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SYSTEMATIC REVIEW

Real-World Evidence of the Clinical and Economic Impact of Long-Acting Injectable Versus Oral Antipsychotics Among Patients with Schizophrenia in the United States: A Systematic Review and Meta-Analysis

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Abstract

Background Long-acting injectable (LAI) antipsychotics, compared with oral antipsychotics (OA), have been found to significantly improve patient outcomes, including reduced hospitalizations and emergency room (ER) admissions and increased medication adherence among adult patients with schizophrenia. In turn, the clinical benefits achieved may translate into lower economic burden. Real-world evidence of the comparative effectiveness of LAI is needed to understand the potential benefits of LAI outside of the context of clinical trials. This study aimed to provide a comprehensive synthesis of recent published real-world studies comparing healthcare utilization, costs, and adherence between patients with schizophrenia treated with LAI versus OA in the United States.

Methods In this systematic literature review, MEDLINE® was searched for peer-reviewed, real-world studies (i.e., retrospective or pragmatic designs) published in English between January 1, 2010 and February 10, 2020. Comparative studies reporting hospitalizations, ER admissions, healthcare costs, or medication adherence (measured by proportion of days covered [PDC]) in adults with schizophrenia treated with LAI versus OA (or pre- vs post-LAI initiation) in the United States were retained. Random effects meta-analyses were conducted among eligible studies to evaluate the association of LAI versus OA use on hospitalizations, ER admissions, healthcare costs, and treatment adherence. A sensitivity analysis among the subset of studies that compared OA with paliperidone palmitate once monthly (PP1M), specifically, was conducted.

Results A total of 1083 articles were identified by the electronic literature search, and two publications were manually added subsequently. Among the 57 publications meeting the inclusion criteria, 25 provided sufficient information for inclusion in the meta-analyses. Compared with patients treated with OA, patients initiated on LAI had lower odds of hospitalization (odds ratio [OR] 0.62, 95% confidence interval [CI] 0.54–0.71, $n = 7$), fewer hospitalizations (incidence rate ratio [IRR] [95% CI] 0.75 [0.65–0.88], $n = 9$), and fewer ER admissions (IRR [95% CI] 0.86 [0.77–0.97], $n = 6$). The initiation of LAI was associated with higher per-patient-per-year (PPPY) pharmacy costs (mean difference [MD] [95% CI] $5603 [3799–7407], $n = 6$), which was offset by lower PPPY medical costs (MD [95% CI] − $5404 [− 7745 to − 3064], $n = 6$), resulting in no significant net difference in PPPY total all-cause healthcare costs between patients treated with LAI and those treated with OA (MD [95% CI] $327 [− 1565 to 2219], $n = 7$). Patients initiated on LAI also had higher odds of being adherent to their medication (PDC ≥ 80%; OR [95% CI] 1.89 [1.52–2.35], $n = 9$). A sensitivity analysis on a subset of publications evaluating PP1M found results similar to those of the main analysis conducted at the LAI class level.

Conclusions Based on multiple studies with varying sub-types of patient populations with schizophrenia in the United States published in the last decade, this meta-analysis demonstrated that LAI antipsychotics were associated with improved medication adherence and significant clinical benefit such as reduced hospitalizations and ER admissions compared with OA. The lower medical costs offset the higher pharmacy costs, resulting in a non-significant difference in total healthcare costs. Taken together, these findings provide strong evidence on the clinical and economic benefits of LAI compared with OA for the treatment of schizophrenia in the real world.

Extended author information available on the last page of the article

Key Points

Long-acting injectables were found to significantly reduce the risk and rate of hospitalizations and improve medication adherence for patients with schizophrenia while remaining cost-neutral relative to oral antipsychotics.

Given the inclusion of real-world studies encompassing patient populations with diverse characteristics and healthcare plans, the findings of this study are potentially generalizable to the broader population of patients with schizophrenia in the United States.

1 Introduction

Schizophrenia is a debilitating mental disorder, in which distortions in cognition, behavior and emotion severely impair daily functioning and require lifelong treatment [1, 2]. In 2016, roughly 23 million people were affected by schizophrenia worldwide, including 3.5 million people in the United States (US). With an estimated overall cost of $155.7 billion in 2013 in the US, schizophrenia places a significant burden on patients, caregivers, payers, and society at large [3–7].

While oral antipsychotics (OA) remain a cornerstone of treatment for schizophrenia, long-acting injectable (LAI) antipsychotics may improve therapeutic continuity and strengthen adherence due to their longer pharmacokinetic half-lives, less frequent dosing frequency, and administration by healthcare providers, compared to daily OA [8]. Current guidelines primarily recommend initiating LAI among patients with a history of poor or uncertain adherence [9, 10], although LAI use is also recommended as maintenance therapy or in response to patient preference, while certain guidelines also recommend the use of LAI for first-episode schizophrenia. Furthermore, a recent clinical trial found LAI to be efficacious for the treatment of acute schizophrenia exacerbations [11]. Despite their potential advantages, LAI continue to be underused, most notably in early disease stages, during which use could reduce the risk of poor outcomes associated with medication non-adherence [12–16].

Since a notable advantage of LAI may reside in their lower frequency of administration and associated better adherence, real-world evidence is of particular importance when evaluating the comparative advantage of these medications. Compliance and regular medication intake studied during clinical trials may not translate into benefits of similar magnitude in the real world.

In several real-world studies, patients treated with LAI have shown significantly improved medication adherence and reduced rates of hospitalization and emergency room (ER) admission as compared to those treated with OA [17–30]. Similarly, a randomized trial designed to reflect real-world conditions found LAI to delay time to psychiatric hospitalization as compared to OA [27]. Hospitalizations and ER admissions are often used as a proxy for relapse in the real-world setting and may be of particular interest from a clinical and economic perspective [23, 28–33]. Prior systematic reviews of the literature have focused on the impact of LAI versus OA on hospitalization and have found LAI to be superior to OA in reducing the likelihood and frequency of hospitalization among patients with schizophrenia [18, 32, 34]. However, the most recent publications included in these meta-analyses are from 2016.

To date, multiple real-world studies have assessed healthcare costs in patients with schizophrenia initiated on LAI versus OA [24, 25, 35–39]. In addition to improving adherence, the use of LAI relative to OA may result in considerable medical cost savings due to fewer hospitalizations [24, 25, 35–40]. However, despite the large volume of real-world evidence on the economic burden and adherence patterns of patients with schizophrenia prescribed LAI versus OA in the US [23–26, 35, 37, 40–42], there is, to the best of the authors' knowledge, no recent comprehensive synthesis of these publications.

To fill this knowledge gap, the present systematic review and meta-analysis compared rates of hospitalizations, rates of ER admissions, healthcare costs, and medication adherence among patients with schizophrenia initiated on an LAI versus an OA or before and after initiation of LAI reported in real-world studies in the US.

2 Methods

2.1 Literature Search Strategy

A systematic literature review was conducted by searching MEDLINE® and MEDLINE In-Process & Other Citations through the OvidSP interface. The search strategy included a combination of terms to identify schizophrenia, medications indicated for the treatment of schizophrenia, and outcomes of interest. The complete search strategy and screening criteria for the electronic search are presented in Online Resource Table S1 (see the electronic supplementary material). Additional relevant abstracts and posters from

recent key congresses were added manually to supplement the electronic search.

2.2 Inclusion Criteria

Peer-reviewed English language articles published between January 1, 2010 and February 10, 2020 (date of the electronic search) were screened for eligibility. Publications were retained if they met the following inclusion criteria: (1) conducted in a real-world setting (i.e., retrospective administrative claims analyses, retrospective chart review studies, pragmatic trials), (2) included adult patients with schizophrenia, (3) had at least one patient treated in the US, (4) reported at least one outcome of interest, and (5) reported these outcomes comparatively among patients treated with LAI versus OA (two-cohort design) or in the same group of patients before versus after initiation of an LAI (mirror-image design). Since the clinical endpoints of interest were expected to vary a lot across different countries' healthcare systems, the research was restricted to studies that included patients treated in the US. In addition, only articles published on or after 2010 were retained as treatment patterns prior to 2010 were expected to be meaningfully different, notably through the less prevalent use of LAI.

2.3 Outcome Measures

The clinical endpoints of interest were all-cause hospitalizations and ER admissions. In addition, all-cause healthcare costs and medication adherence were reported. All-cause healthcare costs included medical, pharmacy, and total costs. Adherence to the medication of interest (i.e., LAI or OA) was evaluated using the proportion of days covered (PDC).

2.4 Study Selection and Data Extraction

Two reviewers (IG and HN) independently assessed each publication for inclusion based on the aforementioned inclusion criteria. Following inclusion, each reviewer independently extracted data, including study design, interventions, sample characteristics, and outcomes, in an Excel-based data extraction grid. All information was taken from the published articles, and authors of the original publications were not contacted. Both extractions were reconciled. Discrepancies in the selection and extraction processes were reviewed and resolved by a third adjudicator (PT-L).

Descriptive statistics including means, medians, and standard deviations (SDs) were extracted for continuous outcomes, while counts and proportions were extracted for binary outcomes. When available in the source publications, odds ratios (ORs) were extracted for binary outcomes, incidence rate ratios (IRRs) were extracted for count outcomes, and mean differences (MDs) were extracted for continuous outcomes.

Because of the heterogeneous study designs and various outcomes of interest included in the scope of this review, a quality assessment exercise was not performed. Rather, a qualitative appraisal of the potential sources of heterogeneity was conducted [43].

2.5 Meta-Analysis

Meta-analyses were conducted to evaluate the association of LAI versus OA use on hospitalizations, ER admissions, healthcare costs, and medication adherence. Hospitalizations and ER admissions during the 12-month period following the initiation of an LAI or an OA were analyzed through the number of admissions (12-month pooled IRR) and the odds of having at least one admission (12-month pooled OR). Pharmacy, medical, and total costs per patient per year (PPPY) were analyzed through the cost difference between treatment arms (12-month pooled MD). Adherence was analyzed through the difference in PDC between treatment arms (12-month pooled MD) and the odds of having a PDC $\geq$ 80% (12-month pooled OR).

Given the substantial heterogeneity expected between studies, DerSimonian and Laird random effects models were conducted using STATA 16 statistical package (StataCorp LP, College Station, TX, USA). Effect sizes (i.e., ORs, IRRs, and MDs) and confidence intervals (CIs) reported in the source publications were inputted directly in the meta-analyses, when available. For source publications that only reported descriptive statistics, effect sizes and CIs were estimated [44–46].

Among all studies meeting inclusion criteria and reporting outcomes of interest, it happened that multiple publications reported the same outcome from the same data source covering a similar time frame (e.g., cited the same Medicaid or commercial claims insurance database for similar years). Therefore, to avoid the inclusion of overlapping samples, the most representative publication was retained for the meta-analysis based on the following criteria: studies of general schizophrenia populations were prioritized over studies of specific subsets of patients with schizophrenia; studies of LAI overall were prioritized over studies of a single, specific LAI; studies with a cohort design (i.e., LAI vs OA) were prioritized over mirror-image studies (i.e., before vs after LAI initiation).

2.6 Sensitivity Analysis

A sensitivity analysis was performed whereby meta-analyses were conducted on studies for which LAI was paliperidone palmitate once monthly (PP1M), exclusively, which was the most common LAI among the publications identified and

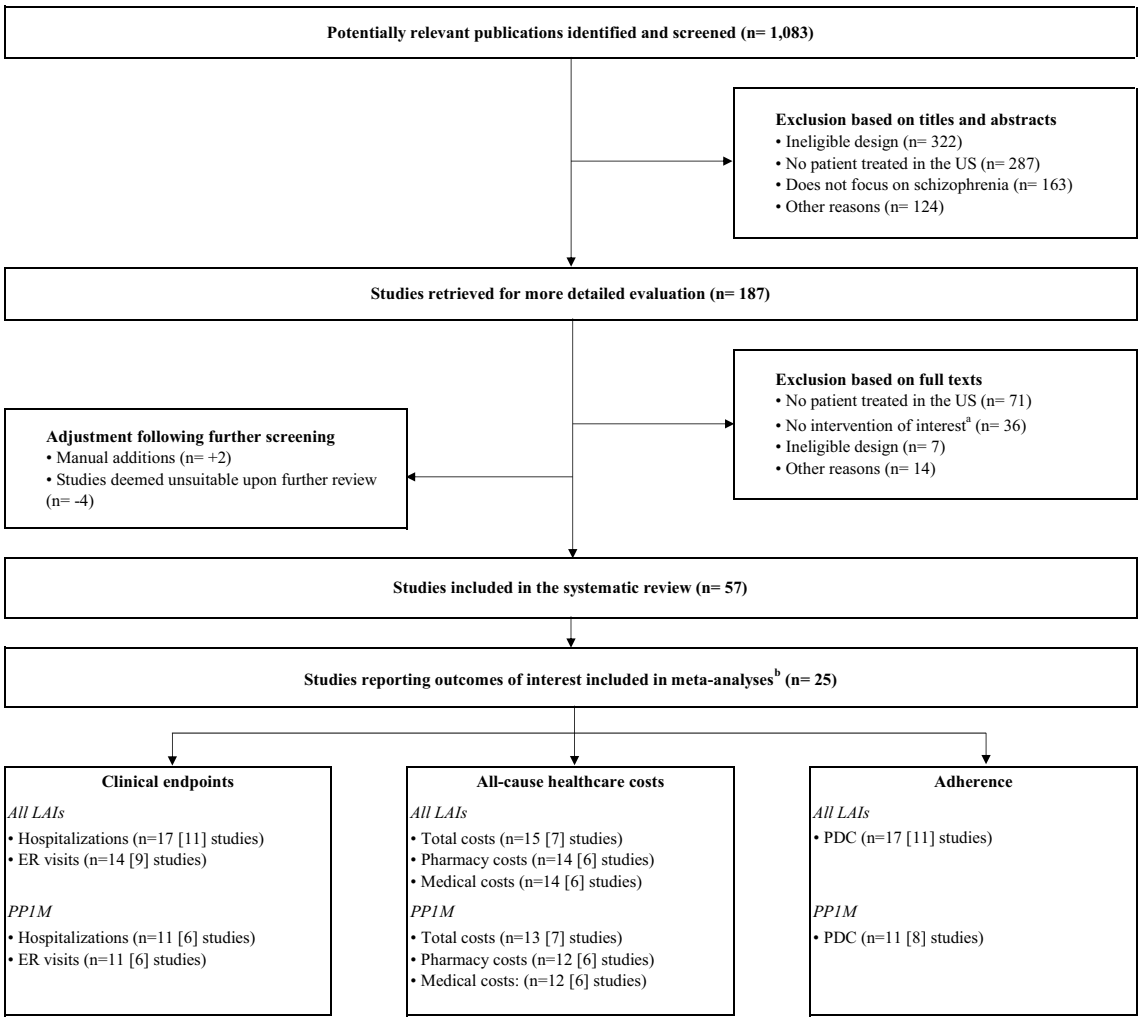
which had previously been found to be used by the majority of patients initiating a second-generation LAI [47].

3 Results

3.1 Study Selection and Characteristics

A total of 1083 articles were identified by the electronic literature search, and subsequently, two publications presented at relevant conferences at the time that the analysis was conducted were manually added. Partial content was available at the time of the electronic search, and these two studies have since been published as full manuscripts: Zhdanava [48], and Patel [49]). Of these, 57 articles were retained for data extraction (Fig. 1). In total, 25 publications reported at least one outcome of interest for inclusion in meta-analyses. One of these publications presented results on two separate populations (Offord [20], presented outcomes among commercially insured patients and Medicare patients, separately) (Table 1).

Studies were published between 2013 and 2020, and the data included ranged between 2005 and 2018. Study types included 21 retrospective cohort studies (84%),



LAI, long-acting injectable; OA, oral antipsychotic; PDC, proportion of days covered; PP1M, paliperidone palmitate once-monthly; US, United States; EA, emergency room

Notes:

[a] Interventions of interest consisted of comparisons between LAIs and OAs or before and after LAI initiation.

[b] The counts of studies included for each outcome are presented as the full count and the count after excluding studies with potentially overlapping samples (# [#]); e.g., "hospitalizations (n=16 [10] studies)" indicates that a total of 16 studies reported hospitalization, among which 10 were retained after excluding potentially overlapping samples.

Fig. 1 Study selection flow diagram

Table 1 Characteristics of studies included in the systematic review

First author, year	Comparison	Population	Years	n_{LAI}[a]	n_{OA}[a]	Age Mean ± SD	Female *N* (%)	Method of statistical adjustment
Medicaid								
Zhdanava, 2021 [48]	PP1M (before and after initiation)	Recently relapsed	2009–2018	1725	1725	39.5 ± 13.1	743 (43.1)	Pre-post design
Patel, 2021 [49]	PP1M vs. OA	Recently relapsed	2009–2018	208	624	PP1M: 38.9 ± 14.3 OA: 39.9 ± 14.2	PP1M: 74 (35.6) OA: 216 (34.6)	PSM
Joshi, 2018 (2) [35]	PP1M vs. OA	Comorbid substance-related disorders	2009–2015	351	4869	PP1M: 38.4 ± 11.5 OA: 41.9 ± 11.4	PP1M: 101 (28.8) OA: 2,005 (41.2)	Multivariable regressions
Lafeuille, 2018 [65]	PP1M vs. OA	Comorbid diabetes and/or CVD	2009–2015	371	8296	PP1M: 45.0 ± 10.7 OA: 47.5 ± 10.5	PP1M: 167 (45.0) OA: 4,228 (51.0)	Multivariable regressions
Manjelievskaia, 2018 [54]	PP1M vs. OA	General	2009–2015	949	14,649	PP1M: 40.3 ± 35.7 OA: 40.0 ± 9.5	PP1M: 3,926 (51.2) OA: 4,053 (51.1)	IPTW
Shah, 2018 [55]	LAI vs. OA[b]	Recently diagnosed	2010–2015	2302	2302	LAI: 37.3 ± 13.03 OA: 37.0 ± 13.09	LAI: 1,037 (46.6) OA: 1,033 (44.9)	PSM
Greene, 2017 [66]	LAI vs. OA[c]	General	2012–2015	2861	2777	LAI: 39.9 ± 13.2 OA: 42.0 ± 13.1	LAI: 1,238 (43.3) OA: 1,526 (55.0)	Multivariable regressions
Pesa, 2017 [37]	PP1M vs. OA	General	2008–2014	722	722	PP1M: 40.4 ± 12.4 OA: 41.2 ± 12.5	PP1M: 331 (45.8) OA: 325 (45.0)	PSM
Pilon, 2017 (1) [22]	LAI vs. OA[d]	General	2009–2015	3307	21,355	LAI: 41.8 ± 12.8 OA: 44.2 ± 13.5	LAI: 1,340 (40.5) OA: 10,675 (50.0)	Multivariable regressions
Pilon, 2017 (2) [24]	PP1M vs. OA	General	2008–2015	2053	22,247	PP1M: 42.9 ± 12.9 OA: 43.6 ± 13.4	PP1M: 5,388 (46.4) OA: 6,293 (49.6)	IPTW
Pilon, 2017 (4) [47]	LAI vs. OA[e]	General	2008–2015	2209	20,478	LAI: 42.2 ± 12.8 OA: 44.8 ± 13.2	LAI: 875 (39.6) OA: 10,006 (48.9)	Multivariable regressions
Xiao, 2016[f] [67]	PP1M vs. OA	Schizoaffective disorder	2009–2013	876	10,778	PP1M: 42.6 ± 31.8 OA: 43.0 ± 9.7	PP1M: 2,966 (53.1) OA: 3,277 (54.0)	Multiple
Kamat, 2015 [68]	LAI (before and after initiation)[g]	General	2006–2010	3094	3094	38.7 ± 12.0	1,392 (45.0)	Pre-post design
Campagna, 2014 [52]	PP1M vs. OA	General	2008–2011	195	369	PP1M: 37.9 ± 12.2 OA: 38.0 ± 12.4	PP1M: 89 (45.6) OA: 205 (55.6)	Not described
VHA								
El Khoury, 2019 [69]	PP1M (before and after initiation)	Transition from oral risperidone/paliperidone	2014–2018	319	319	51.6 ± 14.2	29 (9.1)	Pre-post design
Lefebvre, 2017 [36]	PP1M vs. OA	Comorbid substance-related disorders	2010–2015	1684	5188	PP1M: 52.5 ± 16.7 OA: 51.7 ± 9.5	PP1M: 207 (6.1) OA: 213 (6.1)	IPTW
Young-Xu, 2016 [39]	PP1M vs. OA	General	2009–2014	2285	8005	PP1M: 53.4 ± 17.2 OA: 53.0 ± 9.8	PP1M: 503 (10.0) OA: 479 (9.1)	IPTW
Baser, 2015 [25]	PP1M vs. OA	General	2007–2012	335	335	PP1M: 51.3 ± 9.9 OA: 51.2 ± 10.3	PP1M: 24 (7.0) OA: 29 (9.0)	PSM

Table 1 (continued)

First author, year	Comparison	Population	Years	n_{LAI}[a]	n_{OA}[a]	Age Mean ± SD	Female *N* (%)	Method of statistical adjustment
Other administrative claims[h]								
Joshi, 2018 (1) [70]	PP1M vs. OA	General	2009–2015	295	2296	PP1M: 56.0 ± 28.5 OA: 55.1 ± 9.2	PP1M: 661 (60.8) OA: 655 (55.0)	IPTW
Yan, 2018 [71]	LAI vs. OA[i]	General	2012–2016	408	3361	LAI: 37.3 ± 13.4 OA: 43.6 ± 15.9	LAI: 172 (42.2) OA: 1,751 (52.1)	Multivariable regressions
Lafeuille, 2015 [30]	PP1M vs. OA	Hospitalized at index	2009–2012	374	45,251	PP1M: 41.1 ± 14.8 OA: 45.6 ± 15.6	PP1M: 120 (32.1) OA: 17,444 (38.5)	IPTW
Offord, 2013 (Commercial) [20]	LAI vs. OA[j]	General	2005–2010	394	2610	LAI: 41.7 ± 15.5 OA: 37.1 ± 15.9	LAI: 190 (48.2) OA: 1,298 (49.7)	Multivariable regressions
Offord, 2013 (Medicare) [20]	LAI vs. OA[j]	General	2005–2010	147	518	LAI: 67.2 ± 9.8 OA: 73.2 ± 10.0	LAI: 88 (59.9) OA: 344 (66.4)	Not described
Other								
Rozin, 2019 [50]	LAI vs. OA[k]	Recently diagnosed	2017	10	14	21.9 ± 2.5	2 (8.3)	Not described
Joshi, 2018 (3) [53]	LAI vs. OA[l]	Enrollment in REACH-OUT	2010–2013	599	281	LAI: 41.1 ± 12.4 OA: 42.1 ± 13.4	LAI: 161 (27.5) OA: 94 (34.2)	Not described
Anderson, 2017 [72]	PP1M vs. OA	Enrollment in REACH-OUT	2010–2013	482	281	PP1M: 41.1 ± 12.6 OA: 42.1 ± 13.4	PP1M: 138 (29.0) OA: 94 (34.2)	Multiple

CVD cardiovascular disease, *IPTW*, inverse probability treatment weighting, *LAI* long-acting injectable(s), *OA* oral antipsychotic, *PP1M* paliperidone palmitate once monthly, *PSM* propensity score matching, *REACH-OUT* Research and Evaluation of Antipsychotic Treatment in Community Behavioral Health Organizations, Outcomes, *SD* standard deviation, *VHA* Veterans Health Administration

[a]Sample sizes for matched studies are based on matched cohorts. Sample sizes for studies using IPTW are based on unweighted cohorts

[b]LAI included aripiprazole, fluphenazine decanoate, haloperidol decanoate, olanzapine pamoate, paliperidone palmitate, and risperidone

[c]LAI included aripiprazole monohydrate, fluphenazine decanoate, haloperidol decanoate, olanzapine pamoate, paliperidone palmitate, and risperidone microspheres

[d]LAI included aripiprazole, olanzapine, paliperidone palmitate, and risperidone

[e]LAI included aripiprazole, fluphenazine decanoate, haloperidol decanoate, olanzapine, paliperidone palmitate, and risperidone

[f]The study used both PSM and IPTW as method of adjustment. IPTW results are presented here

[g]LAI included fluphenazine, haloperidol, paliperidone, and risperidone

[h]Joshi, 2018 (1): Humana Research Database; Yan, 2018: Truven Health MarketScan Medicaid, commercial, and supplemental Medicare databases; Lafeuille, 2015: Premier Perspective Comparative Hospital Database; Offord, 2013: MarketScan® Commercial Claims and Encounters and Medicare Supplemental

[i]LAI included aripiprazole

[j]LAI included fluphenazine, haloperidol, and risperidone

[k]LAI included aripiprazole and paliperidone palmitate

[l]LAI included risperidone and paliperidone palmitate

three pre-post studies (12%), and one pragmatic trial (4%). Among retrospective cohort studies ($n = 21$), methods of adjustment to control for confounding included multivariable regressions ($n = 7$, 33%), inverse probability of treatment weighting ($n = 6$, 29%), matching based on propensity scores ($n = 4$, 19%), and use of multiple techniques ($n = 2$, 10%), and two studies (10%) did not specify whether methods of adjustment were used.

Data sources included Medicaid (14 studies/25, 56%), data from the Veterans Health Administration (VHA) (4/25, 16%), other administrative claims databases (4/25, 16%), and other data types (3/25, 12%).

Sample size varied widely, ranging between 24 [50] and 45,625 [30]. The proportion of females in the publications was noticeably lower (10% or less) in studies using data from the VHA and in one chart review study on cannabis users [50]. Patients' mean ages among studies using Medicaid data

were in the late-thirties and forties, and in the early fifties among studies using VHA data.

Additional details on study designs and samples are available in Online Resource Table S2 and Online Resource Table S3 (see the electronic supplementary material).

3.2 Clinical Endpoints

Ten studies reported the likelihood of being hospitalized 12 months following initiation of an LAI compared with an OA (Online Resource Table S4A; see the electronic supplementary material). Among the seven studies included in the meta-analysis, patients initiated on an LAI had lower odds of being hospitalized compared with an OA (OR [95% CI] 0.62 [0.54–0.71], $n = 7$).

Fifteen studies reported on rates of hospitalization (Online Resource Table S4B). Among the eight studies that were included in the meta-analysis (one of which reported outcomes on two separate samples of patients [20]), patients initiated on an LAI had 25% fewer all-cause hospitalizations (IRR [95% CI] 0.75 [0.65–0.88], $n = 9$; Fig. 2).

Seven studies reported the likelihood of being admitted to the ER within 12 months of the initiation of an LAI compared with an OA (Online Resource Table S4C). Among the six studies that were included in the meta-analysis, patients initiated on an LAI had lower odds of being admitted to the ER, although this did not reach statistical significance (OR [95% CI] 0.79 [0.61–1.03], $n = 6$).

Thirteen studies reported the rate of ER visits following initiation of an LAI compared with an OA (Online Resource Table S4D). Among the six studies that were included in the meta-analysis, patients initiated on an LAI had 14% fewer all-cause ER admissions (IRR [95% CI] 0.86 [0.77–0.97], $n = 6$; Fig. 3).

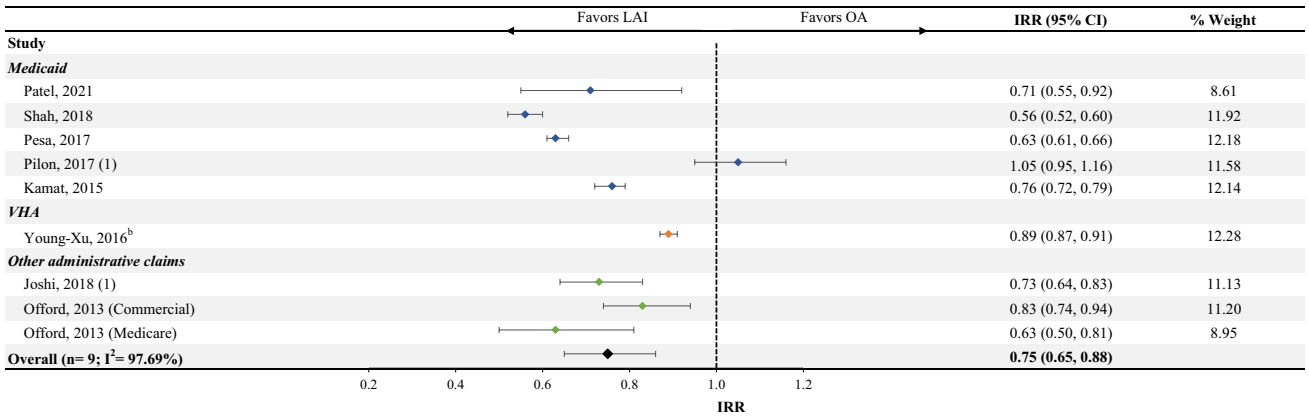
3.3 Healthcare Costs

Fifteen studies reported total costs following the initiation of an LAI compared with an OA (Online Resource Table S4E; see the electronic supplementary material). Among the seven studies included in the meta-analysis, there was no significant difference in total all-cause healthcare costs PPPY between patients initiated on an LAI versus an OA (MD [95% CI] $327 [− 1565 to 2219], $n = 7$; Fig. 4). Of these seven studies, six reported pharmacy and medical costs, separately. While the initiation of an LAI was associated with higher PPPY pharmacy costs (MD [95% CI] $5603 [3799–7407], $n = 6$, Online Resource Table S4F), this was offset by lower PPPY medical costs (MD [95% CI] − $5404 [− 7745 to − 3064], $n = 6$, Online Resource Table S4G).

3.4 Treatment Adherence

Fourteen studies reported mean PDC among patients initiated on an LAI compared with those initiated on an OA (Online Resource Table S4H; see the electronic supplementary material). Among the nine studies that were included in the meta-analysis, patients initiated on an LAI had a mean PDC nine percentage points higher (MD [95% CI] 9% [2–15], $n = 9$).

Sixteen studies reported the likelihood of being adherent to an LAI compared with an OA (Online Resource Table S4I). Among the nine studies that were included in the meta-analysis, patients initiated on an LAI were 89% more likely to be adherent to their medication (OR [95%



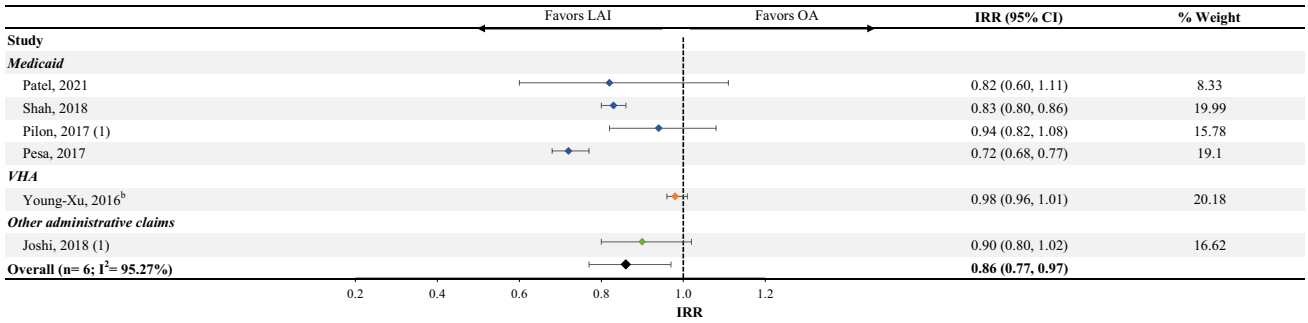
CI: confidence interval; IRR: incidence rate ratio; LAI: long-acting injectable; OA: oral antipsychotic; VHA: Veterans Health Administration

Notes:

[a] This forest plot presents the impact of LAIs on the number of 12-month all-cause hospitalizations among real-world studies using a random effects model of IRRs.

[b] Patients were required to have ≥ 6 months of follow-up; outcomes were annualized for patients with < 12 months of follow-up.

Fig. 2 Number of annual all-cause hospitalizations[a]



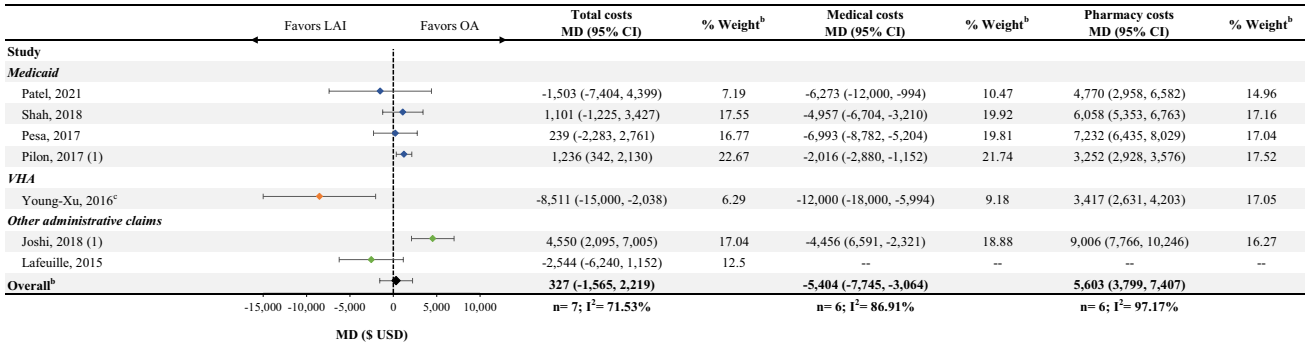
CI: confidence interval; ER: emergency room; IRR: incidence rate ratio; LAI: long-acting injectable; OA: oral antipsychotic; VHA: Veterans Health Administration

Notes:

[a] This forest plot presents the impact of LAIs on the number of 12-month all-cause ER visits among real-world studies using a random effects model of IRRs.

[b] Patients were required to have ≥ 6 months of follow-up; outcomes were annualized for patients with < 12 months of follow-up.

Fig. 3 Number of annual all-cause ER visits[a]



CI: confidence interval; LAI: long-acting injectable; MD: mean difference; OA: oral antipsychotic; USD: United States Dollar; VHA: Veterans Health Administration

Notes:

[a] This forest plot presents the impact of LAIs on annual all-cause total healthcare costs among real-world studies using a random effects model of MDs.

[b] Given that different weights are assigned when combining each outcome and that pharmacy and medical costs were not available for all studies in which total costs were reported, it is expected that the sum of the pooled estimates of the mean differences in medical and pharmacy costs does not equal the pooled estimate of the mean difference in total costs.

[c] Patients were required to have ≥ 6 months of follow-up and outcomes were annualized for patients with < 12 months of follow-up.

Fig. 4 Annual all-cause healthcare cost[a]

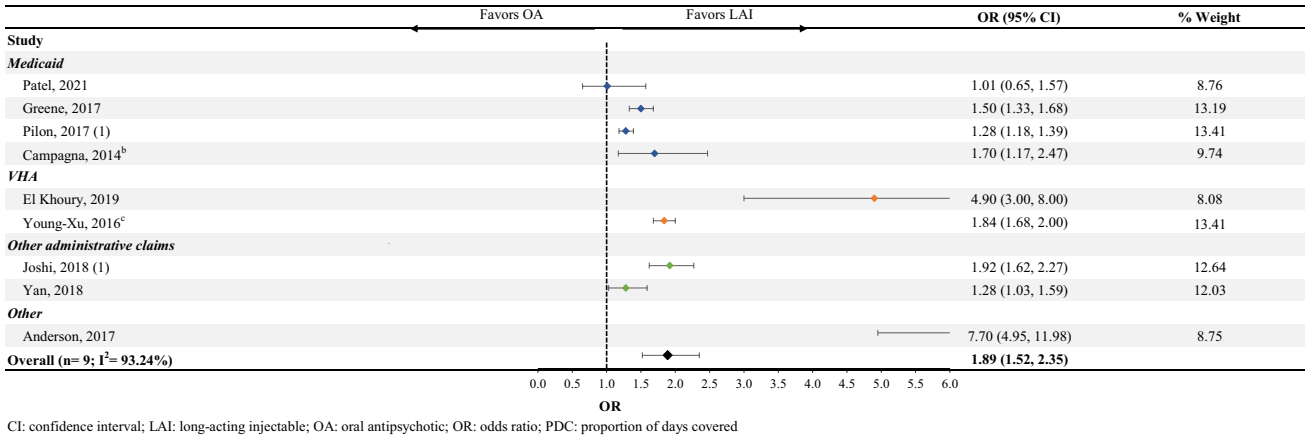
CI] 1.89 [1.52–2.35], $n = 9$) compared with those initiated on an OA (Fig. 5).

3.5 Sensitivity Analysis

Articles comparing PP1M with OA, which included 16 publications out of the 25 articles retained, also found similar associations to those of the main analysis across all outcomes. Patients initiated on PP1M had fewer all-cause hospitalizations (IRR [95% CI] 0.74 [0.62–0.89], $n = 6$, Online Resource Fig. S1, see the electronic supplementary material) and ER admissions (IRR [95% CI] 0.82 [0.69–0.98], $n = 6$, Online Resource Fig. S2) compared with patients initiated on an OA. Similarly to the main analysis, the difference in PPPY total healthcare costs between patients treated with PP1M and those treated with an OA was not significant (MD [95% CI] $107 [− 2268 to 2482], $n = 7$, Online Resource Fig. S3). Treatment with PP1M was also associated with greater likelihood of medication adherence as compared to OA (OR [95% CI] 1.93 [1.54–2.42], $n = 8$, Online Resource Figure S4).

4 Discussion

This study provides a comprehensive synthesis of the literature with regards to clinical endpoints, healthcare costs, and medication adherence among patients with schizophrenia treated with LAI versus those treated with OA in the US. In this meta-analysis, treatment with LAI was associated with reduced risk and rate of hospitalizations and ER admissions, as well as increased medication adherence, relative to OA. These improved patient outcomes were achieved at no additional total cost to the healthcare system.



CI: confidence interval; LAI: long-acting injectable; OA: oral antipsychotic; OR: odds ratio; PDC: proportion of days covered

Notes:

[a] This forest plot presents the impact of LAIs on the odds of 12-month treatment adherence defined as PDC ≥ 80% for the index drug (i.e., OA or LAI) among real-world studies using a random effects model of ORs.
[b] PDC was based on data as received.
[c] Patients were required to have ≥ 6 months of follow-up and outcomes were annualized for patients with < 12 months of follow-up.

Fig. 5 Treatment adherence (PDC ≥ 80%)[a]

The current literature review focused on real-world studies, allowing for a better real-world representation of hospitalizations, ER admissions, cost outcomes, and adherence patterns of patients.

The publications that were identified through the literature review reported on data from different populations in the US. Notably, they used various databases (e.g., Medicaid, VHA, commercial insurance) that included different healthcare plans with varying cost structures and comprised patients with diverse demographic and clinical characteristics. These comprehensive data sources are a useful way to obtain a patient's entire antipsychotic profile. Given the varying tolerability profiles of different antipsychotics and potential polypharmacy, considering all sources of antipsychotic prescribing (including those outside of primary care) is critical [51].

In addition, diverse adjustment methods were used to control between the LAI and OA cohorts of each study, including pre-post designs, propensity score matching, inverse probability of treatment weighting, and multivariable regressions. Since the scope of the search was relatively narrow (i.e., common pathology, recent timeframe, unique country), the heterogeneity observed across the studies was likely a result of sampling rather than fundamental differences in study objectives. The presence of statistical heterogeneity between the studies was confirmed through the I^2 statistic and further motivated the need to use random effects models.

While a uniform risk of bias assessment was not conducted for this review, the main study design characteristics of studies included in this meta-analysis were reviewed qualitatively to assess the comparability of studies. Most included studies used a study design that adjusted for differences between study cohorts, which limits the risk of bias due to confounding. Three studies did not report a method of multivariable adjustment, including two retrospective cohort studies [50, 52] and one pragmatic trial [53]. These studies reported on the likelihood of being hospitalized [50, 53], the likelihood of having an ER visit [53], and adherence [52]. In all cases, the studies' point estimates fell within the range of the other studies reporting on these outcomes, and therefore it is unlikely that descriptive studies that did not adjust for confounding materially impacted this review's conclusions.

All publications were reviewed to ensure that a patient who could be included in more than one publication (e.g., same Medicaid sample for the same years) was only included once in the meta-analyses. Publications that were excluded because of potentially overlapping samples reported point estimates that fell within range of other studies reporting on these outcomes, with a few exceptions. Notably, Zhdanava [48] reported the lowest odds of hospitalizations and ER visits among LAI users of any study, but was excluded from the meta-analysis as some patients could overlap with Patel [49] and because it used a pre-post design. Baser [25] reported the lowest IRR of ER visits as well as the largest decrease in medical costs among LAI users, but was excluded as it potentially overlapped with Young-Xu [39] and had a smaller sample size. Manjelievskaia [54] reported the lowest (but still positive) increase in pharmacy costs associated with LAI, but was excluded as it potentially overlapped with Shah [55]. In all cases, the studies' findings were directionally similar to the meta-analysis, and therefore, it is not expected that their inclusion would have changed the conclusions of this review.

All-cause hospitalizations and ER admissions were selected as outcomes of interest as they are typically considered as proxies for episodes of schizophrenia relapse, which in turn are associated with impaired functioning, reduced quality of life, and potential harm to oneself or others [3, 31, 33, 56]. The reduced risk/rate of hospitalization in the present review is consistent with the results of previous literature reviews and meta-analyses based on real-world data [18, 32, 34]. When compared to OA, treatment with LAI was associated with a 21% greater reduction in hospitalization rates in a meta-regression of both interventional and non-interventional studies [32]. Similarly, treatment with LAI prevented hospitalization and reduced the number of hospitalizations in a meta-analysis of 25 mirror-image studies [18]. In a more recent meta-analysis focused exclusively on non-interventional cohort studies, Kishimoto et al. [34] found that LAI were superior to OA in decreasing hospitalization rate and lowering the risk of hospitalization among patients with schizophrenia in a real-world setting.

Along the same lines, several studies have evaluated schizophrenia-related hospitalization or ER admissions as a proxy for schizophrenia relapses in the real-world setting [23, 28–30]. Consistent with the current meta-analyses that have focused on all-cause hospitalizations and ER admissions in general, these studies have shown that patients with schizophrenia who are treated with LAI have significantly lower rates of relapse compared to those treated with OA [23, 28–30].

Furthermore, the present review found that the total all-cause healthcare costs of LAI and OA were similar, with the medical costs savings associated with LAI offsetting the higher costs of drug acquisition relative to OA. The studies included were based on data spanning 2008 until 2018, across which the consistent result of cost offset suggests generalizability of this finding across time. In addition, these findings are in agreement with observations made in a 2018 review of the clinical and economic burden of commercially insured patients with schizophrenia in the US [55], in which two studies reported that the initiation of LAI was associated with reduced hospitalizations and inpatient costs (compared to pre-LAI initiation and relative to patients initiated on OA), and one study reported that healthcare resource use and costs declined significantly at 6 months after (vs 6 months before) initiating LAI [20, 57, 58]. The offset of higher pharmacy costs by lower medical costs is noteworthy, as stakeholders may be incentivized to prioritize one mode of treatment over the other in cases where pharmacy and medical costs are the responsibility of two different stakeholders.

For this outcome, it is important to consider whether studies that reported on costs were different from those that did not. Among the nine studies reporting on the rate of hospitalization and the seven studies reporting on total costs, six studies overlapped. Studies that did not overlap were not meaningfully different, with the exception of Offord "Medicare" [20], in which patients were older than patients in the other studies, and healthcare costs could differ for such a sample.

In the present review, patients initiated on LAI were significantly more likely to be adherent to treatment than those initiated on OA. According to prior estimates, at least 50% of patients with schizophrenia initiated on antipsychotics are not adherent to their medication, which poses a major challenge in clinical practice [59, 60]. The present results suggest that treatment with LAI may serve as an effective strategy for improving adherence and therapeutic continuity in the real-world setting. Given the association between poor medication adherence and disease relapse, the improved adherence associated with LAI is likely a contributing factor to the lower rates of hospitalizations and the associated costs of care [61, 62].

4.1 Limitations

The results of the present study should be interpreted in the context of certain limitations. First, this review identified studies through MEDLINE® and MEDLINE In-Process, a broad medical literature database, but did not include other databases, unpublished articles, or articles published in languages other than English. While it is expected that MEDLINE contains the vast majority of studies published in the US, it is possible that articles indexed in other international databases were missed. Second, due to the expected heterogeneity of study types and the multiple outcomes included in the analyses, a qualitative appraisal of the potential sources of heterogeneity was conducted instead of a formal quality assessment using a standardized tool (such as the Cochrane Collaboration's tool for assessing risk of bias [63] or the Risk Of Bias In Non-randomised Studies—of Interventions [64]). Third, effect sizes and their variance directly extracted from publications and those calculated based on study results, as well as adjusted and unadjusted values, were included and treated similarly in the meta-analyses. Fourth, because of the relatively low number of studies included in the meta-analyses, sub-group analyses (e.g., based on study types, year of publication) or meta-regressions could not be conducted to control for potentially confounding factors. Fifth, the presence of statistical heterogeneity between studies was confirmed by a high I^2 statistic in all analyses. While random effects meta-analyses aimed to account for heterogeneity between studies, differences may have remained in the studies' definitions of outcomes and patient populations.

5 Conclusion

The findings of the present review suggest that LAI may significantly improve clinical outcomes for patients with schizophrenia. These include reduced hospitalizations and ER admissions, which are commonly used as proxy measures for disease relapses, and in turn are associated with substantial societal and economic burden. Further, the clinical benefits associated with LAI are achieved while remaining cost-neutral relative to OA, through a reduction in medical costs offsetting pharmacy costs. Taken together with the finding of improved medication adherence, this may indicate better disease management among patients initiated on LAI versus OA. Given that the present analysis drew upon a wide range of data sources comprising patients enrolled in various healthcare plans, these clinical and economic outcomes are potentially generalizable to the broader population of patients with schizophrenia in the US and can support evidence-based decisions when considering LAI as a treatment option.

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Declarations

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Conflicts of interest DL, CB, and PM are employees of Janssen Scientific Affairs, LLC and may own stock/stock options. PT-L, IG, HN, M-HL, and PL are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Janssen Scientific Affairs, LLC, to conduct this study.

Author contributions DL, PT-L, IG, HN, M-HL, CB, PM, and PL contributed to the design of the study and interpretation of the data. PT-L, IG, HN, and M-HL contributed to the data collection and data analysis. All authors critically revised the draft manuscript and approved the final content.

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