPs, which may have been dosed higher than necessary leading to dropout or nonadherence due to extrapyramidal side effects. However, the interpretability of the results of potential dose differences is limited by missing information on mean doses in the LAI and OAP arms, especially in old studies, and by substantial differences in the suggested conversion factors from antipsychotic doses to CPZ equivalents, both of which applied mostly to older studies using FGA-LAIs.

In contrast to our results, recent naturalistic studies support the advantages of LAIs over OAPs in relapse prevention[30–32] as do mirror image studies.[33,34] Tiihonen et al.[31] reported in a nationwide cohort that the risk of rehospitalization with LAIs was one-third that of OAPs. Most LAIs showed significant superiority compared with each OAP counterpart regarding all-cause discontinuation. These results are especially important given the potentially conservative bias in that the patients who receive doctor's choice LAIs are more likely to be nonadherent and more severely ill compared with patients receiving doctor's choice OAPs. Moreover, patients consenting to clinical trials of LAIs may not be representative of those prescribed LAIs in real-world settings.[35] Participants in clinical trials might overrepresent patients with better engagement with health care providers, better adherence to the treatment, lower illness severity, and better cognitive capabilities to understand complex issues. This difference in procedures can potentially lead to a cohort bias in that less severely ill patients could be enrolled in newer trials, particularly with increasing stringency of consent processes. This may explain the different results of older vs newer studies.

It is also important to recognize that participation in a controlled trial alters the ecology of treatment delivery and experience. Patients in clinical trials are likely to receive more and different types of attention than those

in routine care, from measures of adherence to reminders to attend clinical/research assessment sessions, or to the provision of free medication.[36] In addition, more frequent monitoring during a trial enables psychiatrists to change dosages according to the symptoms and provide supportive psychotherapy. It is difficult to determine what role these factors might have in altering patterns of medication-taking in contrast to routine care and to what extent they might, therefore, diminish the potential advantages of LAIs in RCTs. The substantial disparity between the large naturalistic cohort study results and those of RCTs in this context would support such concerns.

To this point, we have assumed that LAIs must be more effective than OAPs and have been trying to understand why this is not apparent in the RCTs. We should also consider the possibility that if patients are fully adherent with OAPs, the OAPs may actually be more efficacious than LAIs as suggested by 2 recent trials.[23,37,38] One interesting hypothesis is the potential supersensitivity of the dopamine D2 receptor. Long-term, continuous D2 blockade may increase the number and/or high-affinity state of dopamine receptors.[39,40] In addition, there are data suggesting that transient, rather than continuous blockade of D2 receptors by "extended dosing" (eg, every other day dosing), may be more efficacious in both animal and human studies.[41,42] Therefore, LAIs might result in more continuous D2 blockade and receptor upregulation/supersensitivity compared with OAPs. This effect would be differentially stronger when the OAPs do not consist of high-potency FGAs, as oral SGAs generally have less complete or prolonged D2 blockade.

Regarding our study methodology, 2 points require consideration. First, we utilized relapse rate preferentially based on survival analyses as a primary outcome. We acknowledge that graphically calculated relapse rates from survival curves can result in higher relapse rates compared with raw rates because the denominator decreases as dropout occurs. On the other hand, raw relapse rates do not count the potential relapse among patients who dropped out. Moreover, in case of systematically different dropout rates between the treatment arms resulting in shorter follow-up periods in one treatment compared with another, a bias is introduced that disfavors the treatment with better acceptability and greater persistence, as more time is available for relapses to occur. For these reasons, we believe that estimated rates may yield more accurate data than raw relapse rates. However, we acknowledge the problem of using estimations, rather than observed data, and the mixing of estimated and raw rates from studies not providing survival curves. To deal with this problem, we analyzed the data in several ways, utilizing raw instead of estimated relapse rates, and using raw or estimated rates exclusively. The results remained the same, independent of how relapse rates were calculated.

Second, we used each the safety/efficacy and randomized population as denominators for the analyses. While ITT analysis is the gold standard for clinical trials, ITT definitions varied, which is problematic. Some defined ITT as patients taking the medication at least once, or receiving at least one assessment (modified ITT), while others utilized the randomized population. Moreover, several studies provided survival curves and other results, which were solely based on the modified ITT sample, and 1 study[26] only presented the modified ITT population. It is widely accepted that the reluctance toward injections is an important obstacle for introducing LAIs.[9] Some studies included in our analyses reported that patients dropped out when learning of their LAI allocation. We considered it important to include those patients as dropouts. However, given the fact that more studies provided data using modified ITT populations, we wanted to also examine the risk of relapse once patients are on LAIs. Therefore, we analyzed the results in both populations separately, which we considered the most conservative strategy, and there were no important differences.

Results of these analyses have to be interpreted in the context of several limitations. First, the database, though larger than in the previous meta-analysis, is still limited. For example, no long-term RCTs comparing paliperidone-LAI or aripiprazole-LAI with OAPs were available. Furthermore, relapse definitions varied. We utilized each study-defined relapse measure, and if no definition was available, we used the most-appropriate relapse-related outcome, ie, predominantly psychiatric hospitalization. The problem of heterogeneously defined relapse is not surprising because there is no universally accepted definition. On the other hand, this heterogeneity and broad-based definition could also serve to enhance the generalizability of the results. There was a 14-year gap between the last study published in 1991 and the next study published in 2005, which enabled us to examine the effect of time when the study was conducted. Because clinical and diagnostic concepts of the disease and therapeutic environments have changed over time, it is unclear, which factors in addition to the almost exclusive study of FGA-LAIs earlier and of SGA-LAIs later may have influenced the results. In addition, heterogeneity of the results was seen. Although the majority of studies targeted chronic patients with over 10 years of illness, some targeted patients with even longer illness duration,[12] while some targeted relatively early-onset patients.[43,44] One study included patients with aggressive behavior,[24] another included patients who were hospitalized throughout the study.[23] Such clinical characteristics and different treatment settings may have caused heterogeneity. Of note, risperidone-LAI studies were found to be most heterogeneous ($\tau^2 = 0.09$, $I^2 = 74\%$, $Q = 30.92$, df = 8, $P = .0001$). Moreover, the reporting of drop out due to "adverse events" is not always unambiguously restricted to physiologic/physical adverse effects. Rather, at times, discontinuation due to potential inefficacy-related outcomes,

eg, anxiety, agitation, and worsening of psychosis, may be counted as a side effect-related discontinuation, which complicates the interpretation of this outcome.

Further limitations regarding the design of the analyzed studies include issues like treatment concealment (7/21 were open studies), in- vs outpatient status (6/21 included inpatients throughout the study, or presumably a significant portion of the study), study duration (6/21 were <1 year), and medication allocation (10/21 used different medications in the LAI and OAP arms). We consider the double-blind, double-dummy design favorable, as it reduces expectancy and rater biases. At the same time, however, this design itself is very different from clinical practice, and might have contributed to increased selection bias. Moreover, inpatient studies apparently ensured adherence, which may have strengthened the efficacy of the OAP arm. Because nonadherence can increase over time, one may expect also that the relative superiority of LAI compared with OAPs develops over time. Such an effect may explain the lower risk ratio in the longer term studies when we analyzed separately results from studies lasting <1 year (RR = 1.14, 95% CI: 0.82–1.58, $P = .43$) and those lasting ≥1 year (RR = 0.91, 95% CI: 0.77–1.07, $P = .25$). However, LAIs were not superior to OAPs in either study subgroup, and some recent studies with durations of ≥2 years[12,14,15] also failed to show superiority of LAIs. This calls into question that the study duration is a major determinant. Using different medications in the oral and LAI arms makes it difficult to disentangle the independent efficacy of the delivery method from potential differences in the efficacy of the 2 drugs including inappropriate dose equivalency. We attempted to examine these issues by subgroup analyses, which all yielded the same result of similar outcomes in the LAI and OAP groups.

In conclusion, while we had anticipated that LAIs (with their intrinsically better adherence) would be more effective than OAPs in preventing relapse, this was not evident in a synthesis of the available RCTs. Notably, these results are in contrast to naturalistic cohort studies showing superiority of LAIs in preventing rehospitalization. Further consideration is required to understand the reasons for this discrepancy. In order to evaluate the real-world effectivenss of LAIs compared with OAPs, large and long pragmatic trials are needed, which better resemble common clinical practice.

In our analysis, FGA-LAIs, but not SGA-LAIs, outperformed OAPs. The difference in effect was not statistically significant and in any event could be due to a cohort effect. The only way to determine if the FGA/SGA distinction is important here would be to conduct head-to-head trials of FGA-LAIs vs SGA-LAIs. It is likely that some studies included in this analysis systematically excluded patients who were expected to have poor adherence. If this is true, then the results should not be generalized to these patients and do not refute the possibility that LAIs may be superior to OAPs in this important group.

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## Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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