Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre–post studies

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Summary

Background Evidence of comparative benefits of long-acting injectable antipsychotics (LAIs) versus oral antipsychotics for schizophrenia has been inconsistent across study designs. The aim of this study was to evaluate the comparative benefits of LAIs versus oral antipsychotics in three study designs to inform clinical decision making.

Methods We did a comprehensive systematic review and meta-analysis comparing LAIs versus oral antipsychotics for schizophrenia covering three study designs: randomised controlled trials (RCTs), cohort studies, and pre–post studies. Our literature search was without language restrictions, in MEDLINE and PubMed, the Cochrane Library, Scopus, and Embase, for studies published from database inception up to a last search on March 13, 2020. We also searched for unpublished studies and ClinicalTrials.gov. We included studies lasting at least 6 months that targeted adults with schizophrenia and related disorders (>80% of participants). Studies on penfluridol (neither an LAI or daily oral antipsychotic), case reports, and case series with fewer than 20 patients were excluded. Two investigators independently extracted study-level data and resolved disagreement by consensus, or via a third investigator. Study authors were contacted to obtain additional information as needed. For our primary outcome we meta-analysed the risk ratio (RR) for hospitalisation or relapse with LAIs versus oral antipsychotics by a random-effects model, with hospitalisation used preferentially over relapse. As secondary analyses, we reversed the preferential order to relapse over hospitalisation, and assessed hospitalisation risk and relapse risk individually. Other secondary outcomes included all meta-analysable data, classed by relevance to effectiveness, efficacy, safety, quality of life, cognitive function, and other outcomes, and analysed by study design. Dichotomous outcomes were expressed as pooled RR and continuous outcomes as standardised mean difference (SMD). The protocol is registered with PROSPERO (CRD42019142094).

Findings We identified 14 687 records, of which 137 studies (397 319 patients) met the inclusion criteria (32 RCTs [23·4%; 8577 patients], 65 cohort studies [47·4%; 377 447 patients], and 40 pre–post studies [29·2%; 11 295 patients]) and were analysed. The quality of studies in terms of risk of bias varied across study designs and within each study design from low to high. LAIs were associated with a lower risk of hospitalisation or relapse than oral antipsychotics in each of the three study designs (RCTs: 29 studies, 7833 patients, RR 0·88 [95% CI 0·79–0·99], p=0·033; cohort studies: 44 studies, 106 136 patients, RR 0·92 [0·88–0·98], p=0·0044; pre–post studies: 28 studies, 17 876 patients, RR 0·44 [0·39–0·51], p<0·0001). This association was maintained across the study designs when we reversed the preferential order to risk of relapse over hospitalisation, and in individual analysis of hospitalisation risk. The association was maintained only in pre–post studies for relapse risk alone. In all other outcomes related to effectiveness, efficacy, safety, quality of life, cognitive function, and other outcomes, LAIs were more beneficial than oral antipsychotics in 60 (18·3%) of 328 comparisons, not different in 252 (76·8%) comparisons, and less beneficial in 16 (4·9%) comparisons when analysed by study design. Significant heterogeneity was observed across all three study designs. Publication biases were apparent in cohort and pre-post studies, but effect sizes were similar after trim-and-fill analyses.

Interpretation Although study designs have strengths and weaknesses, including potential low quality of observational studies, we consistently identified significant benefit with LAIs versus oral antipsychotics in preventing hospitalisation or relapse, in settings ranging from restricted research (RCTs) to real-word application (cohort and pre–post studies). Our findings suggest that increased clinical use of LAIs could improve outcomes in schizophrenia.

Funding None.

Lancet Psychiatry 2021; 8: 387–404

Published Online April 13, 2021 https://doi.org/10.1016/S2215-0366(21)00039-0

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Introduction

Schizophrenia is a mental disorder generally characterised by repeated relapses and worsening of psychopathology and social functioning.[1] Although some patients recover well, to a point of mild or no symptoms, adequate self care, and daily functioning, this subgroup is a small

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Research in context

Evidence before this study

To search for previous relevant reviews and meta-analyses, we did a literature search without language restrictions in MEDLINE and PubMed, the Cochrane Library, Scopus, and Embase, for studies published from database inception up to March 13, 2020. Search terms included synonyms of (1) antipsychotic(s); (2) schizophrenia and related disorders, (3) randomised; and (4) depot, (long-acting) injection(s), microsphere, decanoate, palmitate, and enanthate. Five relevant meta-analyses among 902 reviews or meta-analyses, including our three previous meta-analyses, were identified. Our three previous, design-specific meta-analyses of randomised controlled trials (RCTs), cohort studies, and pre–post studies found inconsistent results regarding the comparative effectiveness of long-acting injectable antipsychotics (LAIs) and oral antipsychotics depending on study design. LAIs showed no significant difference to oral antipsychotics regarding relapse or hospitalisation outcomes in RCTs. Conversely, in cohort and pre–post studies, closer to real-world clinical settings, LAIs were significantly better than oral antipsychotics in preventing relapse or hospitalisation. Regarding potential harms, a meta-analysis of RCTs published between 2000 and 2015 reported that LAIs were associated with a greater risk of extrapyramidal syndrome and prolactin-related symptoms. However, that analysis did not take into account differences in the specific antipsychotics used in the LAI and oral antipsychotic groups, with 12 of 15 meta-analysed RCTs utilising risperidone in the LAI formulation, a drug known to be associated with extrapyramidal syndrome and prolactin elevation. Conversely, a meta-analysis of 16 RCTs published between 1975 and 2015, in which the same antipsychotic was used in the LAI and oral antipsychotic groups, found no difference in 115 of the 119 reported adverse effects between LAIs and oral antipsychotics, with a higher incidence of akinesia, low-density lipoprotein cholesterol increase, and anxiety with LAIs than oral antipsychotics, but lower prolactin increase with LAIs. Since these meta-analyses, a substantial number of RCTs, cohort, and pre–post studies have been published, and the meta-analysis results have been not updated.

Added value of this study

To the best of our knowledge, this meta-analysis is the first to have included all available evidence on LAIs versus oral antipsychotics across RCT, cohort, and pre–post study designs, from studies lasting 6 months or longer in patients with schizophrenia and related disorders. Compared with previous meta-analyses targeting each study design separately, this analysis included at least 1·5 times the number of studies, and all meta-analysable outcomes were evaluated. Although the summary effect sizes were small in RCTs and cohort studies, LAIs showed a consistent benefit over oral antipsychotics in all study designs regarding hospitalisation or relapse, and in many other outcomes related to efficacy and effectiveness. LAIs showed no significant difference from oral antipsychotics regarding most adverse events. However, results should be considered in view of the strengths and weaknesses of the study designs, the potentially low quality of observational studies, and heterogeneous adverse event reporting across studies.

Implications of all the available evidence

This updated analysis of RCTs and other study designs consistently showed the risk benefit of LAIs in preventing hospitalisation or relapse. Results might be especially meaningful for the population at high risk of non-adherence, for whom recent RCTs were able to show a benefit of LAIs in preventing hospitalisation or relapse. Taken together, the results suggest increased use of LAIs in clinical practice should be considered.

minority.[2] Antipsychotics are efficacious for relapse prevention in patients with multiple-episode and first-episode schizophrenia,[3–5] providing a 2–6-times reduced risk of relapse versus no antipsychotic treatment.[3–6]

Non-adherence to antipsychotic treatment is frequently observed in patients with schizophrenia[7–9] with a significantly increased risk of relapse.[10] Adherence to medication might be improved by use of long-acting injectable antipsychotics (LAIs), which facilitate adherence by reducing dosing frequency, offering reliable medication delivery and stable pharmacokinetics, and allowing regular monitoring of administration.[11] However, previous studies comparing the effectiveness of LAIs and oral antipsychotics for schizophrenia have reported inconsistent outcomes.

Our previous meta-analysis of randomised controlled trials (RCTs), as the largest in recent years comparing LAIs versus oral antipsychotics, did not find a significant difference between LAIs and oral antipsychotics in preventing relapse or hospitalisation, or in secondary outcomes related to relapse, including drug inefficacy, all-cause discontinuation, and non-adherence.[12] Conversely, subsequent meta-analyses of pre–post studies and cohort studies showed that LAIs were associated with significantly lower risk of hospitalisation or relapse than oral antipsychotics.[13,14]

We did an updated systematic review and meta-analysis of RCTs, pre–post studies, and cohort studies that compared LAIs and oral antipsychotics in people with schizophrenia. Each of these study designs has strengths and weaknesses. For example, RCTs are regarded as the highest standard in terms of evidence, but might overly influence the ecology of care and include the most adherent patients who are unlikely to be given LAIs in real-world settings. Conversely, in cohort and pre–post studies, patients are not randomly assigned, and data are based on real-world application

of LAIs. However, in cohort studies, patients receiving LAIs are more likely to be severely ill, leading to a selection bias that disadvantages LAIs, and in pre–post studies, expectation bias and regression to mean values might preferentially advantage LAIs. Therefore, an overview of a wide range of evidence is important to thoroughly examine the benefits of LAIs versus oral antipsychotics.

Methods

Search strategy and selection criteria

Our systematic review and meta-analysis followed PRISMA guidelines.[15] We did a search without language restrictions, using MEDLINE and PubMed, the Cochrane Library, Scopus, and Embase, for studies published from database inception up to a last search on March 13, 2020. We also searched for unpublished studies, such as conference proceedings on the aforementioned databases and on the ClinicalTrials.gov registry. Search terms included synonyms of antipsychotic(s) AND schizophrenia and related disorders AND depot (long-acting) injection(s), microsphere, decanoate, palmitate, enanthate, and monohydrate (full search terms provided in appendix 8 [p 81]). Reference lists of relevant publications were also searched. When multiple reports referred to the same study or overlapping patient populations (eg, nationwide cohort studies with different publication years, but overlapping study years), we included the newer or larger study. Two independent investigators (among TK, KH, and SK) did the literature searches. Titles and abstracts of the retrieved citations were screened to identify potentially eligible publications. In a first broad screening step, citations were excluded if clearly irrelevant; that is, if a publication was not a study in patients with schizophrenia, or if a publication was not a study in which LAIs and oral antipsychotics were compared. In a second screening step, the full set of eligibility criteria was applied. Potentially relevant articles were then screened as full texts. Disagreement was resolved by consensus or via a third investigator. Summary estimate data from each study were extracted independently by two investigators (among TK, KH, and SK). Data were extracted into Excel sheets. The data extraction sheets were then compared and inconsistencies resolved by consensus or via a third investigator. TK, KH, and SK are fluent in Japanese and English. JK is fluent in English, and CC is fluent in German, English, and Spanish, and these reviewers became involved in data extraction for relevant language studies identified. Articles written in a language not fully understood by the authors were translated by bilingual speakers, and data extraction was confirmed with Google translate. Authors were contacted for unreported information as needed. Duplicate reports were identified throughout the review process by study name, trial number, methodology, and specific patient characteristics, and excluded.

We selected randomised, cohort, and pre–post studies comparing LAIs with oral antipsychotics in adults (age ≥18 years) with schizophrenia and related disorders. As we aimed to focus on the comparative long-term effects of LAIs and oral antipsychotics, we included studies lasting at least 6 months for RCTs and cohort studies. For pre–post studies, we included studies that followed patients for at least 12 months (≥6 months each with LAI and oral antipsychotic). We excluded studies in which more than 20% of patients had a non-schizophrenia spectrum disorder. Additionally, we planned to exclude studies on penfluridol, a once weekly oral antipsychotic, considering it is neither an LAI or daily oral antipsychotic. We also planned to exclude case reports and case series with fewer than 20 patients.

Data analysis

To characterise each study, we extracted all general information (study reference, publication year, country, sponsor, number of patients, setting at time of recruitment, blinding status, mean age, percent men, percent of white participants, trial duration, study hypothesis, duration of illness, mean Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale-total score at baseline, patient inclusion criteria, name of LAIs and oral antipsychotics, and mean antipsychotic dose). We extracted outcomes on hospitalisation, relapse, effectiveness, efficacy, cognitive function, quality of life, individual adverse event, and other miscellaneous outcomes (appendix 8, pp 82–85).

See Online for appendix 8

The primary outcome was prevention of hospitalisation or relapse, presented in this study in terms of hospitalisation or relapse risk. We preferentially used hospitalisation over relapse, but whenever a study did not report on hospitalisation we used relapse. We excluded studies from the primary analysis if they did not report on hospitalisation or relapse. In secondary analyses we reversed the preferential order to relapse over hospitalisation, and individually assessed hospitalisation risk and relapse risk. Other secondary outcomes included study discontinuation, hospitalisation days, hospitalisation rate, psychopathology scale scores, adverse events, laboratory parameters, and other meta-analysable outcomes, a full list of which is in the appendix 8 (pp 82–85). These secondary outcomes were classed by relevance to effectiveness, efficacy, adverse events, quality of life, cognitive function, or other outcomes. For these outcomes, we extracted data from the endpoint of each study. Outcomes we deemed most clinically relevant are presented herein and other outcomes reported in appendix 8 (pp 36–46).

All data were double-entered into and meta-analysed with Comprehensive Meta-Analysis software (version 3; BioStat) according to a random-effects model.[16] We expressed dichotomous outcomes as pooled risk ratio

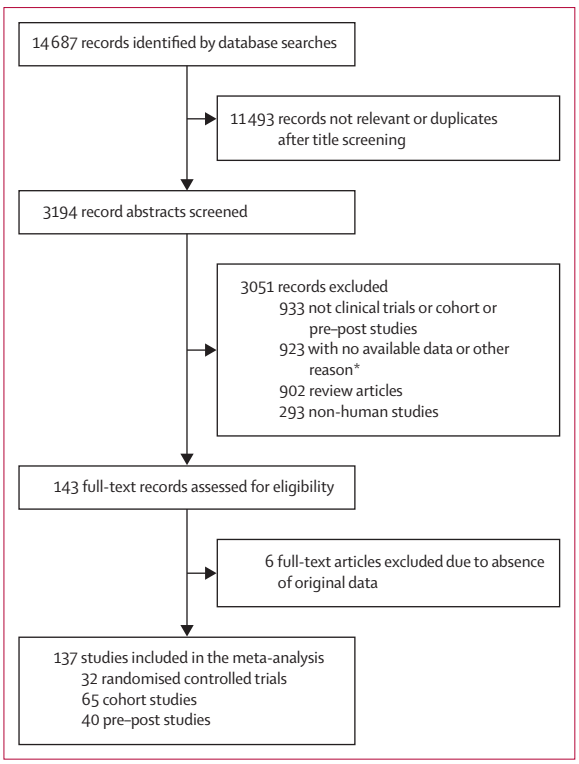


Figure 1: **Search and selection process**
*597 records without available data; 244 not comparing LAIs with OAPs; 46 with follow-up duration less than 6 months; 15 not in adult patients; 15 non-antipsychotic studies; and six with 20% or more patients with non-schizophrenia spectrum disorders.

(RR), and continuous outcomes as standardised mean difference (SMD) using the inverse variance method. RR and SMD values were reported with their 95% CIs. RR values less than 1, and SMDs less than 0 for efficacy outcomes, were considered to indicate relative benefit with LAIs if the effect was significant ($p<0·05$). Conversely, RR values greater than 1, and SMDs greater than 0 for efficacy outcomes, were considered to indicate relative benefit with oral antipsychotics if the effect was significant ($p<0·05$). If LAIs did not significantly separate from oral antipsychotics ($p\geq0.05$), this indicated no difference. In some instances, the originally scaled outcome differed from all others, in that a higher RR represented a beneficial outcome with LAIs versus oral antipsychotics (eg, improved adherence indicated by an increased number of outpatient office visits, day-clinic visits, or pharmacy visits; or improved quality of life indicated by increased scores). In these instances, for consistency, we rescaled the outcome, so that benefit was indicated by an RR lower than 1 and an SMD lower than 0. Hospitalisation or relapse risk was computed as the number of patients who had at least one hospitalisation or relapse divided by the number of patients at risk. The RR was then calculated as the ratio of risk for LAIs versus oral antipsychotics. We also assessed clinical benefit and harm of LAIs for schizophrenia, using number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH; with 95% CIs) when the RR for that outcome was statistically significant. We explored between-study heterogeneity using the χ^2 test of homogeneity and I^2 statistics, with a p value of less than 0·05 and I^2 greater than 50% taken to indicate significant heterogeneity. All analyses were two-tailed with an α of 0·05. No adjustments were made to p values for the multiple comparisons; therefore, the p values should be interpreted with caution. Additionally, we did subgroup analyses, meta-regression analyses, and multivariable meta-regression analyses based on the primary outcome (appendix 8 p 48).

For RCTs, risk of bias in all studies was evaluated in accordance with the Cochrane Collaboration's tool for assessing risk of bias,[17] with regard to adequacy of sequence generation, allocation concealment, masking of participants, personnel and outcome assessors, incomplete outcome data, and selective outcome reporting. For cohort studies and pre–post studies, risk of bias was evaluated with the Newcastle-Ottawa scale.[18] The Newcastle-Ottawa quality scale captures representativeness of the exposed cohort, selection of the unexposed cohort, ascertainment of exposure, absence of the outcome of interest at the start of the study, presence of controls for important or additional factors, assessment of outcome, sufficiency of follow-up length for outcomes to occur, and adequacy of follow-up regimen. Studies were defined as high quality or low quality on the basis of number of low risk ratings per study (for RCTs, high quality was ≥4 domains of low risk; for cohort studies, high quality was ≥8 domains of low risk; and for pre-post studies, high quality was ≥5 domains of low risk). Quality of studies within each design was presented by year.

Publication bias for the primary outcome was assessed by visually inspecting funnel plots for each study design. In addition, we calculated the Egger's regression intercept[19] for the primary outcome, using the trim-and-fill method to account for publication bias.[20] The fail-safe number of negative studies that would be required to nullify a statistically significant effect size (ie, make $p>0·05$) was then calculated. The study protocol is registered with PROSPERO (CRD42019142094).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The initial search provided 14 687 records, of which 11 493 records were excluded after title screening because they were not relevant or duplicates. Of the

remaining 3194 records, 3057 were excluded after screening and assessment of abstracts and full texts, yielding 137 studies (32 RCTs [23·4%; 8577 patients],[21–51] 65 cohort studies [47·4%; 377 447 patients],[52–115] and 40 pre–post studies [29·2%; 11 295 patients];[116–155] figure 1). For one cohort study we extracted all data from the published abstract.[74] Three unpublished studies (two RCTs [NCT00256997 and NCT00992407] and one cohort-study [NCT01894984]) were included in our meta-analyses. Two articles reported different data for the same RCT[32,33] and both datasets were included. Characteristics of the studies, patients, and treatments are summarised in appendix 8 (pp 3–35). The quality of studies included in the analysis varied across study designs and within study designs from low to high (study quality by year presented in appendix 8 [pp 78–80]).

The RCTs were published or done between 1974 and 2019. 11 studies were double blind, seven were rater masked, 13 were open label, and blinding status was not reported in one study. 22 studies were sponsored by industry, seven were sponsored by academia, and sponsors for the remaining three studies were not clear. The median number of participants per study was 136 (IQR 67–399), and the mean duration of follow-up was 62·5 weeks (SD 28·7). The mean age of participants was 37·2 years (SD 7·4), and 5635 (65·7%) of the 8577 participants were men (appendix 8 pp 3–10). The regions of study location are listed in appendix 8 (p 10). Among the 32 RCTs, the comparisons of LAIs versus oral antipsychotics by type of antipsychotics were: first-generation antipsychotic (FGA)-LAIs versus FGA-oral antipsychotics in nine (28·1%) studies, FGA-LAIs versus second-generation antipsychotic (SGA)-oral antipsychotics in one (3·1%) study, SGA-LAIs versus SGA-oral antipsychotics in 18 (56·3%) studies, FGA-LAIs versus mixed-oral antipsychotics in one (3·1%) study, and SGA-LAIs versus mixed-oral antipsychotics in three (9·4%) studies. No study reported that clozapine was used in the oral antipsychotic group.

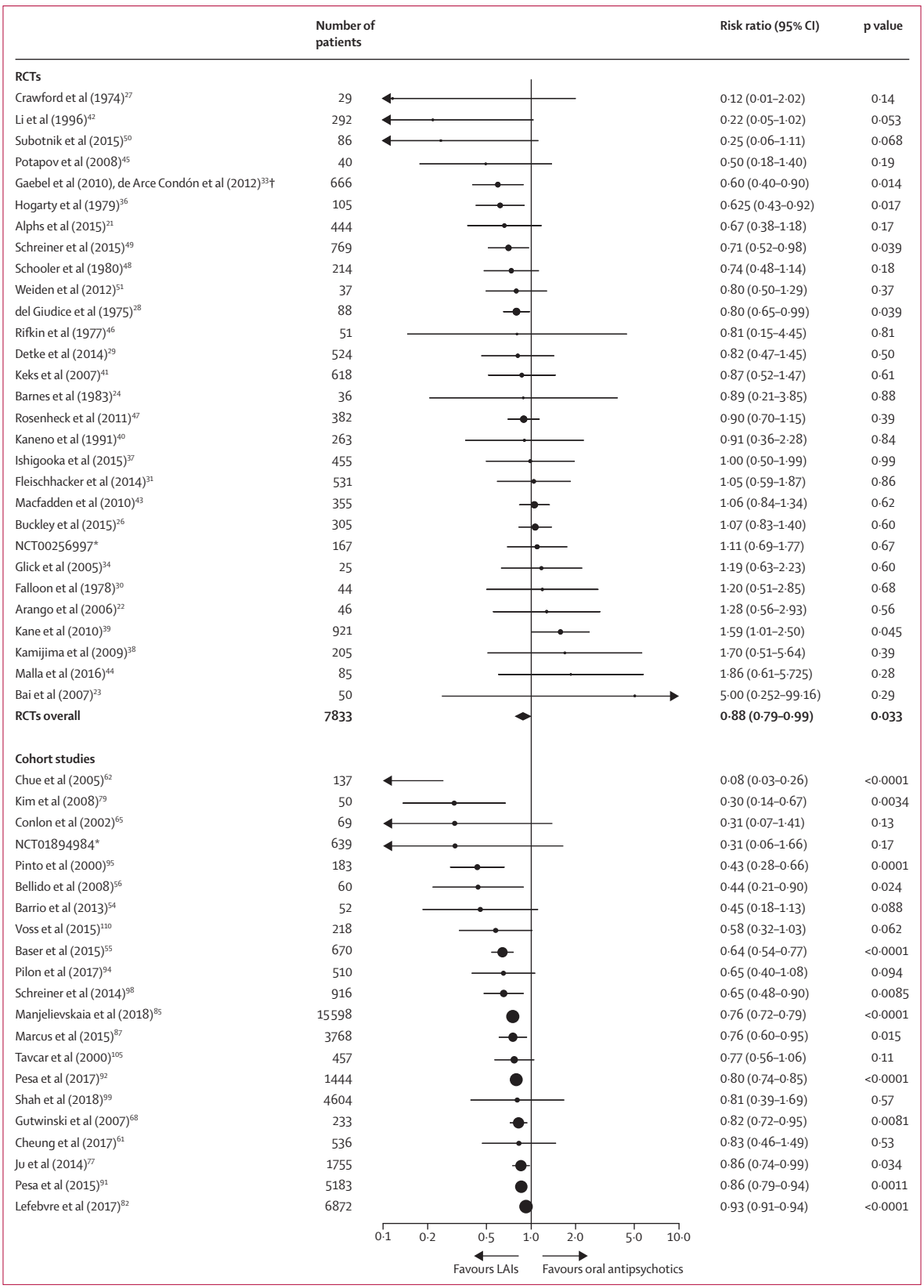
The cohort studies were published or done between 1983 and 2020. 48 studies (345 014 patients) were a retrospective database analysis and 17 studies (32 433 patients) were prospective. 36 studies were sponsored by industry, 28 studies were sponsored by academia, and sponsors for the remaining study were not clear. The median number of participants per study was 838 (IQR 213–5220), the mean follow-up duration was 79·6 weeks (SD 47·4), and mean person-years was 14 370·8 (SD 56 724·5). The mean age of participants was 40·8 years (SD 5·8) and 209 861 (55·6%) of the 377 447 participants were men (appendix 8 pp 10–26). Among the 65 cohort studies, the comparisons of LAIs versus oral antipsychotics by type of antipsychotics were: FGA-LAIs versus FGA-oral antipsychotics in three (4·6%) studies, FGA-LAIs versus SGA-oral antipsychotics in seven (10·8%) studies, SGA-LAIs versus SGA-oral antipsychotics in 20 (30·8%) studies, FGA-LAIs versus mixed-oral antipsychotics in six (9·2%) studies, SGA-LAIs versus mixed-oral antipsychotics in eight (12·3%) studies, mixed-LAIs versus mixed-oral antipsychotics in 17 (26·2%) studies, and other comparisons without reporting types of antipsychotics in four (6·2%) studies. Five (7·7%) studies reported that clozapine was used in the oral antipsychotic cohort.

The pre–post studies were published between 1971 and 2020. 35 studies (8340 patients) were retrospective in design and five studies (2955 patients) were prospective. 15 studies were sponsored by industry, 16 studies were sponsored by academia, and sponsors for the remaining nine studies were not clear. The median number of participants per study was 113 (IQR 56–235), the mean follow-up duration was 68·9 weeks (SD 52·6), and mean person-years was 285·1 (SD 472·3). The mean age of participants was 42·3 years (SD 6·1) and 6506 (57·6%) of the 11 295 participants were men (appendix 8 pp 26–34). Among the 40 pre–post studies, the comparisons of LAIs versus oral antipsychotics by type of antipsychotics were: SGA-LAIs versus SGA-oral antipsychotics in three (7·5%), FGA-LAIs versus mixed-oral antipsychotics in one (2·5%), SGA-LAIs versus mixed-oral antipsychotics in 11 (27·5%), mixed-LAIs versus mixed-oral antipsychotics in five (12·5%), and other comparisons without reporting types of antipsychotics in 20 (50·0%). One study (2·5%) reported that clozapine was included in oral antipsychotic treatment.

The primary outcome was assessed in studies that reported on hospitalisation or relapse. The risk of hospitalisation or relapse, with preferential use of hospitalisation over relapse, was significantly lower with LAIs than oral antipsychotics in each of the three study designs (RCTs: 29 studies, 7833 patients, RR 0·88 [95% CI 0·79–0·99], p=0·033; cohort studies: 44 studies, 106 136 patients, RR 0·92 [0·88–0·98], p=0·0044; pre–post studies: 28 studies, 17 876 patients, RR 0·44 [0·39 to 0·51], p<0·0001; figures 2 and 3). We observed significant heterogeneity among cohort studies (χ^2 p<0·0001, I^2=88·4%) and pre–post studies (χ^2 p<0·0001, I^2=88·7%) but not among RCTs (χ^2 p=0·092, I^2=27·0%). The NNTB was 45 (95% CI 25–540) in the RCTs, 31 (19–95) in the cohort studies, and 4 (3–4) in the pre–post studies.

Figure 3 provides results of comparisons for relapse-related or hospitalisation-related outcomes. Regarding risk of relapse or hospitalisation, with preferential use of relapse over hospitalisation, LAIs were associated with significantly lower risk over oral antipsychotics among all three study designs. When relapse was used preferentially, NNTB was lower for RCTs but mostly unchanged for cohort studies and pre-post studies, compared with values in the primary analysis.

On analysis of hospitalisation risk alone, LAIs were associated with lower risk of hospitalisation than oral



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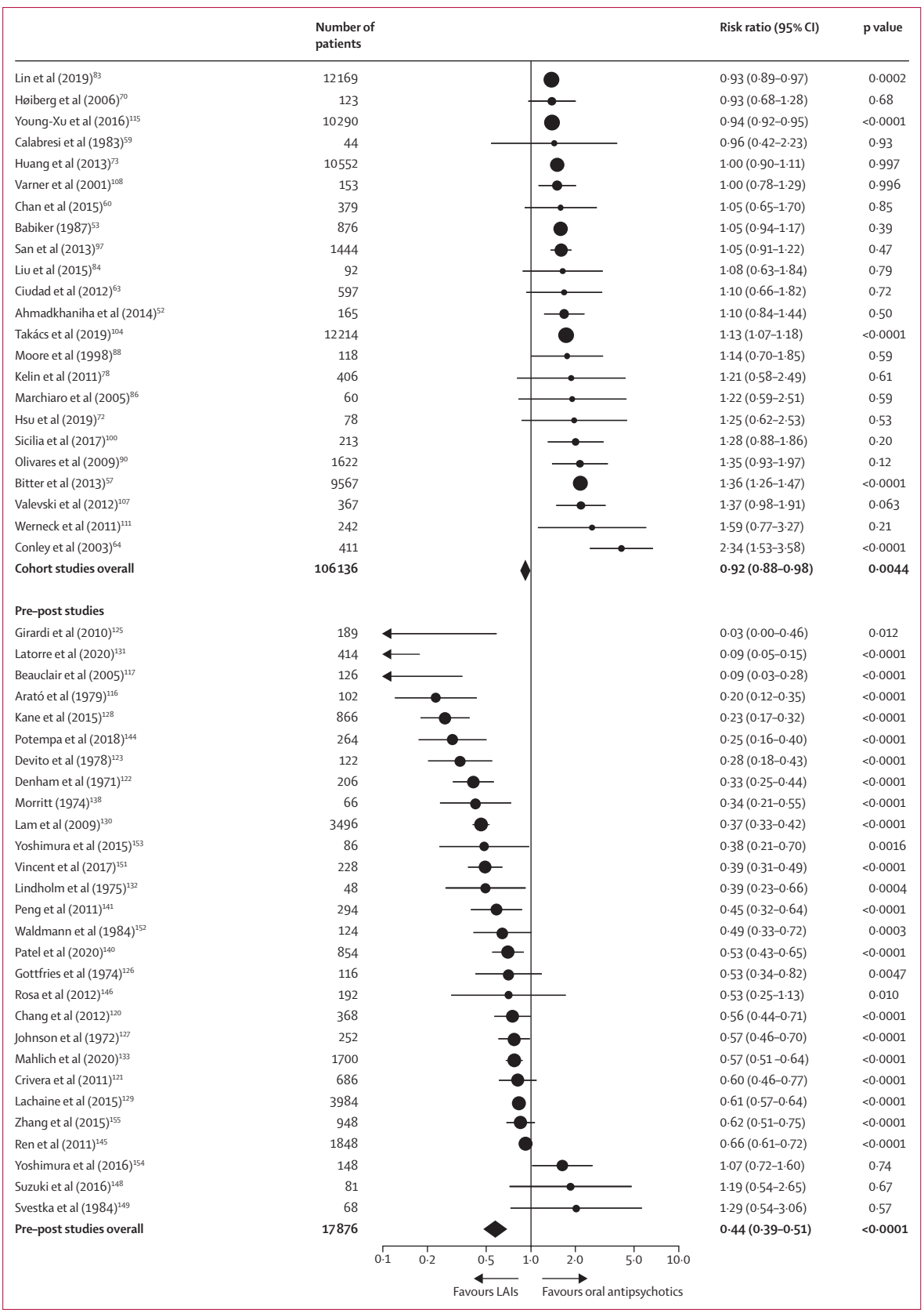

Figure 2: **Forest plot for risk of hospitalisation or relapse with LAIs versus oral antipsychotics**
Hospitalisation was preferentially used over relapse in calculation of risk. Studies that did not report on hospitalisation or relapse were excluded from this analysis. LAI=long-acting injectable antipsychotic. RCT=randomised controlled trial. *On ClinicalTrials.gov. †Two studies of the same RCT.

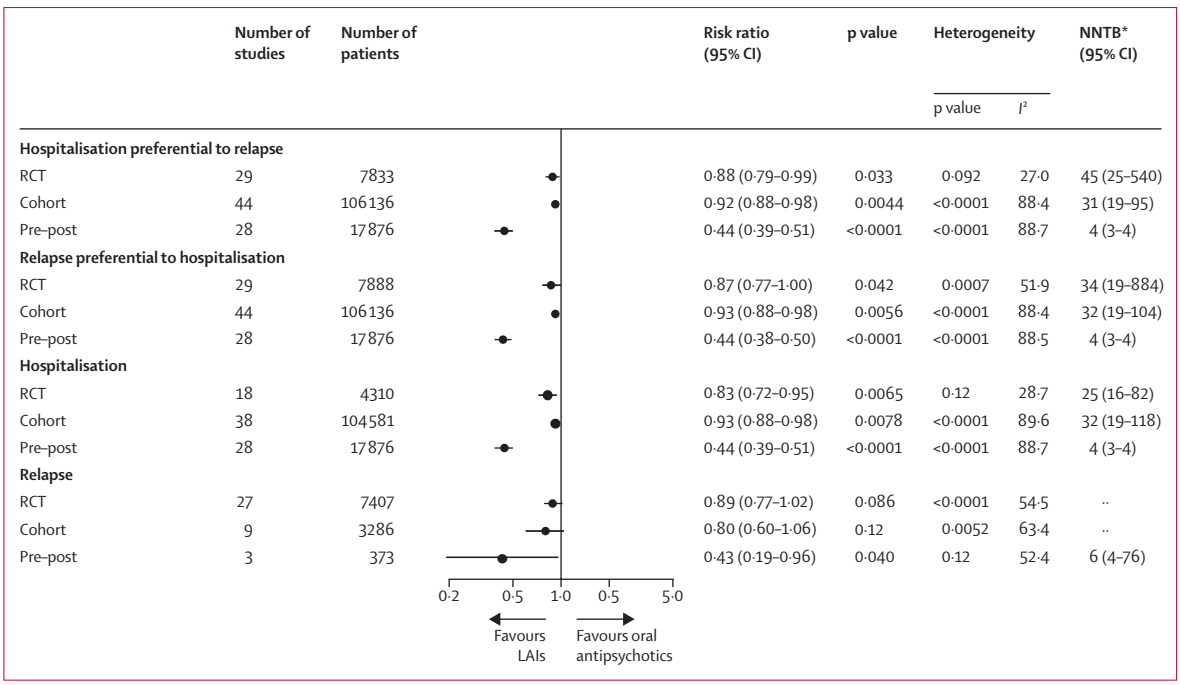

Figure 3: **Forest plot for summary outcomes related to hospitalisation or relapse with LAIs versus oral antipsychotics**
Studies without available data on hospitalisation or relapse were excluded from relevant analyses. LAI=long-acting injectable antipsychotic. NNTB=number needed to treat for an additional beneficial outcome. RCT=randomised controlled trial. *NNTB was calculated when the RR for that comparison was statistically significant (p<0·05).

antipsychotics in all three study designs. NNTB was lower for RCTs but mostly unchanged for cohort and pre–post studies. Relapse risk alone was significantly lower in patients receiving LAIs than in those receiving oral antipsychotics in pre–post studies, but not in RCTs or cohort studies. NNTB was marginally higher in pre–post studies, and not calculated for RCTs or cohort studies (non-significant RRs). Appendix 8 (pp 48–57) provides results of the subgroup and meta-regression analyses.

The table and appendix 8 (pp 36–46) provide results of comparisons and heterogeneity between studies for other secondary outcomes related to effectiveness, efficacy, adverse events, quality of life, cognitive function, and other outcomes, including hospitalisation rate, hospitalisation days, health-care resource use, and adherence. LAIs were significantly advantageous in 60 (18·3%) of 328 comparisons, not different in 252 (76·8%) comparisons, and less beneficial (RR >1 or SMD >0, p<0·05) in 16 (4·9%) comparisons when analysed by study design. Regarding effectiveness-related outcomes, LAIs provided a significant improvement versus oral antipsychotics in 23 (69·7%) of 33 comparisons, and LAIs were not different from oral antipsychotics in the 10 (30·3%) remaining comparisons. When limited to outcomes reported in at least three studies, LAIs were significantly advantageous in 11 (68·8%) of 16 comparisons, and LAIs were not different from oral antipsychotics in the five (31·3%) remaining comparisons. Regarding efficacy-related outcomes, LAIs provided significant improvement versus oral antipsychotics in 5 (10·9%) of 46 comparisons (including Clinical Global Impression [CGI]-Severity scale [CGI-S] mean change in cohort studies, treatment response in a pre–post study involving 202 patients, and CGI-Change scale [at least minimally improved] in RCTs), and LAIs were not different from oral antipsychotics in the remaining 41 (89·1%) comparisons. Limited to outcomes reported in three or more studies, LAIs were significantly advantageous in one (4·5%) of the 22 comparisons (CGI-S mean change in cohort studies), and LAIs were not different from oral antipsychotics for the remaining 21 (95·5%) comparisons. Regarding adverse effect outcomes, LAIs were significantly advantageous to oral antipsychotics in 18 (10·0%) of 180 comparisons, LAIs were not different from oral antipsychotics in 148 (82·2%) comparisons, and LAIs were significantly worse than oral antipsychotics in the remaining 14 (7·8%) comparisons. Limited to outcomes reported in three or more studies, LAIs were significantly advantageous in two (2·3%) of 86 comparisons, LAIs were not different from oral antipsychotics in 77 (89·5%) comparisons, and LAIs were worse than oral antipsychotics in seven (8·1%) comparisons. Regarding outcomes related to quality-of-life, LAIs were significantly more beneficial in two (9·1%) of 22 comparisons, not different in 19 (86·4%) comparisons, and less beneficial in one (4·5%) comparison. Regarding outcomes related to cognitive

	Number of studies	Number of patients in included studies	RR or SMD* (95% CI)	p value	Heterogeneity: p value	Heterogeneity: I^2	NNTB or NNTH† (95% CI)
Effectiveness-related outcomes							
Hospitalisation rate‡							
Cohort	27	653 298	0·83 (0·75 to 0·92)	0·0003	<0·0001	98·9	NA
Pre–post	29	12 019	0·39 (0·32 to 0·46)	<0·0001	<0·0001	93·6	NA
Hospitalisation days*							
RCT	2	893	–0·12 (–0·30 to 0·06)	0·18	0·178	44·9	NA
Cohort	16	50 059	–0·06 (–0·13 to 0·01)	0·096	<0·0001	89·0	NA
Pre–post	18	11 300	–0·53 (–0·75 to –0·32)	<0·0001	<0·0001	96·1	NA
Overall emergency visit rate							
Cohort	14	31 985	0·83 (0·75 to 0·91)	0·0002	<0·0001	98·2	NA
Pre–post	9	8389	0·60 (0·40 to 0·91)	0·015	<0·0001	99·5	NA
Patients with at least one emergency visit							
RCT	2	878	1·25 (0·87 to 1·79)	0·22	0·47	0·0	..
Cohort	8	35 286	0·86 (0·81 to 0·91)	<0·0001	0·0020	69·0	NNTB: 14 (11–22)
Pre–post	5	7246	0·65 (0·46 to 0·93)	0·018	<0·0001	98·9	NNTB: 4 (3–20)
MPR*§							
Cohort	2	8889	–0·21 (–0·41 to –0·01)	0·039	0·0051	87·3	NA
Pre–post	2	5230	–0·48 (–0·60 to –0·36)	<0·0001	0·13	57·2	NA
MPR ≥80%§							
Cohort	2	8988	0·77 (0·59 to 1·01)	0·061	<0·0001	92·9	..
Pre–post	2	5230	0·65 (0·45 to 0·95)	0·026	0·0064	86·5	NNTB: 7 (3–67)
PDC*§							
Cohort	7	33 745	–0·20 (–0·29 to –0·12)	<0·0001	<0·0001	89·1	NA
Pre–post	1	638	–0·67 (–0·83 to –0·51)	<0·0001	..	..	NA
PDC ≥80%§							
Cohort	8	74 075	0·75 (0·65 to 0·86)	<0·0001	<0·0001	96·0	NNTB: 12 (8–25)
Pre–post	1	638	0·26 (0·17 to 0·40)	<0·0001	..	..	NNTB: 5 (4–7)
All-cause discontinuation of antipsychotic							
RCT	30	7726	0·97 (0·88 to 1·06)	0·51	<0·0001	54·5	..
Cohort	28	139 030	0·83 (0·79 to 0·86)	<0·0001	<0·0001	90·5	NNTB: 10 (8–13)
Efficacy outcomes							
Discontinuation of antipsychotic due to absence of efficacy							
RCT	17	6121	0·86 (0·62 to 1·18)	0·35	0·25	17·4	..
Cohort	3	9206	1·18 (0·79 to 1·78)	0·41	0·0018	84·2	..
Remission§							
RCT	4	1512	0·93 (0·77 to 1·13)	0·49	0·014	71·8	..
Cohort	3	1341	0·82 (0·39 to 1·70)	0·59	<0·0001	95·1	..
PANSS-total or Brief Psychiatric Rating Scale-total mean change*							
RCT	17	5725	–0·05 (–0·15 to 0·05)	0·37	<0·0001	66·6	NA
Cohort	5	1001	–0·15 (–0·39 to 0·09)	0·22	0·073	53·3	NA
Positive symptom mean change on PANSS-total or BPRS-total*							
RCT	11	3379	–0·04 (–0·19 to 0·12)	0·64	<0·0001	72·8	NA
Cohort	1	52	–0·36 (–0·91 to 0·19)	0·20	..	..	NA
Negative symptom mean change on PANSS-total or BPRS-total*							
RCT	10	3322	0·01 (–0·11 to 0·12)	0·90	0.019	54·6	NA
Cohort	1	52	–0·42 (–0·97 to 0·13)	0·14	..	..	NA
PANSS-general psychopathology score mean change*							
RCT	7	1885	–0·04 (–0·13 to 0·05)	0·42	0·48	0·0	NA
Cohort	1	52	–0·69 (–1·25 to –0·13)	0·016	..	..	NA

(Table continues on next page)

function, LAIs were significantly more beneficial in two (10·5%) of 19 comparisons, not different in 16 (84·2%) comparisons, and less beneficial in one (5·3%) comparison. Finally, regarding other outcomes, LAIs were significantly more beneficial in ten (35·7%) of 28 comparisons, and LAIs were not different from oral antipsychotics in the 18 (64·3%) remaining comparisons.

Publication bias for the primary outcome was assessed by funnel plots, fail-safe estimates, and Egger's tests for all included studies (appendix 8 pp 74–77). In cohort and

	Number of studies	Number of patients in included studies	RR or SMD* (95% CI)	p value	Heterogeneity: p value	Heterogeneity: I^2	NNTB or NNTH† (95% CI)
(Continued from previous page)							
Clinical Global Impression–Severity scale mean change*							
RCT	13	4848	–0·06 (–0·17 to 0·05)	0·31	<0·0001	66·5	NA
Cohort	5	2331	–0·30 (–0·43 to –0·17)	<0·0001	0·16	38·7	NA
Adverse effect outcomes: overall							
Discontinuation of antipsychotic due to adverse effect							
RCT	20	6669	1·11 (0·84 to 1·46)	0·46	0·21	19·6	..
Cohort	3	9451	1·23 (0·69 to 2·20)	0·49	0·016	75·9	..
At least one adverse effect							
RCT	14	4953	1·04 (1·00 to 1·08)	0·027	0·22	21·4	NNTH: 36 (19–314)
Cohort	2	1723	0·92 (0·74 to 1·14)	0·45	0·19	41·5	..
Serious adverse effect							
RCT	12	4636	0·97 (0·81 to 1·16)	0·74	0·11	34·8	..
Cohort	2	1723	2·63 (0·24 to 29·16)	0·43	0·076	68·3	..
Adverse effect outcomes: movement disorders							
Akathisia							
RCT	15	4565	1·19 (0·94 to 1·49)	0·14	0·27	16·8	..
Cohort	1	640	4·31 (0·53 to 34·84)	0·17	..	..	..
Pre–post	1	68	1·13 (0·49 to 2·57)	0·78	..	..	..
Extrapyramidal symptoms							
RCT	8	2731	1·27 (0·94 to 1·71)	0·12	0·19	29·5	..
Cohort	2	8368	1·53 (0·69 to 3·39)	0·29	0·0048	87·4	..
Pre–post	2	332	1·10 (0·12 to 9·84)	0·93	0·0005	91·7	..
Restlessness							
RCT	4	1322	2·08 (0·92 to 4·67)	0·078	0·56	0·0	..
Tardive dyskinesia							
RCT	6	1562	0·54 (0·20 to 1·43)	0·21	0·97	0·0	..
Cohort	1	7728	1·96 (1·47 to 2·60)	<0·0001	..	..	NNTH: 16 (11–37)
Pre–post	1	68	3·00 (0·13 to 71·15)	0·50	..	..	..
Tremor							
RCT	10	2914	1·28 (0·90 to 1·83)	0·17	0·16	30·7	..
Pre–post	1	68	1·00 (0·64 to 1·57)	1·00	..	..	..
Adverse effect outcomes: arousal-related							
Insomnia							
RCT	19	6821	1·12 (0·97 to 1·29)	0·12	0·21	20·0	..
Cohort	2	1723	0·38 (0·11 to 1·40)	0·15	0·28	14·8	..
Sedation							
RCT	8	3116	0·85 (0·58 to 1·24)	0·39	0·63	0·0	..
Somnolence							
RCT	14	4975	0·83 (0·58 to 1·12)	0·32	0·023	48·1	..
Cohort	2	1723	0·16 (0·05 to 0·55)	0·0037	0·79	0·0	NNTB: 57 (51–107)
Pre–post	1	68	1·06 (0·68 to 1·63)	0·81	..	..	..

(Table continues on next page)

	Number of studies	Number of patients in included studies	RR or SMD* (95% CI)	p value	Heterogeneity: p value	Heterogeneity: I^2	NNTB or NNTH† (95% CI)
(Continued from previous page)							
Adverse effect outcomes: CNS							
Anxiety							
RCT	13	5384	1·24 (1·04 to 1·48)	0·017	0·69	0·0	NNTH: 53 (27–317)
Cohort	2	1723	0·64 (0·20 to 2·02)	0·44	0·24	28·7	..
Depression							
RCT	12	3546	1·46 (1·15 to 1·87)	0·0023	0·38	6·6	NNTH: 41 (22–156)
Pre–post	2	922	0·79 (0·66 to 0·95)	0·014	0·69	0·0	NNTB: 14 (8–59)
Adverse effect outcomes: gastrointestinal							
Constipation							
RCT	9	1910	1·10 (0·79 to 1·51)	0·58	0·80	0·0	..
Cohort	1	640	0·05 (0·00 to 0·84)	0·038	..	..	NNTB: 41 (23–240)
Pre–post	1	68	19·00 (1·15 to 314·00)	0·040	..	..	NNTH: 4 (3–9)
Diarrhoea							
RCT	10	3020	0·80 (0·58 to 1·12)	0·19	0·57	0·0	..
Adverse effect outcomes: metabolic and endocrine							
Any weight gain¶							
RCT	16	5758	1·04 (0·89 to 1·22)	0·61	0·41	3·9	..
Cohort	3	1953	0·89 (0·62 to 1·30)	0·55	0·99	0·0	..
Pre–post	1	176	0·18 (0·11 to 0·28)	<0·0001	..	..	NNTB: 2 (2–2)
≥7% weight gain							
RCT	9	4066	1·04 (0·80 to 1·35)	0·77	<0·0001	79·9	..
Cohort	1	7728	0·86 (0·70 to 1·06)	0·15	..	..	..
Body weight change*							
RCT	9	3658	–0·03 (0·11 to 0·05)	0·49	0·22	24·6	NA
Cohort	2	8249	–0·01 (–0·10 to 0·08)	0·87	0·44	0·0	NA
Fasting glucose change*							
RCT	5	1922	0·07 (–0·03 to 0·16)	0·16	0·85	0·0	NA
Pre–post	1	66	–2·91 (–3·60 to –2·22)	<0·0001	..	..	NA
Total cholesterol change*							
RCT	7	2337	0·17 (0·02 to 0·32)	0·031	0·0093	64·7	NA
Pre–post	1	66	–2·03 (–2·63 to –1·44)	<0·0001	..	..	NA
High-density lipoprotein cholesterol change*							
RCT	4	1926	0·00 (–0·09 to 0·10)	0·92	0·65	0·0	NA
Low-density lipoprotein cholesterol change*							
RCT	4	1894	0·10 (0·01 to 0·19)	0·034	0·61	0·0	NA
Triglycerides change*							
RCT	6	2254	–0·01 (–0·09 to 0·07)	0·82	0·72	0·0	NA
Pre–post	1	66	–2·73 (–3·40 to –2·06)	<0·0001	..	..	NA
Hyperprolactinaemia							
RCT	5	2423	2·97 (0·79 to 11·20)	0·11	0·012	68·8	..
Prolactin increase¶							
RCT	5	1609	1·75 (0·73 to 4·23)	0·21	0·0060	72·3	..
Pre–post	1	176	0·29 (0·21 to 0·41)	<0·0001	..	..	NNTB: 2 (2–2)
Prolactin change*							
RCT	8	2357	–0·08 (–0·35 to 0·19)	0·55	<0·0001	88·8	NA

(Table continues on next page)

	Number of studies	Number of patients in included studies	RR or SMD* (95% CI)	p value	Heterogeneity: p value	Heterogeneity: I^2	NNTB or NNTH† (95% CI)
(Continued from previous page)							
Adverse effect outcomes: death or suicide-related							
Death							
RCT	14	5676	0·80 (0·42 to 1·51)	0·49	0·88	0·0	..
Cohort	3	22 697	0·81 (0·58 to 1·14)	0·22	0·090	58·4	..
Suicidal ideation							
RCT	10	4317	0·94 (0·70 to 1·26)	0·68	0·81	0·0	..
Cohort	1	491	0·36 (0·24 to 0·56)	<0·0001	..	..	NNTB: 7 (5–13)
Death by suicide							
RCT	8	3257	0·93 (0·29 to 3·01)	0·90	0·68	0·0	..
Suicide attempt							
RCT	7	2289	1·02 (0·56 to 1·86)	0·94	0·51	0·0	..
Cohort	3	29 509	1·08 (0·79 to 1·47)	0·64	0·11	54·3	..

RR=risk ratio. SMD=standardised mean difference. NNTB=number needed to treat for an additional beneficial outcome. NNTH=number needed to treat for an additional harmful outcome. NA=not applicable. RCT=randomised controlled trial. MPR=medication possession ratio. PANSS=Positive and Negative Syndrome Scale. BPRS=Brief Psychiatric Rating Scale. PDC=proportion of days covered. *SMDs are given for continuous outcomes; SMD values lower than 0 on efficacy outcomes indicate that LAI is advantageous over oral antipsychotic; SMD values lower than 0 for laboratory parameters (eg, total cholesterol) indicate that a specific continuous outcome was lower with LAIs versus oral antipsychotics. †NNTBs greater than 0 indicate that LAI treatment is associated with fewer cases of secondary outcomes than oral antipsychotic treatment; NNTHs greater than 0 indicate that LAI treatment is associated with more cases of secondary outcomes than oral antipsychotic treatment (NNTB and NNTH were calculated when the risk for the comparison was statistically significant at p<0·05). ‡Rate ratio, calculated as [number of events/(number of people × years of follow-up)]. §For consistency the outcome was rescaled so that benefit was indicated by an RR lower than 1 or an SMD lower than 0. ¶Per individual study definitions.

Table: **Pooled results for secondary outcome**

pre–post studies, the funnel plots were asymmetrical. Subsequently, we used the trim-and-fill method to adjust the potential publication biases, and found that effect sizes were similar after adjustment, and that the significance of RRs did not change.

Discussion

We found that LAIs were significantly and consistently more efficacious than oral antipsychotics in preventing hospitalisation of patients with schizophrenia in RCTs, cohort studies, and pre–post studies. The summary effect size was small in RCTs and cohort studies but large in pre–post studies. As addressed in our previous meta-analyses,[12–14] RCTs tend to include patients who are more adherent than in a real-world setting, which minimises the ability to show LAI benefits. Conversely, cohort studies can include a conservative bias toward LAIs, in that patients who receive LAIs by clinician's choice are more likely to be more severely ill compared with patients receiving oral antipsychotics. Therefore, the fact that we found comparative benefit with LAIs in RCTs and cohort studies, although the effect sizes were small, is noteworthy. Furthermore, pre–post studies can be biased toward an advantage with LAIs, as in most of the pre–post studies the medication was switched from oral antipsychotics to LAIs (instead of from LAIs to oral antipsychotics), leading to a potential expectation bias toward LAIs, and the LAI results might further benefit from regression to the mean. Nevertheless, the significant and substantial risk benefit of LAIs over oral antipsychotics that we observed in pre–post studies might also reflect real-world clinical practice, in which risk of hospitalisation or relapse decreases substantially after the introduction of LAIs. Our previous meta-analysis of RCTs[12] showed no significant difference between LAIs and oral antipsychotics in terms of relapse prevention. However, our new results consistently show improved relapse risk with LAIs over oral antipsychotics in all study designs, providing evidence to encourage more prevalent use of LAIs in the treatment of schizophrenia.

The present analysis provides an important update: at least 1·5 times as many studies were included than in our previous meta-analyses (21 *vs* 32 RCTs, 25 *vs* 40 pre–post studies, and 42 *vs* 65 cohort studies); and at least 1·3 times as many studies were included in our analysis of the primary outcome relating to hospitalisation or relapse risk (21 *vs* 29 RCTs, 16 *vs* 28 pre–post studies, and 33 *vs* 44 cohort studies).[12–14] The much larger evidence base (5176 *vs* 8577 patients in RCTs, 5940 *vs* 11 295 patients in pre–post studies, and 101 624 *vs* 377 447 patients in cohort studies), obtained by our extensive literature search of both published and unpublished data, allowed us to investigate additional important outcomes, such as health-care resource use, measures of adherence, and changes in psychotic symptoms. We were also able to include more first-episode populations and recent-onset populations with onset of psychosis within the past 5 years.

We adopted hospitalisation or relapse as the primary outcome, both of which are especially important in

clinical practice and somewhat interchangeable. We preferred hospitalisation over relapse (when both were reported), as we assumed hospitalisation to be the most frequently reported outcome across study designs on the basis of our previous meta-analyses, and hospitalisation is less subjective and heterogeneous than relapse. This difference between hospitalisation and relapse should be interpreted with some caution, as, reflecting the nature of study designs, in RCTs relapse was more often reported than hospitalisation, and hospitalisation was sometimes not reported (but included within the criteria for relapse). Conversely, among cohort and pre–post studies, most reported the objective outcome of hospitalisation, as opposed to relapse, which requires a predetermined definition and detailed symptomatic assessment during the study that generally is only possible in RCTs (appendix 8 pp 10–34). A similar caution applies to the definition of relapse. Relapse is in many cases defined either by symptomatic exacerbation (expressed as a worsening in a psychopathology measure) or by clinical events, such as hospitalisation or an increased level of care. Distinguishing the exact causes of relapse in a given study is difficult, which is also likely to be true in clinical practice. A notable finding was that reversing the preferential order of relapse and hospitalisation did not change the observed effect with LAIs over oral antipsychotics.

Hospitalisation risk, calculated by dividing the number of patients hospitalised by the total population, was selected as the main outcome a priori given the nature of cohort and pre–post studies, in which a Positive and Negative Syndrome Scale assessment or other psychopathology ratings are unavailable in most cases. Thus, dimensionally defined relapse would be far less reported than the endpoint of hospitalisation across study designs. However, as patients receiving LAIs are more likely to adhere to treatment than those receiving oral antipsychotics, the LAI group is more likely to be observed for a longer time, causing a potential negative bias against LAIs. Therefore, rate ratios, rather than our ratios of risk, might more precisely represent the differential treatment effects, as we had used in our previous meta-analysis of cohort studies.[14] However, as the mean follow-up and number of hospitalisations were not reported in all RCTs, we were unable to calculate rate ratios in RCTs,[12] limiting our analyses to cohort and pre–post studies, whereby LAIs showed a benefit over oral antipsychotics in both designs.[13,14]

Again, contrary to the results of our previous meta-analysis, in this updated meta-analysis, LAIs were associated with a significantly lower risk of hospitalisation or relapse than oral antipsychotics in RCTs. This change in outcome in RCTs might be due to more high-risk groups for non-adherence being included in recent RCTs (eg, first-episode patients,[50] patients with recent-onset illness,[44,49] patients recently incarcerated,[21] and many patients with substance misuse[21]), which would accentuate the benefit of LAIs. The benefits of LAIs in patients at an early phase of illness[49,50] also point to the potential value of preventive use of LAIs in a group at high risk of becoming non-adherent in the future. This finding is reflected increasingly by guidelines that recommend LAI use across the entire illness course, most notably by the Florida Best Practice Psychotherapeutic Medication Guidelines,[156] which put a switch to LAIs at the same level as continued oral antipsychotics even in patients with stable schizophrenia or adherent patients with first-episode schizophrenia. The value of LAIs in first-episode and early-phase schizophrenia was confirmed in a 2020 cluster-randomised study.[157]

Comparative benefit with LAIs over oral antipsychotics was observed for many secondary outcomes, including hospitalisation-related outcomes, health-care resource use, adherence, and effectiveness-related outcomes. Consistent with a previous meta-analysis,[158] LAIs showed no significant difference from oral antipsychotics in most reported adverse events (albeit with a conservative bias, in that adherence is not assured with oral antipsychotic treatment). However, few pre–post or cohort studies reported adverse events that can arise from long-term use, such as tardive dyskinesia and weight gain. Additionally, especially in cohort and pre–post studies, the methods and quality of adverse event reporting are often unclear. Since long-term data are easier to collect in non-RCT settings, which also provide more generalisable data in real-world populations, future cohort and pre–post studies should include adverse effects that accumulate over time and report results based on specific antipsychotics, clarifying the method of ascertaining adverse events. Furthermore, considering that fewer antipsychotics are available as LAIs than oral antipsychotics, the reason some adverse events (such as cardiometabolic effects) were not always common in LAIs might be the selection of the antipsychotic, rather than the treatment modality.

Since the quality of observational studies is often low, and the studies are prone to bias, guidance has been provided regarding the analytical methods for comparative effectiveness research with observational data.[159] However, none of the included observational studies strictly followed this guideline. Future observational studies should be done in accordance with the guideline. Developing a scale that assesses the quality of observational studies in accordance with the guideline would be beneficial, as would standard formatting guidelines for such studies, so that readers can easily evaluate the quality of comparative effectiveness research with observational data. The cohort and pre–post studies in this analysis were evaluated by the Newcastle-Ottawa Scale, and 50 (47·6%) of 105 studies were high quality (ie, ≥7 of

9 possible stars in the Newcastle-Ottawa Scale). Furthermore, the results did not change even in the subgroup analysis in which only the high-quality studies were analysed. We also found no significant correlation between study quality score and the primary outcome in meta-regression analysis.

Results should be interpreted in view of the following limitations. First, results were significantly heterogeneous for hospitalisation and relapse risk outcomes in cohort and pre–post studies, meaning that effects varied significantly across the meta-analysed studies and suggesting that the studies differed regarding setting, population, and treatment variables. Via subgroup analyses, we identified several moderators that strengthened or weakened group differences between LAIs and oral antipsychotics. Although in a number of subgroup analyses, LAI effects became non-significant, in many cases this was because the standard deviation widened due to reduced sample size, rather than due to a shift in effect size to null. Furthermore, 25 (67·6%) of the 37 subgroup analyses showed no significant differences between subgroups, supporting the overall robustness of the results. Based on the data, we were unable to identify the most important moderator, as most of the significant moderators drove the effect in favour of LAIs. Second, most of the studies identified in the systematic review were from high-income countries, and thus results should be extrapolated to low-income and middle-income countries with caution. Furthermore, the threshold for hospitalisation can vary, largely reflecting the local medical and insurance system and the year or period that the study was done. Therefore, the population-level effect of LAIs might vary in specific countries at different times. Third, illness severity was not reported in many studies. Most of the patients included in our analysis were chronically ill. However, we could not determine their level of stability, insight, severity of negative symptoms, cognitive deficits, and functioning, all of which might influence the effectiveness of drug treatments. Fourth, too few studies reported data on non-adherence to do a meta-regression analysis and examine the degree to which non-adherence influenced the results. Finally, the specific antipsychotics in the LAI and oral antipsychotic groups were different in most of the studies included. This limitation calls for the conduct of head-to-head comparisons of the same antipsychotic in LAI or oral antipsychotic formulations. As adverse effects vary greatly among antipsychotics, comparing long-term adverse effects, such as tardive dyskinesia and cardiometabolic burden, between different routes of administration of the same antipsychotic would be valuable.

In summary, a risk benefit of LAIs over oral antipsychotics in preventing hospitalisation or relapse was consistently shown across RCT, cohort, and pre–post study designs. LAIs were non-inferior and at least equal to oral antipsychotics in most outcomes related to effectiveness and efficacy. LAIs also showed no significant difference to oral antipsychotics with regard to most adverse events. The present results should be interpreted with care, considering the strengths and weaknesses of the study designs, potentially low quality of observational studies, and heterogeneous reporting of adverse events across studies. Nevertheless, this updated analysis of RCTs and other study designs that consistently showed LAIs to prevent hospitalisation or relapse is meaningful and suggests potential benefits of increased use of LAIs in clinical practice.

Contributors

TK, KH, CUC, and JMK designed the study. TK, KH, and SK did the literature search and extracted data. All authors had access to all the data. TK and KH accessed, verified, and analysed the data. TK, KH, and CC drafted the paper and all authors critically reviewed the manuscript. All approved the final version and accept responsibility to submit for publication.

Declaration of interests

TK reports personal fees from Banyu, Eli Lilly, Janssen, Kyowa Pharmaceutical Industry, Lundbeck, Novartis, Otsuka, Sumitomo Dainippon Pharma, and Takeda, and grants from Sumitomo Dainippon Pharma and Otsuka, outside the submitted work. KH is an employee of Sumitomo Dainippon Pharma. SK reports personal fees from Sumitomo Dainippon Pharma, Meiji Seika Pharma, and Mochida Pharmaceutical, outside the submitted work. JMK reports personal fees from Alkermes, Acadia, Sumitomo Dainippon Pharma, Intracellular Therapies, Merck, Neurocrine, Reviva, Roche, Saladex, Sunovion, Takeda, Teva, and LB Pharma, and grants and personal fees from H Lundbeck, Janssen, and Otsuka, outside the submitted work. JMK is also a shareholder of LB Pharma and Vanguard Research Group. CUC reports personal fees from Acadia, Alkermes, Allergan, Angelini, Axsome, Bristol Myers Squibb, Gedeon Richter, Intra-Cellular Therapies, Janssen, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedinCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon Pharma, Sunovion, Supernus, Takeda, and Teva, and royalties from UpToDate, outside the submitted work. CUC is also a stock option holder of LB Pharma.

Data sharing

Data from this study is not available for sharing.

Acknowledgments

We thank the following individuals for their help with translating the abstract of this Article: Tianmei Si and Xin Yu (Chinese translation), S Christy Rohani-Montez (French translation), Hans-Christoph Steinhausen (German translation), Marco Solmi (Italian translation), Ary Gadelha (Portuguese translation), and Andrés Estradé (Spanish translation).

References

1 Kahn RS, Sommer IE, Murray RM, et al. Schizophrenia. *Nat Rev Dis Primers* 2015; **1:** 15067.

2 Jääskeläinen E, Juola P, Hirvonen N, et al. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull* 2013; **39:** 1296–306.

3 Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 1999; **56:** 241–47.

4 Leucht S, Barnes TR, Kissling W, Engel RR, Correll C, Kane JM. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry* 2003; **160:** 1209–22.

5 Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012; **379:** 2063–71.

6 Leucht S, Arbter D, Engel RR, Kissling W, Davis JM. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Mol Psychiatry* 2009; **14:** 429–47.

7 Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. *World Psychiatry* 2013; **12:** 216–26.

8 Perkins DO. Predictors of noncompliance in patients with schizophrenia. *J Clin Psychiatry* 2002; **63:** 1121–28.

9 Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry* 2002; **63:** 892–909.

10 Carbon M, Correll CU. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. *Dialogues Clin Neurosci* 2014; **16:** 505–24.

11 Park EJ, Amatya S, Kim MS, et al. Long-acting injectable formulations of antipsychotic drugs for the treatment of schizophrenia. *Arch Pharm Res* 2013; **36:** 651–59.

12 Kishimoto T, Robenzadeh A, Leucht C, et al. Long-acting injectable *vs* oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull* 2014; **40:** 192–213.

13 Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. *J Clin Psychiatry* 2013; **74:** 957–65.

14 Kishimoto T, Hagi K, Nitta M, et al. Effectiveness of long-acting injectable *vs* oral antipsychotics in patients with schizophrenia: a meta-analysis of prospective and retrospective cohort studies. *Schizophr Bull* 2018; **44:** 603–19.

15 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339:** b2535.

16 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–88.

17 The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions (version 5.1.0). March, 2011. https://handbook-5-1.cochrane.org/ (accessed Aug 31, 2019).

18 Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2019. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed May 11, 2020).

19 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315:** 629–34.

20 Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56:** 455–63.

21 Alphs L, Benson C, Cheshire-Kinney K, et al. Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study. *J Clin Psychiatry* 2015; **76:** 554–61.

22 Arango C, Bombin I, Gonzalez-Salvador T, Garcia-Cabeza I, Bobes J. Randomised clinical trial comparing oral versus depot formulations of zuclopenthixol in patients with schizophrenia and previous violence. *Eur Psychiatry* 2006; **21:** 34–40.

23 Bai YM, Ting Chen T, Chen JY, et al. Equivalent switching dose from oral risperidone to risperidone long-acting injection: a 48-week randomized, prospective, single-blind pharmacokinetic study. *J Clin Psychiatry* 2007; **68:** 1218–25.

24 Barnes TR, Milavic G, Curson DA, Platt SD. Use of the social behaviour assessment schedule (SBAS) in a trial of maintenance antipsychotic therapy in schizophrenic outpatients: pimozide versus fluphenazine. *Soc Psychiatry* 1983; **18:** 193–99.

25 Bozzatello P, Bellino S, Mancini I, Sandei L, Zanalda E, Rocca P. Effects on satisfaction and service engagement of paliperidone palmitate compared with oral paliperidone in patients with schizophrenia: an open label randomized controlled trial. *Clin Drug Investig* 2019; **39:** 169–78.

26 Buckley PF, Schooler NR, Goff DC, et al. Comparison of SGA oral medications and a long-acting injectable SGA: the PROACTIVE study. *Schizophr Bull* 2015; **41:** 449–59.

27 Crawford R, Forrest A. Controlled trial of depot fluphenazine in out-patient schizophrenics. *Br J Psychiatry* 1974; **124:** 385–91.

28 del Giudice J, Clark WG, Gocka EF. Prevention of recidivism of schizophrenics treated with fluphenazine enanthate. *Psychosomatics* 1975; **16:** 32–36.

29 Detke HC, Weiden PJ, Llorca PM, et al. Comparison of olanzapine long-acting injection and oral olanzapine: a 2-year, randomized, open-label study in outpatients with schizophrenia. *J Clin Psychopharmacol* 2014; **34:** 426–34.

30 Falloon I, Watt DC, Shepherd M. A comparative controlled trial of pimozide and fluphenazine decanoate in the continuation therapy of schizophrenia. *Psychol Med* 1978; **8:** 59–70.

31 Fleischhacker WW, Sanchez R, Perry PP, et al. Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. *Br J Psychiatry* 2014; **205:** 135–44.

32 Gaebel W, Schreiner A, Bergmans P, et al. Relapse prevention in schizophrenia and schizoaffective disorder with risperidone long-acting injectable vs quetiapine: results of a long-term, open-label, randomized clinical trial. *Neuropsychopharmacology* 2010; **35:** 2367–77.

33 de Arce Cordón R, Eding E, Marques-Teixeira J, Milanova V, Rancans E, Schreiner A. Descriptive analyses of the aripiprazole arm in the risperidone long-acting injectable versus quetiapine relapse prevention trial (ConstaTRE). *Eur Arch Psychiatry Clin Neurosci* 2012; **262:** 139–49.

34 Glick ID, Marder SR. Long-term maintenance therapy with quetiapine versus haloperidol decanoate in patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 2005; **66:** 638–41.

35 Green AI, Brunette MF, Dawson R, et al. Long-acting injectable *vs* oral risperidone for schizophrenia and co-occurring alcohol use disorder: a randomized trial. *J Clin Psychiatry* 2015; **76:** 1359–65.

36 Hogarty GE, Schooler NR, Ulrich R, Mussare F, Ferro P, Herron E. Fluphenazine and social therapy in the aftercare of schizophrenic patients. Relapse analyses of a two-year controlled study of fluphenazine decanoate and fluphenazine hydrochloride. *Arch Gen Psychiatry* 1979; **36:** 1283–94.

37 Ishigooka J, Nakamura J, Fujii Y, et al. Efficacy and safety of aripiprazole once-monthly in Asian patients with schizophrenia: a multicenter, randomized, double-blind, non-inferiority study versus oral aripiprazole. *Schizophr Res* 2015; **161:** 421–28.

38 Kamijima K, Ishigooka J, Kodama Y. Comparison study between risperidone long-acting injectable and risperidone tablets in patients with schizophrenia. *Jpn J Clin Psychopharmacol* 2009; **12:** 1199–222 [in Japanese].

39 Kane JM, Detke HC, Naber D, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry* 2010; **167:** 181–89.

40 Kaneno S, Ohkuma T, Yamashita I, et al. A double-blind comparison study on the efficacy and safety of fluphenazine decanoate (SQ10,733) and oral haloperidol in the treatment of schizophrenic patients. *Clin Eval* 1991; **19:** 15–45.

41 Keks NA, Ingham M, Khan A, Karcher K. Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder. Randomised, controlled, open-label study. *Br J Psychiatry* 2007; **191:** 131–39.

42 Li R, Zhang M, Shi S, et al. The effect of haloperidol decanoate on negative and positive symptoms of schizophrenia. *Chinese Journal of Nervous and Mental Diseases* 1996; **22:** 9–12.

43 Macfadden W, Ma YW, Thomas Haskins J, Bossie CA, Alphs L. A prospective study comparing the long-term effectiveness of injectable risperidone long-acting therapy and oral aripiprazole in patients with schizophrenia. *Psychiatry (Edgmont)* 2010; **7:** 23–31.

44 Malla A, Chue P, Jordan G, et al. An exploratory, open-label, randomized trial comparing risperidone long-acting injectable with oral antipsychotic medication in the treatment of early psychosis. *Clin Schizophr Relat Psychoses* 2016; **9:** 198–208.

45 Potapov A, Eduard T, Sergey M. Response, remission and relapse during the long-term treatment of schizophrenia patients with long-acting injectable risperidone versus olanzapine. *Int J Neuropsychopharmacol* 2008; **11:** 158.

46 Rifkin A, Quitkin F, Rabiner CJ, Klein DF. Fluphenazine decanoate, fluphenazine hydrochloride given orally, and placebo in remitted schizophrenics. I. Relapse rates after one year. *Arch Gen Psychiatry* 1977; **34:** 43–47.

47 Rosenheck RA, Krystal JH, Lew R, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med* 2011; **364:** 842–51.

48 Schooler NR, Levine J, Severe JB, et al. Prevention of relapse in schizophrenia. An evaluation of fluphenazine decanoate. *Arch Gen Psychiatry* 1980; **37:** 16–24.

49 Schreiner A, Aadamsoo K, Altamura AC, et al. Paliperidone palmitate versus oral antipsychotics in recently diagnosed schizophrenia. *Schizophr Res* 2015; **169:** 393–99.

50 Subotnik KL, Casaus LR, Ventura J, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. A randomized clinical trial. *JAMA Psychiatry* 2015; **72:** 822–29.

51 Weiden PJ, Schooler NR, Weedon JC, Elmouchtari A, Sunakawa-McMillan A. Maintenance treatment with long-acting injectable risperidone in first-episode schizophrenia: a randomized effectiveness study. *J Clin Psychiatry* 2012; **73:** 1224–33.

52 Ahmadkhaniha HR, Bani-Hashem S, Ahmadzad-Asl M. Depot typical antipsychotics versus oral atypical antipsychotics in relapse rate among patients with schizophrenia: a five -year historical cohort study. *Iran J Psychiatry Behav Sci* 2014; **8:** 66–71.

53 Babiker IE. Comparative efficacy of long-acting depot and oral neuroleptic medications in preventing schizophrenic recidivism. *J Clin Psychiatry* 1987; **48:** 94–97.

54 Barrio P, Batalla A, Castellví P, et al. Effectiveness of long-acting injectable risperidone versus oral antipsychotics in the treatment of recent-onset schizophrenia: a case-control study. *Int Clin Psychopharmacol* 2013; **28:** 164–70.

55 Baser O, Xie L, Pesa J, Durkin M. Healthcare utilization and costs of Veterans Health Administration patients with schizophrenia treated with paliperidone palmitate long-acting injection or oral atypical antipsychotics. *J Med Econ* 2015; **18:** 357–65.

56 Bellido I, López C, Gómez-Luque A. Depot antipsychotics in outpatients with schizophrenia improved compliance and reduced the incidence of relapses. *Methods Find Exp Clin Pharmacol* 2008; **30** (suppl 2)**:** 137–41.

57 Bitter I, Katona L, Zambori J, et al. Comparative effectiveness of depot and oral second generation antipsychotic drugs in schizophrenia: a nationwide study in Hungary. *Eur Neuropsychopharmacol* 2013; **23:** 1383–90.

58 Bushe CJ, Slooff CJ, Haddad PM, Karagianis JL. Weight change from 3-year observational data: findings from the worldwide schizophrenia outpatient health outcomes database. *J Clin Psychiatry* 2012; **73:** e749–55.

59 Calabresi M, Marchetti G. The long-term pharmacological treatment of schizophrenic patients: comparing effects resulting from daily administered neuroleptics and "long acting". *Riv Sper Freniatr Med Leg Alien Ment* 1983; **107:** 1205–23 [in Italian].

60 Chan HW, Huang CY, Feng WJ, Yen YC. Risperidone long-acting injection and 1-year rehospitalization rate of schizophrenia patients: a retrospective cohort study. *Psychiatry Clin Neurosci* 2015; **69:** 497–503.

61 Cheung S, Hamuro Y, Mahlich J, Nakahara T, Sruamsiri R, Tsukazawa S. Drug utilization of Japanese patients diagnosed with schizophrenia: an administrative database analysis. *Clin Drug Investig* 2017; **37:** 559–69.

62 Chue P, Lam A, Chandra K, Luong D, Camacho F. Hospitalization and medication use in schizophrenia patients receiving risperidone long-acting injectable or oral atypical antipsychotic medication. *Value Health* 2005; **8:** A202.

63 Ciudad A, San L, Bernardo M, et al. Relapse and therapeutic interventions in a 1-year observational cohort study of non-adherent outpatients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; **36:** 245–50.

64 Conley RR, Kelly DL, Love RC, McMahon RP. Rehospitalization risk with second-generation and depot antipsychotics. *Ann Clin Psychiatry* 2003; **15:** 23–31.

65 Conlon L, Fahy TJ, R OT, Gilligan J, Prescott P. Risperidone in chronic schizophrenia: a detailed audit, open switch study and two-year follow-up of patients on depot medication. *Eur Psychiatry* 2002; **17:** 459–65.

66 Greene M, Yan T, Chang E, Hartry A, Touya M, Broder MS. Medication adherence and discontinuation of long-acting injectable versus oral antipsychotics in patients with schizophrenia or bipolar disorder. *J Med Econ* 2018; **21:** 127–34.

67 Grimaldi-Bensouda L, Rouillon F, Astruc B, et al. Does long-acting injectable risperidone make a difference to the real-life treatment of schizophrenia? Results of the cohort for the general study of schizophrenia (CGS). *Schizophr Res* 2012; **134:** 187–94.

68 Gutwinski S, Müller P, Koller M. Intervals between hospitalisations in schizophrenia patients under antipsychotics in depot-form versus oral second generation antipsychotics. *Psychiatr Prax* 2007; **34:** 289–91 [in German].

69 Haro JM, Suarez D, Novick D, Brown J, Usall J, Naber D. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. *Eur Neuropsychopharmacol* 2007; **17:** 235–44.

70 Høiberg MP, Nielsen B. Antipsychotic treatment and extrapyramidal symptoms amongst schizophrenic inpatients. *Nord J Psychiatry* 2006; **60:** 207–12.

71 Hori H, Katsuki A, Atake K, Yoshimura R. Effects of continuing oral risperidone *vs.* switching from risperidone to risperidone long-acting injection on cognitive function in stable schizophrenia patients: a pilot study. *Front Psychiatry* 2018; **9:** 74.

72 Hsu HF, Kao CC, Lu T, Ying JC, Lee SY. Differences in the effectiveness of long-acting injection and orally administered antipsychotics in reducing rehospitalization among patients with schizophrenia receiving home care services. *J Clin Med* 2019; **8:** E823.

73 Huang SS, Lin CH, Loh W, Yang HY, Chan CH, Lan TH. Antipsychotic formulation and one-year rehospitalization of schizophrenia patients: a population-based cohort study. *Psychiatr Serv* 2013; **64:** 1259–62.

74 Ibach B, Schreiner A. Long-term treatment with long acting injectable risperidone and oral second generation antipsychotics in patients with schizophrenia (LARA): an interim-analysis. *Int J Neuropsychopharmacol* 2008; **11** (suppl 1)**:** 157 (abstr).

75 Joshi K, Mao L, Biondi DM, Millet R. The research and evaluation of antipsychotic treatment in community behavioral health organizations, outcomes (REACH-OUT) study: real-world clinical practice in schizophrenia. *BMC Psychiatry* 2018; **18:** 24.

76 Joshi K, Lafeuille MH, Kamstra R, et al. Real-world adherence and economic outcomes associated with paliperidone palmitate versus oral atypical antipsychotics in schizophrenia patients with substance-related disorders using Medicaid benefits. *J Comp Eff Res* 2018; **7:** 121–33.

77 Ju PC, Chou FH, Lai TJ, et al. Long-acting injectables and risk for rehospitalization among patients with schizophrenia in the home care program in Taiwan. *J Clin Psychopharmacol* 2014; **34:** 23–29.

78 Kelin K, Lambert T Jr, Brnabic AJ, et al. Treatment discontinuation and clinical outcomes in the 1-year naturalistic treatment of patients with schizophrenia at risk of treatment nonadherence. *Patient Prefer Adherence* 2011; **5:** 213–22.

79 Kim B, Lee SH, Choi TK, et al. Effectiveness of risperidone long-acting injection in first-episode schizophrenia: in naturalistic setting. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; **32:** 1231–35.

80 Kim HO, Seo GH, Lee BC. Real-world effectiveness of long-acting injections for reducing recurrent hospitalizations in patients with schizophrenia. *Ann Gen Psychiatry* 2020; **19:** 1.

81 Lafeuille MH, Laliberté-Auger F, Lefebvre P, Frois C, Fastenau J, Duh MS. Impact of atypical long-acting injectable versus oral antipsychotics on rehospitalization rates and emergency room visits among relapsed schizophrenia patients: a retrospective database analysis. *BMC Psychiatry* 2013; **13:** 221.

82 Lefebvre P, Muser E, Joshi K, et al. Impact of paliperidone palmitate versus oral atypical antipsychotics on health care resource use and costs in veterans with schizophrenia and comorbid substance abuse. *Clin Ther* 2017; **39:** 1380–95.e4.

83 Lin CH, Chen FC, Chan HY, Hsu CC. Time to rehospitalization in patients with schizophrenia receiving long-acting injectable antipsychotics or oral antipsychotics. *Int J Neuropsychopharmacol* 2019; **22:** 541–47.

84 Liu CC, Shan JC, Chiang CL, et al. Initiating long-acting injectable antipsychotics during acute admission for patients with schizophrenia—a 3-year follow-up. *J Formos Med Assoc* 2015; **114:** 539–45.

85 Manjelievskaia J, Amos TB, El Khoury AC, Vlahiotis A, Cole A, Juneau P. A comparison of treatment patterns, healthcare resource utilization, and costs among young adult Medicaid beneficiaries with schizophrenia treated with paliperidone palmitate or oral atypical antipsychotics in the US. *J Med Econ* 2018; **21:** 1221–29.

86 Marchiaro L, Rocca P, LeNoci F, et al. Naturalistic, retrospective comparison between second-generation antipsychotics and depot neuroleptics in patients affected by schizophrenia. *J Clin Psychiatry* 2005; **66:** 1423–31.

87 Marcus SC, Zummo J, Pettit AR, Stoddard J, Doshi JA. Antipsychotic adherence and rehospitalization in schizophrenia patients receiving oral versus long-acting injectable antipsychotics following hospital discharge. *J Manag Care Spec Pharm* 2015; **21:** 754–68.

88 Moore DB, Kelly DL, Sherr JD, Love RC, Conley RR. Rehospitalization rates for depot antipsychotics and pharmacoeconomic implications: comparison with risperidone. *Am J Health Syst Pharm* 1998; **55** (24 suppl 4)**:** S17–9.

89 Offord S, Wong B, Mirski D, Baker RA, Lin J. Healthcare resource usage of schizophrenia patients initiating long-acting injectable antipsychotics *vs* oral. *J Med Econ* 2013; **16:** 231–39.

90 Olivares JM, Rodriguez-Morales A, Diels J, et al. Long-term outcomes in patients with schizophrenia treated with risperidone long-acting injection or oral antipsychotics in Spain: results from the electronic schizophrenia treatment adherence registry (e-STAR). *Eur Psychiatry* 2009; **24:** 287–96.

91 Pesa JA, Muser E, Montejano LB, Smith DM, Meyers OI. Costs and resource utilization among Medicaid patients with schizophrenia treated with paliperidone palmitate or oral atypical antipsychotics. *Drugs Real World Outcomes* 2015; **2:** 377–85.

92 Pesa JA, Doshi D, Wang L, Yuce H, Baser O. Health care resource utilization and costs of California Medicaid patients with schizophrenia treated with paliperidone palmitate once monthly or atypical oral antipsychotic treatment. *Curr Med Res Opin* 2017; **33:** 723–31.

93 Pilon D, Tandon N, Lafeuille MH, et al. Treatment patterns, health care resource utilization, and spending in Medicaid beneficiaries initiating second-generation long-acting injectable agents versus oral atypical antipsychotics. *Clin Ther* 2017; **39:** 1972–85.e2.

94 Pilon D, Amos TB, Germain G, Lafeuille MH, Lefebvre P, Benson CJ. Treatment persistence and hospitalization rates among patients with schizophrenia: a quasi-experiment to evaluate a patient information program. *Curr Med Res Opin* 2017; **33:** 713–21.

95 Pinto L, Paiva A, Chainho J, Filipe D. Terapêutica medicamentosa da esquizofrenia: a utilização de neurolépticos orais versus neurolépticos depôt monitorizados: um estudo retrospectivo de três anos (1994/1996). *Psicologia* 2000; **14:** 45–50.

96 Remington G, Khramov I. Health care utilization in patients with schizophrenia maintained on atypical versus conventional antipsychotics. *Prog Neuropsychopharmacol Biol Psychiatry* 2001; **25:** 363–69.

97 San L, Bernardo M, Gómez A, Martínez P, González B, Peña M. Socio-demographic, clinical and treatment characteristics of relapsing schizophrenic patients. *Nord J Psychiatry* 2013; **67:** 22–29.

98 Schreiner A, Svensson A, Wapenaar R, et al. Long-acting injectable risperidone and oral antipsychotics in patients with schizophrenia: results from a prospective, 1-year, non-interventional study (InORS). *World J Biol Psychiatry* 2014; **15:** 534–45.

99 Shah A, Xie L, Kariburyo F, Zhang Q, Gore M. Treatment patterns, healthcare resource utilization and costs among schizophrenia patients treated with long-acting injectable versus oral antipsychotics. *Adv Ther* 2018; **35:** 1994–2014.

100 Sicilia V, Del Bello V, Verdolini N, Tortorella A, Moretti P. Oral versus long-acting injectable antipsychotics: hospitalisation rate of psychotic patients discharged from an Italian psychiatric unit. *Psychiatr Danub* 2017; **29** (suppl 3)**:** 333–40.

101 Song X, El Khoury AC, Brouillette M, Smith D, Joshi K. Treatment discontinuation of long-acting injectables or oral atypical antipsychotics among Medicaid recipients with schizophrenia. *J Med Econ* 2019; **22:** 1105–12.

102 Suzuki H, Hibino H, Inoue Y, Takaya A. Treatment continuation of 3 second-generation antipsychotic long-acting injections, and oral paliperidone in patients with schizophrenia for 2 years. *J Clin Psychopharmacol* 2018; **38:** 649–50.

103 Taipale H, Mehtälä J, Tanskanen A, Tiihonen J. Comparative effectiveness of antipsychotic drugs for rehospitalization in schizophrenia—a nationwide study with 20-year follow-up. *Schizophr Bull* 2018; **44:** 1381–87.

104 Takács P, Czobor P, Fehér L, et al. Comparative effectiveness of second generation long-acting injectable antipsychotics based on nationwide database research in Hungary. *PLoS One* 2019; **14:** e0218071.

105 Tavcar R, Dernovsek MZ, Zvan V. Choosing antipsychotic maintenance therapy—a naturalistic study. *Pharmacopsychiatry* 2000; **33:** 66–71.

106 Tiihonen J, Mittendorfer-Rutz E, Majak M, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. *JAMA Psychiatry* 2017; **74:** 686–93.

107 Valevski A, Gilat Y, Olfson M, Benaroya-Milshtein N, Weizman A. Antipsychotic monotherapy and adjuvant psychotropic therapies in schizophrenia patients: effect on time to readmission. *Int Clin Psychopharmacol* 2012; **27:** 159–64.

108 Varner RV, Hays JR, Wagner AL, Averill P. Outcome comparison of patients receiving oral or depot neuroleptic medication. *Psychol Rep* 2001; **89:** 169–74.

109 Verdoux H, Pambrun E, Tournier M, Bezin J, Pariente A. Risk of discontinuation of antipsychotic long-acting injections *vs.* oral antipsychotics in real-life prescribing practice: a community-based study. *Acta Psychiatr Scand* 2017; **135:** 429–38.

110 Voss EA, Ryan PB, Stang PE, Hough D, Alphs L. Switching from risperidone long-acting injectable to paliperidone long-acting injectable or oral antipsychotics: analysis of a Medicaid claims database. *Int Clin Psychopharmacol* 2015; **30:** 151–57.

111 Werneck AP, Hallak JC, Nakano E, Elkis H. Time to rehospitalization in patients with schizophrenia discharged on first generation antipsychotics, non-clozapine second generation antipsychotics, or clozapine. *Psychiatry Res* 2011; **188:** 315–19.

112 Xiao Y, Muser E, Lafeuille MH, et al. Impact of paliperidone palmitate versus oral atypical antipsychotics on healthcare outcomes in schizophrenia patients. *J Comp Eff Res* 2015; **4:** 579–92.

113 Xiao Y, Muser E, Fu DJ, et al. Comparison of Medicaid spending in schizoaffective patients treated with once monthly paliperidone palmitate or oral atypical antipsychotics. *Curr Med Res Opin* 2016; **32:** 759–69.

114 Yan T, Greene M, Chang E, Hartry A, Touya M, Broder MS. Medication adherence and discontinuation of aripiprazole once-monthly 400 mg (AOM 400) versus oral antipsychotics in patients with schizophrenia or bipolar I disorder: a real-world study using US claims data. *Adv Ther* 2018; **35:** 1612–25.

115 Young-Xu Y, Duh MS, Muser E, et al. Impact of paliperidone palmitate versus oral atypical antipsychotics on health care resource use and costs in veterans with schizophrenia. *J Clin Psychiatry* 2016; **77:** e1332–41.

116 Arató M, Erdós A. Experience with depot neuroleptics. *Orv Hetil* 1979; **120:** 1015–21 [in Hungarian].

117 Beauclair L, Lam A, McCormick J, Luong D, Camacho F. Impact of risperidone long-acting injectable on hospitalization and medication use in patients with schizophrenia. *Value Health* 2005; **8:** A202–03.

118 Bourin M, Jolliet P, Hery P, Guitton B. Is rehospitalization a measure of the efficacy of neuroleptics in the treatment of schizophrenia? *Int J Psychiatry Clin Pract* 1998; **2:** 275–78.

119 Carswell C, Wheeler A, Vanderpyl J, Robinson E. Comparative effectiveness of long-acting risperidone in New Zealand: a report of resource utilization and costs in a 12-month mirror-image analysis. *Clin Drug Investig* 2010; **30:** 777–87.

120 Chang HC, Tang CH, Huang ST, McCrone P, Su KP. A cost-consequence analysis of long-acting injectable risperidone in schizophrenia: a one-year mirror-image study with national claim-based database in Taiwan. *J Psychiatr Res* 2012; **46:** 751–56.

121 Crivera C, DeSouza C, Kozma CM, Dirani RD, Mao L, Macfadden W. Resource utilization in patients with schizophrenia who initiated risperidone long-acting therapy: results from the schizophrenia outcomes utilization relapse and clinical evaluation (SOURCE). *BMC Psychiatry* 2011; **11:** 168.

122 Denham J, Adamson L. The contribution of fluphenazine enanthate and decanoate in the prevention of readmission of schizophrenic patients. *Acta Psychiatr Scand* 1971; **47:** 420–30.

123 Devito RA, Brink L, Sloan C, Jolliff F. Fluphenazine decanoate *vs* oral antipsychotics: a comparison of their effectiveness in the treatment of schizophrenia as measured by a reduction in hospital readmissions. *J Clin Psychiatry* 1978; **39:** 26–34.

124 El Khoury A, Patel C, Huang A, Wang L, Bashyal R. Transitioning from oral risperidone or paliperidone to once-monthly paliperidone palmitate: a real-world analysis among Veterans Health Administration patients with schizophrenia who have had at least one prior hospitalization. *Curr Med Res Opin* 2019; **35:** 2159–68.

125 Girardi P, Serafini G, Pompili M, Innamorati M, Tatarelli R, Baldessarini RJ. Prospective, open study of long-acting injected risperidone versus oral antipsychotics in 88 chronically psychotic patients. *Pharmacopsychiatry* 2010; **43:** 66–72.

126 Gottfries CG, Green L. Flupenthixol decanoate—in treatment of out-patients. *Acta Psychiatr Scand Suppl* 1974; **255:** 15–24.

127 Johnson DA, Freeman H. Long-acting tranquillizers. *Practitioner* 1972; **208:** 395–400.

128 Kane JM, Zhao C, Johnson BR, et al. Hospitalization rates in patients switched from oral anti-psychotics to aripiprazole once-monthly: final efficacy analysis. *J Med Econ* 2015; **18:** 145–54.

129 Lachaine J, Lapierre ME, Abdalla N, Rouleau A, Stip E. Impact of switching to long-acting injectable antipsychotics on health services use in the treatment of schizophrenia. *Can J Psychiatry* 2015; **60** (suppl 2)**:** S40–47.

130 Lam A, Chue P, Ligate L, Akhras K, Jacobs A. Efficacy outcomes of risperidone long acting injection in patients previously on oral atypicals versus conventional depots. *Eur Neuropsychopharmacol* 2009; **19:** S549–50.

131 Latorre V, Papazacharias A, Lorusso M, et al. Improving the "real life" management of schizophrenia spectrum disorders by LAI antipsychotics: a one-year mirror-image retrospective study in community mental health services. *PLoS One* 2020; **15:** e0230051.

132 Lindholm H. The consumption of inpatient psychiatric resources prior to and during treatment with a depot neuroleptic, perphenazine enanthate. A mirror study. *Nord J Psychiatry* 1975; **29:** 513–20.

133 Mahlich J, Olbrich K, Wilk A, Wimmer A, Wolff-Menzler C. Hospitalization rates and therapy costs of German schizophrenia patients who are initiated on long-acting injectable medication: a mirror-image study. *Clin Drug Investig* 2020; **40:** 355–75.

134 Malm U. Fluphenazine depot. The usefulness of neuroleptics in perspective. *Nord Psykiatr Tidsskr* 1971; **25:** 309–14 [in Swedish].

135 Martínez-Andrés JA, García-Carmona JA. Clozapine, a controversial gold standard antipsychotic for the 21st century: switching to paliperidone palmitate 3-monthly improves the metabolic profile and lowers antipsychotic dose equivalents in a treatment-resistant schizophrenia cohort. *Schizophr Res* 2019; **212:** 234–36.

136 Michel G, Vásquez R, Basso L. Follow-up study of patients treated with depot phenothiazines in Valparaiso, Chile. *Bol Oficina Sanit Panam* 1981; **91:** 418–27 [in Spanish].

137 Miura G, Misawa F, Kawade Y, Fujii Y, Mimura M, Kishimoto T. Long-acting injectables versus oral antipsychotics: a retrospective bidirectional mirror-image study. *J Clin Psychopharmacol* 2019; **39:** 441–45.

138 Morritt C. Long-acting phenothiazines and schizophrenia. *Nurs Mirror Midwives J* 1974; **138:** 57–59.

139 Oh SY, Jon DI, Hong HJ, et al. The impact of paliperidone palmitate on hospitalization in patients with schizophrenia: a retrospective mirror-image study. *Clin Psychopharmacol Neurosci* 2019; **17:** 531–36.

140 Patel C, Emond B, Lafeuille MH, et al. Real-world analysis of switching patients with schizophrenia from oral risperidone or oral paliperidone to once-monthly paliperidone palmitate. *Drugs Real World Outcomes* 2020; **7:** 19–29.

141 Peng X, Ascher-Svanum H, Faries D, Conley RR, Schuh KJ. Decline in hospitalization risk and health care cost after initiation of depot antipsychotics in the treatment of schizophrenia. *Clinicoecon Outcomes Res* 2011; **3:** 9–14.

142 Poloni N, Ielmini M, Caselli I, et al. Oral antipsychotic versus long-acting injections antipsychotic in schizophrenia spectrum disorder: a mirror analysis in a real-world clinical setting. *Psychopharmacol Bull* 2019; **49:** 17–27.

143 Polonowita A, James NM. Fluphenazine decanoate maintenance in schizophrenia: a retrospective study. *N Z Med J* 1976; **83:** 316–18.

144 Potempa C, Rychlik R. Hospitalization rates and resource utilization of schizophrenic patients switched from oral antipsychotics to aripiprazole-depot in Germany. *Health Econ Rev* 2018; **8:** 30.

145 Ren XS, Crivera C, Sikirica M, Dirani R, Qian S, Kazis LE. Evaluation of health services use following the initiation of risperidone long-acting therapy among schizophrenia patients in the Veterans Health Administration. *J Clin Pharm Ther* 2011; **36:** 383–89.

146 Rosa F, Schreiner A, Thomas P, Sherif T. Switching patients with stable schizophrenia or schizoaffective disorder from olanzapine to risperidone long-acting injectable. *Clin Drug Investig* 2012; **32:** 267–79.

147 Su KP, Chang HC, Tsai SJ, Yen FC, Tang CH. Relapse and long-acting injectable risperidone: a 1-year mirror image study with a national claims database in Taiwan. *Value Health* 2009; **12** (suppl 3)**:** S118–21.

148 Suzuki H, Hibino H, Inoue Y, Takaya A. Comparison of hospitalization risk before and after changing from risperidone long-acting injection to another long-acting injection or oral antipsychotic in patients with schizophrenia: mirror-image study. *Psychiatry Clin Neurosci* 2016; **70:** 365–66.

149 Svestka J, Náhunek K, Cesková E, Rysánek R. A 1-year experience with the administration of clopenthixol decanoate in schizophrenic psychoses. *Cesk Psychiatr* 1984; **80:** 146–54 [in Czech].

150 Tan CT, Ong TC, Chee KT. The use of fluphenazine decanoate (Modecate)depot therapy in outpatient schizophrenics—a retrospective study. *Singapore Med J* 1981; **22:** 214–18.

151 Vincent PD, Demers MF, Doyon-Kemp V, Duchesneau J, Halme A, Masson V. One year mirror-image study using paliperidone palmitate for relapse prevention of schizophrenia in four university hospitals in Canada. *Schizophr Res* 2017; **185:** 96–100.

152 Waldmann KD, Neumann J. Clinical experience with depot neuroleptic treatment. *Z Arztl Fortbild (Jena)* 1984; **78:** 853–56 [in German].

153 Yoshimura B, Shinkawa I, Konishi A. Hospitalization risk in patients with schizophrenia before and after initiation of risperidone long-acting injection in Japan. *Asian J Psychiatr* 2015; **14:** 67–68.

154 Yoshimura B, Kishi Y. Hospitalization risk before and after discontinuation of long-acting injectable antipsychotics. *J Clin Psychopharmacol* 2016; **36:** 86–87.

155 Zhang F, Si T, Chiou CF, et al. Efficacy, safety, and impact on hospitalizations of paliperidone palmitate in recent-onset schizophrenia. *Neuropsychiatr Dis Treat* 2015; **11:** 657–68.

156 The University of South Florida, Florida Medicaid Drug Therapy Management Program. 2017–2018 Florida best practice psychotherapeutic medication guidelines for adults. 2018. http://floridabhcenter.org/documents/2018-Psychotherapeutic%20Medication%20Guidelines%20for%20Adults%20with%20References.pdf (accessed Oct 10, 2020).

157 Kane JM, Schooler NR, Marcy P, et al. Effect of long-acting injectable antipsychotics *vs* usual care on time to first hospitalization in early-phase schizophrenia: a randomized clinical trial. *JAMA Psychiatry* 2020; **77:** 1217.

158 Misawa F, Kishimoto T, Hagi K, Kane JM, Correll CU. Safety and tolerability of long-acting injectable versus oral antipsychotics: a meta-analysis of randomized controlled studies comparing the same antipsychotics. *Schizophr Res* 2016; **176:** 220–30.

159 Johnson ML, Crown W, Martin BC, Dormuth CR, Siebert U. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: the ISPOR good research practices for retrospective database analysis task force report—part III. *Value Health* 2009; **12:** 1062–73.