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REVIEW ARTICLE

The effect of long-acting injectable antipsychotic medications compared with oral antipsychotic medications among people with schizophrenia: A systematic review and meta-analysis

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ABSTRACT: *Long-acting injectable (LAI) antipsychotic medications may be an important modality of reducing costs, improving symptoms, and fostering quality of life outcomes for those with schizophrenia. Our objective was to systematically review and conduct a meta-analysis of the effectiveness of LAIs compared with oral antipsychotics on medication adherence, symptom remission/relapse, rehospitalization, outpatient visits, emergency department visits, healthcare costs, and social functioning. We performed a systematic search of PsycInfo, CINAHL, PubMed, and Scopus databases to examine studies meeting inclusion criteria prior to August 30th, 2020. Randomized controlled trials, retrospective studies, prospective studies among people with schizophrenia with at least 6-month follow-up data were obtained. Overall effect sizes and associated 95% confidence intervals (CI) were estimated with random-effects modeling. We found 75 articles meeting our inclusion criteria, including 341 730 individuals with schizophrenia. Systematic review results indicated that LAIs compared with orals improved medication adherence (25/29 studies), symptom remission/relapse (10/18 studies), rehospitalizations (26/49 studies), emergency department visits (9/17 studies), medical costs (11/15 studies), and social functioning (5/9 studies); however, LAIs also increased outpatient visits (7/16 studies) and pharmacy costs (10/10 studies). Meta-analytic results of studies with similar outcome measures did not find differences between LAIs and orals in respect to outcomes, except lowering emergency department visits and increasing pharmacy costs. The differences between the results of the*

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narrative synthesis and the meta-analyses were possibly because of the low availability of studies with similar outcomes in the pooled analyses. Our overall results suggest that LAIs are at least comparable to orals in supporting important healthcare outcomes for those with schizophrenia. These findings support clinical practice in encouraging providers to prescribe LAIs when indicated.

KEY WORDS: *adherence, antipsychotic medications, healthcare utilization, rehospitalization, symptom remission, schizophrenia.*

INTRODUCTION

Schizophrenia is an often chronic mental illness, affecting more than 21 million people worldwide (Charlson *et al*. 2018). Antipsychotic medications are a mainstay to effectively manage symptoms of the disorder (Keating *et al*. 2017). However, about 26.5% to 58.8% of those with schizophrenia are non-adherent to their antipsychotic medication regimen (Higashi *et al*. 2013; Salzmann-Erikson & Sjödin 2018). Some factors linked with nonadherence in these patients include not being well informed about medications and negative perceptions of taking medications (Higashi *et al*. 2013; Salzmann-Erikson & Sjödin 2018; Velligan *et al*. 2017). Poor adherence is associated with increasing the risk for rehospitalization, symptom recurrence, poor quality of life, and healthcare costs (Barbosa *et al*. 2018; Faden *et al*. 2021; Pappa & Mason 2020). Thus, it is important to understand factors that affect medication adherence among people living with schizophrenia.

A key factor to enhance medication adherence is proper treatment prescription. Two types of antipsychotic formulations are currently prescribed to treat schizophrenia, including long-acting injectables (LAIs) and orals. LAIs can be useful in reducing nonadherence and rehospitalization among patients with schizophrenia. Two meta-analyses showed that LAIs are associated with significant symptom remission, reductions in medication nonadherence, and lower rehospitalizations among those with schizophrenia (Kishimoto *et al*. 2013; Lafeuille *et al*. 2014). Although, several systematic reviews and meta-analyses have compared the efficacy of LAIs with orals (Basu *et al*. 2018; Kishimoto *et al*. 2013), these studies have compared the two based on different criteria. For example, some reviews included only randomized control trials (Adams *et al*. 2001; Kishimoto *et al*. 2013, 2014; Misawa *et al*. 2016; Ostuzzi *et al*. 2017) or focused on specific outcomes such as symptom relapse, medication discontinuation (Kishi *et al*. 2016; Misawa *et al*. 2016; Park *et al*. 2018), and rehospitalization (Kishimoto *et al*. 2021; Lafeuille *et al*. 2014; Park *et al*. 2018). Furthermore, no review to date, as far as we know, has incorporated social functioning as a main outcome.

Most recently, Kishimoto *et al*. (2021) conducted a meta-analysis of 137 articles (32 Randomized Controlled Trials, 65 cohort, 40 pre-post) assessing the difference in LAIs versus orals in rehospitalization, emergency department (ED), symptom remission, and antipsychotic discontinuation because of adverse effects. However, other outcomes such as medication adherence, outpatient visits, healthcare costs, and social functioning are important additional aspects to assess. Therefore, the present study summarizes the existing literature on the impact of LAIs compared with orals among those with schizophrenia in key outcomes. The specific aims were to (i) systematically review the comparative effectiveness of LAIs compared with orals on medication adherence, symptom remission/relapse, rehospitalization, outpatient visits, ED visits, healthcare costs, and social functioning and (ii) conduct a meta-analysis on the effectiveness of LAIs compared with orals on medication adherence, symptom remission/relapse, rehospitalization, outpatient visits, ED visits, healthcare costs, and social functioning. The overarching hypothesis for the study was that LAIs would be comparable to orals on our main outcomes.

METHODS

We adhered to standard guidelines in establishing the protocol for the review (Liberati *et al*. 2009). Studies were retrieved from PsycInfo, CINAHL, PubMed, and Scopus databases. Keywords for the search were "Schizophrenia OR Schizoaffective OR Psychotic disorder", "Fluphenazine Decanoate AND Haloperidol Decanoate AND Aripiprazole Monohydrate AND Aripiprazole Lauroxil AND Olanzapine Pamoate AND Paliperidone Palmitate AND Risperidone

Microspheres", and "Adherence AND Outpatient Visit AND Hospitalization AND Incarceration AND Readmission" (see supplementary material). The search was limited to articles published prior to August 2020. The search process resulted in 1587 articles. In addition, in July 2021, we cross referenced studies from a recent meta-analysis (Kishimoto *et al*. 2021), which resulted in an additional 19 articles (Figure 1). This systematic review was not registered.

Study selection

The initial database searches were performed in September 2020. After pooling the retrieved articles, all duplicates were removed. Then, titles and abstracts were screened. Finally, two authors screened the full texts independently.

Inclusion and exclusion criteria

Included articles were from peer reviewed journals, written in English, and focused on comparisons between oral or LAI antipsychotic users. However, articles that did not specify antipsychotic type did not delineate the main outcomes of interest, investigated the outcomes of switching from oral to LAIs, or included participants with bipolar disorder were excluded. Review articles, meta-analyses, commentaries,

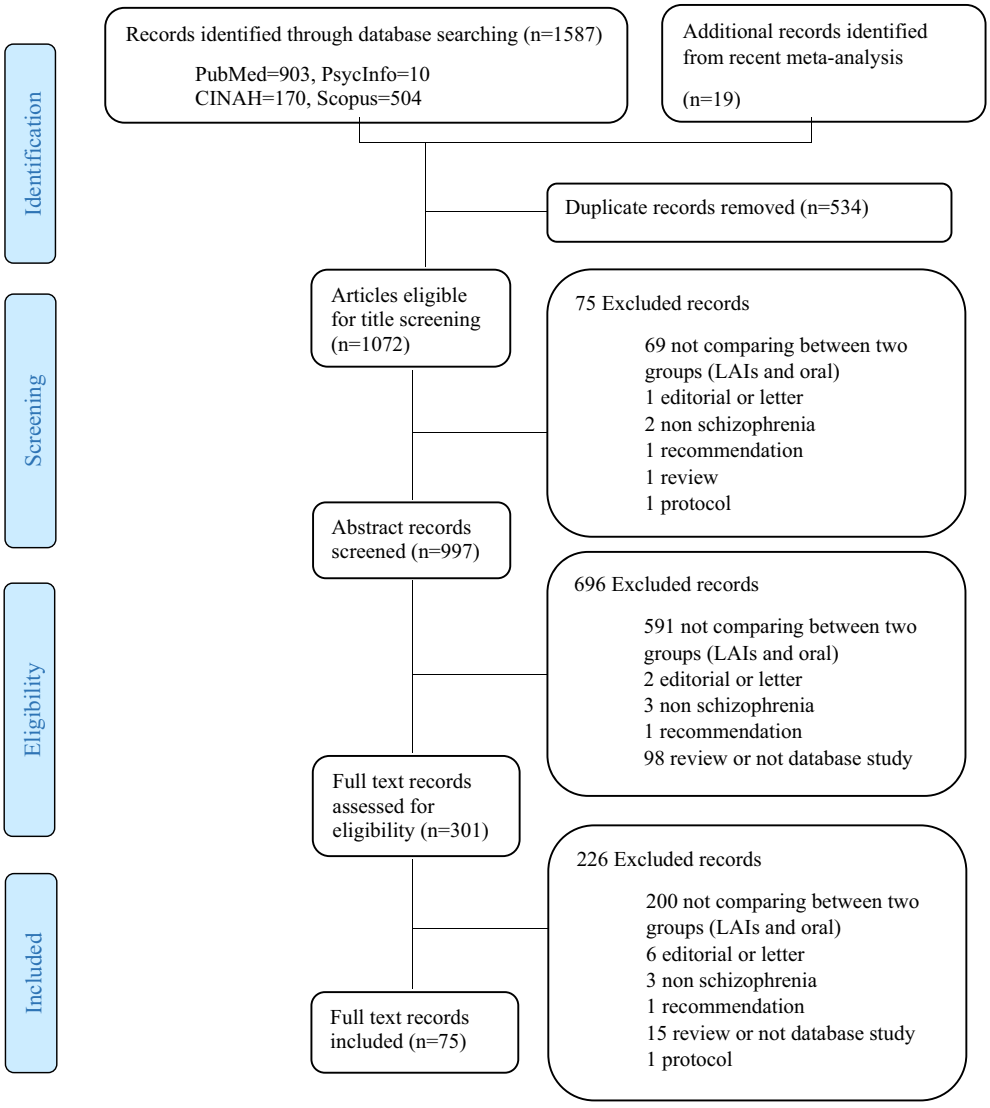

FIG. 1 PRISMA flow chart illustrating the selection strategies of articles for the systematic review.

editorials, letters, qualitative studies, and studies with incomplete study descriptions were also excluded.

Assessment of methodological quality

Included articles were assessed for methodological rigor by two independent reviewers from October to December 2020 following a standardized quantitative checklist (Kmet *et al*. 2004) (see supplemental materials). The mean scores based on the two raters were 19.85 and 20.38. The interclass correlation coefficient was $r = 0.915$, $P < 0.001$.

Data extraction & synthesis

Data extracted from the included studies were author, year of publication, country, study design, participant characteristics (sample size, age, gender, and ethnicity), measures of our primary outcomes, study time points, and key findings. This process began in January 2021. Statistical pooling from some studies was not possible because of using different statistical approaches and measurements. Therefore, for the systematic review, quantitative data were presented in narrative form. The narrative synthesis was conducted using Joanna Briggs Institute System for the Unified Management, Assessment, and Review of Information (Moola *et al*. 2020). The findings were then categorized based on our main outcomes.

Meta-analytic methods

Meta-analyses using the Comprehensive Meta-Analysis software Version 3 began in February 2021 (Borenstein *et al*. 2013). Overall effect sizes and associated 95% confidence intervals (CIs) were estimated with random effect modeling (Higgins *et al*. 2019). Effect sizes were estimated using standardized mean differences with 95% CIs. Values less than zero indicated superiority of LAIs and values greater than zero indicated inferiority of LAIs compared with orals. For binary data, we used risk ratios with 95% CIs as the effect size, with values more than one indicating superiority and values less than one indicating inferiority of LAIs compared with orals. Prediction intervals were used to assess the heterogeneity of the true effects (dispersion of effects) for outcomes that included ten or more studies. The τ^2, I^2, Q, and P values were also reported. Publication bias was examined using Egger's regression test (Egger *et al*. 1997) for outcomes that included ten or more studies followed by Duval and Tweedie's trim and fill methods (Duval & Tweedie 2000).

RESULTS

Characteristics of included studies

We identified 75 studies which included 341 730 individuals with schizophrenia (65 791 received LAIs and 273 351 orals) for at least 6 months. The mean size for all included studies was 4338.1067, and range of studies sizes were 22 to 70 969. These studies included 16 randomized controlled trials (Alphs *et al*. 2016; Bai *et al*. 2007; Barnett *et al*. 2012; Bartzokis *et al*. 2012; Bozzatello *et al*. 2019; Buckley *et al*. 2015; Detke *et al*. 2014; Green *et al*. 2015; Keks *et al*. 2007; Leatherman *et al*. 2014; Macfadden *et al*. 2010; Malla *et al*. 2016; Rosenheck *et al*. 2011; Subotnik *et al*. 2015; Weiden *et al*. 2009, 2012), 11 prospective cohort studies (Aykut 2019; Bellido *et al*. 2008; Conley *et al*. 2003; Devito *et al*. 1978; Joshi *et al*. 2018b; Kim *et al*. 2008; Moore *et al*. 1998; Olivares *et al*. 2009; San *et al*. 2013; Schreiner *et al*. 2014; Tavcar *et al*. 2000), and 48 retrospective cohort studies (Anderson *et al*. 2017; Ascher-Svanum *et al*. 2013; Barrio *et al*. 2013; Baser *et al*. 2015; Bitter *et al*. 2013; Chan *et al*. 2015; Emsley *et al*. 2008; Fan *et al*. 2018; Foster *et al*. 2017; Greene *et al*. 2018; Grimaldi-Bensouda *et al*. 2012; Haro *et al*. 2007; Høiberg & Nielsen 2006; Huang *et al*. 2013; Joshi *et al*. 2018a, 2018c; Ju *et al*. 2014; Lafeuille *et al*. 2013, 2015, 2018; Lefebvre *et al*. 2017; Levitan *et al*. 2016; Lin *et al*. 2020; Liu *et al*. 2015; Lu *et al*. 2020; Manjelievskaia *et al*. 2018; Marchiaro *et al*. 2005; Marcus *et al*. 2015; Mohamed *et al*. 2009; Offord *et al*. 2013; Pesa *et al*. 2015, 2017; Petrić *et al*. 2019; Pilon *et al*. 2017a, 2017b, 2017c; Remington & Khramov 2001; Song *et al*. 2019; Stanković & Ille 2013; Taipale *et al*. 2018; Tiihonen *et al*. 2011; Tomko *et al*. 2016; Valevski *et al*. 2012; Varner *et al*. 2001; Xiao *et al*. 2015, 2016; Yan *et al*. 2018; Young-Xu *et al*. 2016) (including retrospective analyses of data from randomized controlled trials or prospective studies).

Measurements used to assess the main outcomes

For the systematic review, medication adherence was assessed using Proportion of Days Covered (PDC) and the Drug Attitude Inventory scale (DAI), rates of discontinuation of medication, the Medication Possession Ratio (MPR) for 80% or greater, the Medication Satisfaction Questionnaire (MSQ), persistence to index medication at 12 months (no gap 30-, 60-, and 90 days), taking medications at least 70% to 75% of the days in the treatment period, the Morisky Medication Adherence Scale, the Compliance Rating Scale (CRS),

and the Medication Adherence Rating Scale (MARS). Symptom severity/remission was measured using the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning scale (GAF), the Clinical Global Impressions scale (CGI), time to relapse (days), time in remission (days), and the Brief Psychiatric Rating Scale (BPRS). Rehospitalization/readmission was assessed using the mean number of institutionalizations, hospitalization rates, the number of days hospitalized, the mean days of acute psychiatric hospital stays, any hospitalization or inpatient visits, the lengths of hospital stay, rehospitalization risk, all-cause rehospitalization, time to hospitalization, proportion of patients with inpatient hospitalization, the median number of hospitalizations, mental health institute admissions, relapse/readmission at 6 and 12 months, and first rehospitalization. Outpatient and ED visits were measured using the number of outpatient visits per patient, the number of ED visits, any ED visits, nurse practitioner, therapist, or nurse visits, schizophrenia related outpatient visits, outpatient visits with physicians and non-physician caretakers, and outpatient services within 7 or 30 days of discharge. Healthcare costs (medical costs and pharmacy costs) were assessed using the total costs of both the medical and pharmacy costs, inpatient costs, pharmacy costs, ED costs, outpatient office costs, all-cause medical costs, monthly medical costs, annual medical costs, schizophrenia related medical costs, monthly mental-health related costs (inpatient, ED, outpatient, pharmacy, total), and 1-day mental health institute visit costs. Finally, social functioning was assessed using the Personal and Social Performance (PSP) scale, the Self-Administered Quality of Well– Being scale (QWB), the Wisconsin Quality of Life Index (WQLI), and the Heinrichs-Carpenter Quality of Life scale (HCQL).

For the meta-analyses, we pooled the effect sizes for all our outcomes using the studies that had at least a three of the same measures which assessed the same outcome. Medication adherence was measured by the proportion of patients that had 80% or more PDC ($n = 8$), and the DAI ($n = 3$). Symptom remission/relapse was measured by PANSS ($n = 9$) and CGI ($n = 5$). Measures for rehospitalization/readmission ($n = 13$), outpatient visits ($n = 8$), and ED visits ($n = 9$) were evaluated using the mean number of each. Healthcare costs were measured by annual mean medical costs ($n = 4$) and pharmacy costs ($n = 4$). Social functioning was measured by changes in the PSP scores ($n = 4$) among LAI compared with oral users.

Systematic review and meta-analyses of included studies

The following is the results of the systematic review and meta-analyses of the included studies by main study outcomes:

Medication adherence

Twenty-nine studies (Anderson *et al*. 2017; Aykut 2019; Bartzokis *et al*. 2012; Bellido *et al*. 2008; Bitter *et al*. 2013; Green *et al*. 2015; Greene *et al*. 2018; Haro *et al*. 2007; Joshi *et al*. 2018a, 2018c; Kim *et al*. 2008; Lafeuille *et al*. 2018; Lefebvre *et al*. 2017; Manjelievskaia *et al*. 2018; Marcus *et al*. 2015; Mohamed *et al*. 2009; Offord *et al*. 2013; Pesa *et al*. 2017; Pilon *et al*. 2017b, 2017c; San *et al*. 2013; Schreiner *et al*. 2014; Song *et al*. 2019; Stanković & Ille 2013; Tiihonen *et al*. 2011; Weiden *et al*. 2009, 2012; Yan *et al*. 2018; Young-Xu *et al*. 2016) assessed medication adherence or discontinuation (Table 1). Most reported better medication adherence and lower medication discontinuation for LAI compared with oral users. Exceptions were a study (Mohamed *et al*. 2009) reporting lower medication adherence and three studies (Schreiner *et al*. 2014; Stanković & Ille 2013; Weiden *et al*. 2012) finding no differences in LAI compared with oral users. Eight studies (Anderson *et al*. 2017; Greene *et al*. 2018; Joshi *et al*. 2018a, 2018c; Lefebvre *et al*. 2017; Manjelievskaia *et al*. 2018; Pilon *et al*. 2017b, 2017c; Yan *et al*. 2018; Young-Xu *et al*. 2016) in the pooled analysis showed no differences between LAIs and orals regarding the proportion of patients that had 80% or more PDC ($n = 59042$, 95% CI = 0.804–3.695, $P < 0.162$; $\tau^2 = 1.142$, $I^2 = 94.605\%$, $Q = 129.759$, df = 7, $P < 0.001$) (Figure 2). The true effect in 95% of all comparable populations fell within the prediction interval 0.16–23.50 (see supplemental materials). Furthermore, three studies (Joshi *et al*. 2018b; Rosenheck *et al*. 2011; Stanković & Ille 2013) found no differences in mean scores on the DAI ($n = 1075$, 95% CI = −0.399 to 2.731, $P = 0.144$; $\tau^2 = 1.876$, $I^2 = 98.89\%$, $Q = 180.473$, df = 2, $P < 0.001$).

Symptom remission/relapse

Eighteen Seventeen articles (Anderson *et al*. 2017; Aykut 2019; Bai *et al*. 2007; Barnett *et al*. 2012; Barrio *et al*. 2013; Bellido *et al*. 2008; Bozzatello *et al*. 2019; Emsley *et al*. 2008; Foster *et al*. 2017; Joshi *et al*. 2018b; Keks *et al*. 2007; Macfadden *et al*. 2010; Malla *et al*. 2016; Petrić *et al*. 2019; Remington & Khramov 2001; Schreiner *et al*. 2014; Stanković & Ille 2013;

TABLE 1 *Characteristics of included studies*

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
1. Alphs *et al.* (2016), United States	RCT Patients with prior incarcerations	Paliperidone Palmitate (PP), (n = 93) Oral Antipsychotics (OAs), (n = 88)	Number of institutionalizations Number of psychiatric hospitalizations	15 months	PP compared with OA had significantly lower number of institutionalizations (1.27 ± 0.132 vs 0.82 ± 0.095, P = 0.011) but not psychiatric hospitalizations (0.29 ± 0.075 vs 0.15 ± 0.037, P = 0.074)
2. Anderson *et al.* (2017), United States	Retrospective cohort Data from 46 Community Behavioral Health Organizations	Paliperidone Palmitate (PP) All: N = 482, male (72.0%), White (50.0%), mean age (41.1 years) PP-N (new user): n = 174, male (74.0%), White (42.0%), mean age (39.6 years) PP-C (continuous): n = 308, male (72.0%), White (57.0%), mean age (42.0 years) Oral antipsychotic therapy (OAT) users: n = 281, male (66.0%), White (49.0%), mean age (42.1 years)	Discontinuation of medication rate Medication possession ratio (MPR) for 80% or greater Proportion of days covered in the 1-year post index (PDC) for 80% or greater Remission status: Structured Clinical Interview for Symptoms of Remission (SCI-SR) using the Positive and Negative Syndrome Scale (PANSS) items	12 months	In PP compared with OAT groups, there were significantly lower rates of discontinuation (20% vs 51%, P < 0.001) and higher MPR (74% vs 25%, P < 0.001) and PDC (44% vs 9%, P < 0.001) Paliperidone Palmitate users were significantly more likely to achieve remission in follow-up than OAT users (PP-N vs OAT: OR = 2.65, 95%CI = 1.39 to 5.05; PP-C vs OAT: OR = 1.83, 95%CI = 1.03 to 3.25) PP-N and PP-C group compared with OAT group had significantly higher remission rates (45% vs 39% vs 23%, P < 0.001). PP-N users in remission represented a 25% increase relative to 14% increase in OAT group
3. Ascher-Svanum *et al.* (2013), United States	Retrospective analysis of data from an RCT Multicenter From various settings	Olanzapine—Long-acting injection (LAI), (n = 598), male (65.5%), mean age (38.8 years) Oral olanzapine (n = 322), male (64.9%), mean age (39 years) Sub-therapeutic olanzapine—Long-acting injection (LAI), (n = 144), male (66.7%), mean age (39.5years)	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impressions-Severity of Illness scale (CGI-S) Drug Attitude Inventory (DAI-10) Hospitalization rate Number of hospitalizations Number of days hospitalized	6 months	Among both groups, there was no significant (all P value for group comparisons were > 0.05) difference in the PANSS total (olanzapine-LAI = 55.4 ± 15.5) vs oral olanzapine = 56.1 ± 15.6), CGI (olanzapine-LAI = 3.1 ± 0.9) vs oral olanzapine = 3.1 ± 1.0), DAI (olanzapine-LAI = 7.4 ± 1.8) vs oral olanzapine = 7.5 ± 1.7) No difference between Olanzapine-LAI and Oral Olanzapine in hospitalization rate (5.2% vs 4.0%, P = 0.436), average number of hospitalizations (0.1 ± 0.4 vs 0.1 ± 0.5, P = 0.438), and number of days hospitalized (1.5 ± 12.26 vs 2.3 ± 17.2, P = 0.463)
4. Aykut (2019), Turkey	Prospective cohort (Controlled Trial)		Positive and Negative Syndrome Scale (PANSS)	6 months	PP compared with oral had no significant difference in PANSS scores (16 vs 16,

(*Continued*)

TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
	Patients at outpatient psychiatric clinics Jan to July 2014	Paliperidone Palmitate (PP), (n = 33), male (72.7%), mean age (36.9 years) Second-generation oral antipsychotic, (n = 51), male (64.7%), mean age (37.2 years)	Clinical Global Impression (CGI) Morisky Medication Adherence Scale (score less than 1 is high adherence)		P = 0.902) but had significant differences in CGI improvement (2 vs 1, P = 0.023) PP group compared with Oral group had higher proportion with high adherence (66.7% vs 23.5%, P < 0.001)
5. Bai *et al.* (2007), Taiwan	RCT Between 2004 and 2005	Risperidone long-acting injectable (RLAI), (n = 25), male (48.0%), mean age (44.7 years) Oral Risperidone, (n = 25), male (52.0%), mean age (48.1 years)	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression– Severity (CGI–S) Global Assessment of Functioning (GAF)	12 months	There were no differences between groups on the PANSS (RLAI = 2.32 ± 11.3 vs Oral = −0.52 ± 11.3, P = 0.058), CGI (RLAI = 0.04 ± 0.35 vs Oral = 0.04 ± 0.35, P = n/a), or GAF (RLAI = −16.4 ± 18.5 vs Oral = −9.2 ± 20.4, P = n/a)
6. Barnett *et al.* (2012), United States	Comparative Effectiveness RCT VA patients	Long-acting injectable (LAI) Risperidone, (n = 187), male (92.0%), White (46.5%), age (50.7) Standard care (oral antipsychotic), (n = 182), male (92.2%), Black (47.8%), age (51.3)	Positive and Negative Syndrome Scale (PANSS) Health related quality life: Self-Administered Quality of Well – Being (QWB) Scale Acute medical/surgical hospital stays (mean total days) Acute psychiatric hospital stays (mean days)	18 months 24 months	LAI compared with oral did not have any significant difference in mean PANSS score (74.1 ± 0.91 vs 74.7 ± 0.92, P = 0.65) No significant differences between the LAI Risperidone (0.66 ± 0.02) and oral antipsychotic (0.67 ± 0.02) on QWB, P = 0.63 LAI compared with oral did not have any significant difference in total acute medical/surgical stays (0.2 ± 0.05 vs 0.2 ± 0.08, P = 0.764) or psychiatric hospital stays (2.8 ± 0.6 vs 3.2 ± 0.9, P = 0.730)
7. Barrio *et al.* (2013), Spain	Retrospective (Case–control study) Patients with schizophrenia from a psychiatry unit 2004 to 2008	Risperidone long-acting injectable (RLAI), (n = 26), male (61.5%), White (84.6%), age (26.9) Oral antipsychotics, (n = 26), male (57.7%), White (92.3%), age (27.4)	Number of hospital admissions Personal and Social Performance Scale (PSP) Positive and Negative Syndrome Scale (PANSS) Negative and general psychopathology	24 months	No significant difference in readmission between the RLAI and OA group (19.2% vs 42.3%, P = 0.136) RLAI group had significantly higher PSP scores compared with oral group (RLAI = 72.4 ± 14.8 vs oral = 59.7 ± 13.5, P < 0.001) suggesting better psychosocial functioning RLAI compared with oral showed a significantly greater reduction in mean PANSS scores (47.7 ± 12.0 vs 66.2 ± 18.5, P < 0.001), negative (14.3 ± 6.1 vs

(*Continued*)

TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					19.4 ± 6.4, $P = 005$) and general (23.4 ± 6.3 vs 32.7 ± 8.1, $P < 0.001$) psychopathology
8. Bartzokis *et al.* (2012), United States	RCT Participants from a UCLA Aftercare Research Program	Long-acting injection risperidone RLAI ($N = 9$) Oral Risperidone ($N = 13$)	Medication adherence	6 months	Patients treated with RLAI had better medication adherence χ^2 not reported, $P < 0.05$)
9. Baser *et al.* (2015), United States	Retrospective cohort VA Medical records July 2007 to May 2012	Paliperidone Palmitate Long-Acting Injection (PP), ($n = 381$), male (92%), age (50.2 years) Oral Atypical Antipsychotics (OAT), ($n = 3537$), male (92%), mean age (52.2)	Any hospitalization Number of hospitalizations Number of inpatient days per patient Outpatient visits Number of outpatient visits per patient Any Emergency room visits Inpatient costs Pharmacy costs ER costs Outpatient office costs Other costs Total costs	12 months	PP compared with OAT had significantly lower hospitalizations (34% vs 53%, $P < 0.001$), number of hospitalizations (0.81 vs 1.30, $P < 0.001$), and number of inpatient days (13.24 vs 24.18, $P = 0.002$) Compared with OAT, PP had significantly lower outpatient visits (335 vs 327, $P = 0.004$) but not outpatient visits per patient (46.68 vs 42.71, $P = 0.189$) No significantly different in number of ER visits (7% vs 10%, $P = 0.163$) PP compared with OAT had significantly lower mean inpatient ($18 560 vs $31505, $P = 0.002$) and ER cost ($20 vs $64, $P = 0.015$). But had significantly higher pharmacy ($10 063 vs $4167, $P < 0.001$) costs No significant difference in outpatient office ($16 723 vs $16, 556, $P = 0.908$), other outpatient ($163 vs $276, $P = 0.099$), or total costs ($45 529 vs $52 569, $P = 0.128$)
10. Bellido (2008), Spain	Prospective cohort*	$N = 60$ Long-Acting Injection (LAI, e.g., depot) = 35 (58.3%) Oral = 25 (41.7%)	Adherence Rehospitalization Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression (CGI)	12 months	LAI had greater adherence compared with Oral ($P < 0.05$) LAI had lower rehospitalization compared with oral (28.6% vs 44.0%, P = n/a) LAI had lower PANSS total score compared with Oral ($P < 0.01$) LAI had lower CGI score compared with Oral ($P < 0.01$)
11. Bitter *et al.* (2013), Hungary	Retrospective cohort National Central Register Between 2006 and 2008	Amisulpride ($n = 920$) Aripiprazole ($n = 601$) Clozapine ($n = 790$) Olanzapine ($n = 1633$)	All-cause discontinuation	12 months	Patients treated with RLAI had a significantly longer time to discontinuation with a median of 215 days (95% CI = 181 to 242 days) compared with olanzapine

(*Continued*)

TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
		Quetiapine (n = 1587) Risperidone (n = 2480) Risperidone Long-Acting (RLAI), (n = 1095) Ziprasidone (n = 461)			(136 days, 95% CI = 121 to 153 days), aripiprazole (102 days, 95% CI = 81 to 126 days), ziprasidone (93 days, 95% CI = 82 to 119 days), quetiapine (89 days, 95% CI = 81 to 100 days), clozapine (76 days, 95% CI = 54 to 92 days), amisulpride (73 days, 95% CI = 62 to 85 days), and risperidone (55 days, 95% CI = 41 to 63 days)
12. Bozzatello *et al.* (2019), Italy	Open label RCT	Long-Acting Paliperidone Palmitate Once Monthly (PP1M) (N = 36) Oral Paliperidone Extended Release (ER) (N = 36)	Clinical Global Impression–Schizophrenia (CGI–SCH) Personal and Social Performance (PSP)	6 months	PP1M compared with oral had significant improvements in negative symptoms (CGI-S negative; PP1M = 2.91 ± 1.06 vs Paliperidone ER = 3.87 ± 1.48, P = 0.012) There was no significant difference between the two groups on the total CGI-S (PP1M = 4.18 ± 1.24 vs Paliperidone ER = 3.7 ± 1.32, P = 0.136) There was no significant difference between the two groups on the PSP (PP1M = 65.41 ± 9.91 vs Paliperidone ER = 62.39 ± 13.33, P = 0.112)
13. Buckley *et al.* (2015), United States	RCT	Long-Acting Injectable (LAI-R), (n = 153), male (71%), Caucasian (53%) Oral Second-Generation Antipsychotic (n = 152), male (72%), Caucasian (51%) Subjects in treatment duration analysis: LAI-R (n = 146); SGA(n = 150)	Time to first relapse Hospitalization Clinical Global Impressions (CGI) Brief Psychiatric Rating Scale (BPRS)	30 months	No significant differences between LAI-R and oral SGA treatment in overall relapse (LAI vs SGA: 61/146 and 48/150, P = 0.08), time to first relapse (log rank χ, P = 0.08, df = 1, P = 0.13), and hospitalization (log rank χ = 1, df = 1, P = 0.30) No significant differences between LAI-R and oral treatment in CGI (3.6, 95% CI = 3.4 to 3.7 vs 3.6, 95% CI = 3.5 to 3.8) There was a significant difference between LAI-R and oral SGA treatment in overall BPRS total score (treatment F = 4.17, df = 1, 274, P = 0.042, Cohen's d = 0.25; visit F = 8.25, df = 9, 1264, P < 0.0001; treatment × visit F = 0.70, df = 9, 1264, P = 0.71)

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
14. Chan *et al.* (2015), Taiwan	Retrospective cohort Regional hospital with outpatient department or psychiatric wards	Long-Acting Injection Risperidone (RLAI) (N = 43), male (n = 20), mean age (33.8 years) All Oral Antipsychotic (N = 336), male (n = 178), mean age (39.4 years) Oral Risperidone (N = 103), male (n = 58), mean age (39 years)	Rehospitalization rate Lengths of hospital stay Emergency room visits	12 months	All three groups were similar in rehospitalization rates (all oral antipsychotic = 28.9%, oral risperidone = 30.1%, RLAI = 30.2%, $P > 0.999$) RLAI compared with all-oral antipsychotic and oral risperidone had a significantly higher rate of ED (all oral antipsychotic = 12.8%, oral risperidone = 8.7%, RLAI = 23.3%, $P < 0.029$) There was no significant difference in average hospital length of stay (in days) between RLAI, all-oral antipsychotic, and oral risperidone groups (34.5 vs 28.7 vs 31.8%, $P = 0.621$)
15. Conley *et al.* (2003), United States	Retrospective cohort Inpatient records from 6 public psychiatric hospitals in Maryland 1997	Second-generation antipsychotics (SGAs): Clozapine (N = 41), male (61%), White (64%), mean age (36.9) Risperidone (N = 149), male (63%), White (67%), mean age (38 years) Olanzapine (n = 103), male (58%), White (74%), mean age (39.7 years) Depot group: Fluphenazine decanoate (n = 59), male (72%), White (44%), mean age (39.9 years) Haloperidol decanoate (n = 59), male (68%), White (36%), mean age (35.1 years)	Rehospitalization in any public hospital for a psychiatric condition	Between January 1, 1997 and December 31, 1997	One-year readmission risks were 10%, 95% CI = 1 to 19 for clozapine, 12%, 95% CI = 7 to 18 for risperidone, 13%, 95% CI = 6 to 20 for olanzapine, 21%, 95% CI = 10 to 31 for Fluphenazine decanoate, and 35%, 95% CI = 22 to 47) These risks were not significantly lower than the readmission risk for fluphenazine decanoate (21%, P value not reported) but were significantly lower than haloperidol decanoate (35%, $P < 0.05$) for all three SGAs
16. Detke *et al.* (2014), United States	RCT	Olanzapine long-acting injection (LAI), (n = 264), male (66.3%), White (61.0%), mean age (41.7 years) Oral olanzapine, (n = 260), male (68.1%), White (63.1%), mean age (40.1 years	Hospitalization rate Mean duration of hospitalization days Mean number of hospitalizations days	24 months	Olanzapine LAI group compared with the oral group did not have significantly fewer hospitalization due to psychiatric reasons (7.6%, 95%CI = 4.7 to 11.5 vs 9.2%, 95% CI = 6.0 to 13.4) However, mean duration of hospitalization was lower for Olanzapine LAI compared with oral (6 vs 20, $P = 0.02$)

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					LAI had significant lower mean number of hospitalization day (0.43 ± 2.0 compared with oral group (1.80 ± 9.3), $P = 0.020$
17. Devito *et al.* (1978), United States	Prospective cohort (Ex post facto)	Fluphenazine Decanoate, ($n = 61$), male ($n = 31$), White ($n = 60$) Oral Antipsychotics (comparison group), ($n = 61$), male ($n = 23$), White ($n = 60$)	Readmissions	12 months	Fluphenazine decanoate had significantly fewer readmissions ($n = 25$) during the one-year study period compared with the oral antipsychotics group ($n = 34$), P = n/a
18. Emsley *et al.* (2008), South Africa	Retrospective cohort (derived from data from two studies) Patients	Risperidone Long-Acting Injection (RLAI), ($n = 50$), male (64.0%) mixed (White and Black; 78.0%), mean age (25.4 years) Oral antipsychotics ($n = 47$), male (57.4%) mixed (White and Black; 40%), mean age (25.9 years)	Clinical response: a 20% decrease in the PANSS total score	24 months	The RLAI group compared with the oral group had a greater proportion of those with a clinical response (84.0% vs 80.9%, $P = 0.790$), although non-significant There was a greater reduction on the PANSS total score (−39.7 ± 21.1 vs −25.7 ± 30.2, $P = 0.009$)
19. Fan *et al.* (2018), Taiwan	Retrospective matched cohort National Health Research Institute Database- Psychiatric Inpatient Medical Claim Dataset	Long-Acting Injectable (LAI) Risperidone ($n = 691$), male (45.88%), age; 16–30 (36.90%) and 31–45 (37.05%) Oral Risperidone ($n = 1382$), male (45.88%), age; 16–30 (37.12%), and 31–45 (37.05%)	Hospital admissions Outpatient visits Emergency room visits Length of stay Medical costs (outpatient, emergency room, total psychiatric services)	12 months	LAI compared with oral had significantly more hospital admissions (2.67 ± 2.23 vs 2.41 ± 2.59, $P < 0.01$) and shorter lengths of stay (179.83 ± 110.08 days vs 214.4 ± 117.46 days, $P < 0.01$) LAI compared with oral group had no differences in outpatient visits (68.35 ± 36.66 vs 66.06 ± 38.44, $P = 0.13$) LAI compared with oral had significantly higher ER visits (0.18 ± 0.34 vs 0.16 ± 0.25, $P < 0.01$) LAI compared with Oral group had significantly higher costs in outpatient services ($287.74 ± 194.862 vs $208.25 ± 180 643, $P < 0.01$), ED services ($0.35 ± 1.070 vs $0.25 ± 0.620, $P < 0.01$), and total psychiatric services ($591.65 ± 224.727 vs $511.78 ± 232.887, $P < 0.01$)
20. Foster *et al.* (2017), United States	Retrospective analysis from pragmatic trial data	Long-Acting Injectable ($n = 20$) Oral Antipsychotic medications (OA) ($n = 206$)	Time to first relapse	30 months	No significant difference in the relapse rate among groups ($\chi^2 = 3.85$, $P = 0.146$) LAI group's mean time (594 days) to first relapse was not significantly different from

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
		Combination of two or more antipsychotics (CA) (n = 50)			the other groups (OA = 562 days, CA = 409 days, log-rank χ^2 = 6.81, df. = 2, P = 0.033)
21. Green *et al.* (2015), United States	RCT Adults from community mental health and veterans affairs clinics Between 2005 and 2008	Long-Acting Injection (LAI) Risperidone, (n = 49), male (75.5%), White (51.0%), mean age (41.73 years) Oral Risperidone, (n = 2296), male (78.3%), White (52.2%), mean age (41.72 years)	Good adherence: Taking medications at least 75% of the days in the treatment period	6 months	LAI Risperidone group compared with oral group had higher proportion with good adherence (88% vs 61%, P < 0.005)
22. Greene *et al.* (2018), United States	Retrospective cohort	Schizophrenia (N = 5638) Long-Acting Injection (LAIs) group, (n = 2861), male (56.7%), African American (57.7%), age (39.9 years) Oral group, (n = 2777), male (45%), African American (41.3%) and White (41.4%), age (42.0 years)	Discontinuation of medication rate Proportion of days covered (PDC) for 80% or greater in the 1 year immediately post-index Median time to medication discontinuation	12 months	In LAI compared with oral, there were significantly lower discontinuation (63.2% vs 72.0%, P < 0.001), higher PDC (33.9% vs 25.5%, P < 0.001), and lower median time to medication discontinuation (196 days vs 123 days, P < 0.001)
23. Grimaldi-Bensouda *et al.* (2012), France	Retrospective cohort Patients from 15 regions in France from psychiatric centers	Risperidone Long-Acting Injectable (RLAI; n = 489), male (67.3%), mean age (36.7 years) Non-R-LAI group (n = 1370), male (69%), mean age (38.6 years)	Full-time hospital stays in a psychiatric ward or for psychiatric reasons	12 months	R-LAI compared with non-R-LAI were 34% significantly less likely to be hospitalized (R-LAI: adjusted rate ratio = 0.66, 95% CI = 0.46 to 0.96, vs non- R-LAI; adjusted rate ratio = 0.66, 95% CI = 0.32 to 0.0.88)
24. Haro *et al.* (2007), 10 European Countries	Retrospective analysis of RCT Schizophrenia Outpatient Health Outcomes study data	N = 7728 Long-Acting Injectable (LAI) Typicals (n = 348) Oral Typicals (n = 471) Olanzapine (n = 4247) Risperidone (n = 1549) Quetiapine (n = 583) Amisulpride (n = 256) Clozapine (n = 274)	Discontinuation (for lack of compliance) Rehospitalization	36 months	Between LAI (depot) typicals and other groups, depot typicals (9.9%, HR = 0.89, 95% CI = 0.57 to 1.38) had a lower proportion of discontinuation rates for lack of compliance than oral typicals (12.8%, HR = 2.15. 95% CI = 1.54 to 3.01, P < 0.01), Risperidone (12.4%, HR = 2.15. 95% CI = 1.54 to 3.01, P < 0.05), Quetiapine (17.8%, HR = 2.15. 95% CI = 1.54 to 3.01, P < 0.001), and Amisulpride (15.6%, HR = 2.15. 95% CI = 1.54 to 3.01, P < 0.05), but not Olanzapine (9.0%, HR = 1) and clozapine

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					(8.9%, HR = 0.92, 95% CI = 0.58 to 1.46, *P* value not reported). This discontinuation rate was not significantly lower than olanzapine Between LAI (depot) typicals and other groups, depot typicals (RR = 1.44, 95% CI = 1.10 to 1.88, $P < 0.01$) had significantly higher re-hospitalization due to exacerbation of schizophrenia as compared with oral typicals (RR = 1.39, 95% CI = 1.08 to 1.79, $P < 0.01$)
25. Høiberg and Nielsen (2006), Norway	Retrospective cohort Between 1999 and 2000 Patients from a University Hospital	$N = 123$ Typical oral antipsychotic ($n = 17$) Typical depot antipsychotic ($n = 47$) Atypical oral antipsychotic ($n = 59$)	Rehospitalization	12 months	Compared with those receiving typical depot antipsychotic, there were no differences in days to rehospitalization for those receiving typical oral or atypical antipsychotics (56 days vs 20 days vs 66 days, $P = 0.148$)
26. Huang *et al.* (2013), Taiwan	Retrospective cohort Taiwan National Health Research Institutes data	Long-Acting Injectable (LAI) antipsychotics (Risperidone, Haloperidol, or Flupenthixol), ($N = 726$) Oral Antipsychotics (Risperidone, a different second-generation antipsychotic, or first-generation antipsychotic), ($N = 6943$)	Rehospitalization rates	12 months	There was no difference between patients treated with LAI and oral antipsychotics in reducing rehospitalization rates (27.3% vs 27.3%, *P* = n/a)
27. Joshi *et al.* (2018), United States	Prospective cohort study 46 CBHOs outpatient services	Long-Acting Injection Antipsychotics Therapy (LAI-APT), ($n = 599$), male (72.5%), White (50.6%), (32.8%), mean age (41.1years) Oral Antipsychotics Therapy (APT), ($n = 281$), male (65.8%), White (49.1%), age (42.1 years)	Structured Clinical Interview for Symptoms of Remission (SCI-SR) Nurse practitioner visits Therapist visits, Nurse visits, Group sessions Emergency Room visits Drug Attitude Inventory 10-item scale (DAI-10) Medication Satisfaction Questionnaire (MSQ) Lehman's Quality of Life Interview	12 months	LAI APT compared with oral APT had significantly higher remission (40.0% vs 23.6%), *P* = n/a LAI APT compared with oral APT had significantly higher mean rates of nurse practitioner visits (0.8 ± 1.74 vs 0.4 ± 1.29), therapist visits (5.8 ± 15.2 vs 2.7 ± 7.87), Nurse visits (6.7 ± 7.29 vs 1.6 ± 3.11), and group sessions attended (7.2 ± 22.3 vs 1.9 ± 8.47), *P* = n/a

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
			Personal and Social Performance (PSP) scale Hospitalizations		LAI APT compared with oral had no significant difference in ER visits (13.6% vs 13.6%), P = n/a The mean total DAI-10 scores were 6.1 ± 3.83 for total users of LAI APT and 5.2 ± 4.10 for participants in the oral APT cohort, P = n/a The proportion of participants satisfaction were ranged from 25.0% to 36.0% in LAI APT and 27.4% in the oral APT cohort, P = n/a Mean general life satisfaction scores were 5.0 ± 1.30 for total LAI APT and 4.8 ± 1.31 for oral APT cohorts, P = n/a Among patients treated with LAI APT, the mean total PSP scores were 65.2 ± 16.43 compared with patients treated with oral APT 61.2 ± 13.08, P = n/a LAI APT compared with oral had no significant difference in hospitalizations (13.4% vs 17.0%), P = n/a
28. Joshi *et al.* (2018), United States	Retrospective cohort Medicaid databases from 6 US states (Iowa, Kansas, Mississippi, Missouri, New Jersey, Wisconsin) July 2009 to March 2015	Paliperidone Palmitate Once Monthly (PP1M), (n = 351), male (71.2%), mean age (38.4 years) Oral Atypical Antipsychotics (OAA), (n = 4869), male (58.8%), mean age (41.9 years)	Proportion of days covered (PDC) Persistence: having no continuous gap in days of supply of medication ≥90 days Charlson Comorbidity Index (CCI) Medication possession ratio (MPR) Outpatient visits All-cause medical costs Pharmacy costs	12 months	In PP1M compared with OAA, there were higher PDC (28.5% vs 18.1%, P < 0.001), higher persistence (47.3% vs 31.8%, P < 0.001), and higher MPR (65.2% vs 57.6%, P = 0.005) MPR >80%, 65% vs 58%, P = 0.005 PP1M compared with OAA had significantly lower rates of outpatient visits (IRR = 0.90, P = 0.036) PP1M compared with OAA had significantly lower medical, MMCD = $191, P < 0.020, higher pharmacy MMCD = $250, P < 0.001, and similar total costs MMDC = $59, P = 0.517, but higher pharmacy costs ($250, P < 0.0001)
29. Joshi *et al.* (2018), United States	Retrospective cohort Medicare Advantage Claims Data	Long-Acting Injectable Paliperidone Palmitate (PP), (n = 295), male (50.8%),	Proportion of days covered (PDC) for 80% or greater in the 1 year immediately post-index	6 months 12 months	PP as compared with OAA were significantly more adherent (48.1% vs 32.6%, P < 0.001)

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
		White (65.8%), mean age (48.7 years) Oral Atypical Antipsychotics (OAA), (n = 2296), male (45.5%), White (72.3%), mean age (55.9 years)	Emergency department (ED) visits Outpatient visits Hospitalizations Medical costs Pharmacy costs		No significant difference between PP and OAA groups in mean number of outpatients' visits (18.03 ± 30.8 vs 19.24 ± 12.2, P = 0.228) and ED visits (2.29 ± 9.7 vs 2.54 ± 4, P = 0.432) Significant difference between PP and OAA groups in mean number of hospitalizations (0.62 ± 2.1 vs 0.85 ± 1.3, P = 0.002) PP had lower odds of hospitalization compared with oral antipsychotics (OR = 0.81, 95%CI = 0.68 to 0.96) PP compared with OAA had significantly lower medical costs ($11 095, 95% CI = $10374 to 11867 vs $15 551, 95% CI = $14584 to 16583), but higher pharmacy costs ($14 787, 95% CI = $14117 to 15488 vs $5781, 95% CI = $5530 to 6043)
30. Ju *et al.* (2014), Taiwan	Retrospective cohort Psychiatric Inpatient Medical Claims Data Between 2004 and 2009	Long-Acting Injection (LAI), N = 810 Oral Antipsychotic Medications, N = 945	Rehospitalization risk	12 months	Patients treated with LAIs are at a significantly lower risk for psychiatric rehospitalization than those treated with oral antipsychotics (28.2% vs 32.9%, OR = 0.80, 95% CI = 0.65-0.98, P = n/a)
31. Keks *et al.* (2007), Australia, Belgium, France, Germany, Greece, Luxembourg, Poland, Russia, Spain, Netherlands and UK	RCT 48 centers (Australia, Belgium, France, Germany, Greece, Luxembourg, Poland, Russia, Spain, Netherlands, and UK)	Long-Acting Injectable Risperidone (n = 247), Male (56%), White (96%), mean age (35.1 years) Oral Olanzapine, (n = 300), Male (58%), White (97%), mean age (35.2 years)	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression– Severity (CGI–S) Wisconsin Quality of Life Index	12 months	Patients treated LAI Risperidone had significant improvements on the total PANSS score than in those treated with oral Olanzapine (91 vs 79%, P < 0.001) There were reductions in the overall severity CGI score in the LAI Risperidone and Olanzapine groups (−1.1 ± 1.2 and −1.3 ± 1.2, P = n/a) Among both groups, there was similarity in improvements in patients' quality of life from baseline to endpoint on all sub-scale ratings, but no comparisons between groups
32. Kim *et al.* (2008), South Korea	Prospective, naturalistic, controlled, and open-label study	Risperidone Long-Acting Injection (RLAI), (n = 22),	Medication adherence: the number of actual visits for injection/oral medications divided by the number of	24 months	RLAI compared with the Oral group had higher 12-month (85.7 ± 21.4 vs 54.3 ± 32.8, P < 0.001) and 24-month

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
	Department of Psychiatry, Bundang CHA General Hospital 2004 to 2007	male (32%), mean age (32.5 years) Oral Risperidone (n = 28), male (40%), mean age (31.0 years)	days patients were scheduled to visit during the study period Relapse: Positive and Negative Syndrome Scale (PANSS), Global Assessment of Functioning (GAF), Clinical Global Impressions (CGI)		(81.4 ± 26.6 vs 54.6 ± 32.1, $P < 0.001$) compliance and proportion with good adherence (68% vs 32%) There was no significant difference between groups effect in all three scales: PANSS (57.0 ± 12.5 vs 59.1 ± 9.9, $P = 0.907$), GAF (51.0 ± 10.8 vs 2.0 ± 12.7, $P = 0.067$), and the CGI (3.6 ± 0.9 vs 3.9 ± 0.8, $P = 0.265$)
33. Lafeuille *et al.* (2013), United States	Retrospective cohort Premier Hospital Database 2006 to 2010	Atypical Long-Acting treatment (LAT), (N = 1032), male (56.4%), White (46.8%), mean age (42.1 years) Oral Antipsychotic (Oral-AP), (N = 2796), male (55.4%), White (46.6%), mean age (42.4 years)	Number of rehospitalizations Mean number of days in hospital Time to first rehospitalization Frequency of rehospitalizations Number of Emergency room visits	30 months	Atypical LAT patients compared with oral AP patients had significantly lower mean rehospitalizations related to all-cause (1.25 ± 2.09 vs 1.61 ± 2.82, $P < 0.0001$), mental-disorder-related (1.24 ± 2.08 vs 1.59 ± 2.79, $P < 0.0001$), schizophrenia related (1.15 ± 2.00 vs 1.41 ± 2.54, $P < 0.0005$), and all-cause ER visits (2.33 vs 2.67, $P < 0.0158$) Atypical LAT patients compared with oral AP patients had significantly lower mean frequency of rehospitalizations related to all-cause (within 1-month = 0.15 ± 0.41 vs 0.20 ± 0.49, $P = 0.0286$, 3-month = 0.30 ± 0.62 vs 0.38 ± 0.76, $P = 0.0288$, 6 months = 0.48 ± 0.84 vs 0.58 ± 1.05, $P = 0.0029$) Atypical LAT patients compared with oral AP patients had significantly lower mean frequency of mental disorder-related rehospitalizations (within 1-month = 0.15 ± 0.41 vs 0.20 ± 0.49, $P = 0.0360$, 3-month = 0.30 ± 0.62 vs 0.37 ± 0.76, $P = 0.0333$, 6 months = 0.48 ± 0.84 vs 0.58 ± 1.05, $P = 0.0032$) Atypical LAT patients compared with Oral AP patients had significantly lower mean number of days in hospital after rehospitalization related to all-cause (13.46 ± 27.48 vs 15.69 ± 30.49, $P = 0.008$) and mental-

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					disorder-related (13.44 ± 27.46 vs 15.62 ± 30.41, $P = 0.009$), but not schizophrenia-related (12.79 ± 27.07 vs 14.28 ± 29.14, $P = 0.089$)
34. Lafeuille *et al.* (2015), United States	Retrospective Cohort Premier Perspective Comparative Hospital Database	Paliperidone Palmitate Cohort ($n = 374$), male (67.9%), White (47.6%), mean age (41.1 years) Oral Antipsychotic Cohort ($n = 45\,251$), male (61.5%), White (45.1%), mean age (45.6 years)	Emergency room visits Outpatient hospital visits All-cause rehospitalization All-cause costs (including costs of rehospitalization, ER visits, and outpatient hospital visits)	12 months	Paliperidone palmitate cohort compared with oral antipsychotic significantly less likely to visit ER (HR = 0.53, $P < 0.0001$) Mean proportion of hospital stay spent in ER was 0.08 ± 0.10 in Paliperidone Palmitate group and 0.13 ± 0.19 in oral antipsychotics, and it was significant ($P < 0.001$) Paliperidone palmitate cohort compared with oral antipsychotic significantly less likely to be hospitalized (HR, 0.64; $P < 0.0001$) Paliperidone Palmitate Cohort compared with Oral Antipsychotic had non-significant lower costs (-$212, $P = 0.2164$)
35. Lafeuille *et al.* (2018), United States	Retrospective cohort Medicaid databases from 6 states (Iowa, Kansas, Mississippi, Missouri, New Jersey, Wisconsin) July 2009 to 2015	Paliperidone Palmitate Once Monthly (PP1M), ($n = 371$), mean age (45 years) Oral Atypical Antipsychotics ($n = 8296$), mean age (47.5 years)	Persistence to index medication at 12 months (no gap 90 days) Schizophrenia related outpatient visits Emergency room visits All-cause and schizophrenia related inpatient admissions Monthly medical costs	12 months	PP1M compared with OAA had significantly higher persistence of no gap for greater than 60 days (34% vs 27%, $P = 0.001$) or 90 days (40% vs 33%, $P = 0.006$), but not 30 days (21% vs 18%, $P = 0.154$) PP1M compared with OAA had no significant differences in all-cause of outpatient visits (IRR = 0.98, 95% CI = 0.86 to 1.11), but there was significantly higher schizophrenia-related outpatient visits (IRR = 1.44, 95%CI = 1.23 to 1.67) No significant differences in ER visits of all-cause among PP1M compared with OAA (IRR = 0.80, 95% CI = 0.56 to 1.10) nor the schizophrenia-related ER visits among PP1M compared with OAA (IRR = 0.73, 95%CI = 0.46 to 1.02) PP1M compared with OAA had no difference in rates of all cause (IRR = 0.89, 95% CI = 0.72 to 1.08, $P = 0.156$) and

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Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					schizophrenia related (IRR = 1.07, 95% CI = 0.83 to 1.34, $P = 0.658$) inpatient visits PP1M compared with OAA had significantly lower all-cause medical costs (-$369, $P = 0.004$), but higher all-cause pharmacy costs ($279, $P < 0.0001$)
36. Leatherman *et al.* (2014), United States	RCT VA patients	Long-Acting Injectable (LAI) Risperidone, ($n = 187$), male (91.98%), White (46.52%), age ≥ 53 (53.4%) Oral ($n = 182$), male (90.66%), White (43.41%), age ≥ 53 (54.95%)	Positive and Negative Syndrome Scale (PANSS) Quality of life: Heinrichs-Carpenter Quality of Life Scale Time to hospitalization	24 months	There was a significant difference between groups on the mean of HCQT who were hospitalized at randomization (2.72 vs 2.58, $P = 0.05$ There was no benefit either on time to psychiatric hospitalization or on standard measures of symptoms and quality of life between LAI risperidone with oral medication
39. Lefebvre *et al.* (2017), United States	Retrospective cohort The VHA's Corporate Data Warehouse January 2010 to June 2015	Paliperidone Palmitate (PP), ($n = 1684$), male (93.3%), mean age (49.0 years) Oral Antipsychotic (OAA), ($n = 5188$), male (93.5%), mean age (52.4 years)	Proportion of days covered (PDC) for 80% or greater in the 1-year immediately post-index Proportion of patients with 60-day treatment gap Annual Medical costs Global Assessment of Functioning (GAF) Quan-Charlson Comorbidity Index Outpatient services Mental Health intensive case management Other outpatient visits Number of Emergency room visits Proportion of patients with inpatient hospitalization Mean time to first admission in days Median number of hospitalizations Mean days in inpatient setting Number of days in mental health setting	18 months	In PP compared with OAA, there were significantly lower treatment gap (60.2% vs 75.9%, $P < 0.001$) and higher PDC (37.0% vs 20.0%, $P < 0.001$) PP group had fewer inpatient (2.4 ± 4.6 vs 2.8 ± 3.0, $P < 0.001$) mental health-related inpatient (1.9 ± 3.9 vs 2.1 ± 2.1, $P < 0.001$), and long-term care stays (0.1 ± 0.3 vs 0.1 ± 0.6, $P < 0.001$), but more frequent mental health intensive case management visits (13.3 ± 38.9 vs 8.8 ± 19.4, $P < 0.001$) vs OAA PP compared with OAA had significantly lower mean annual all-cause (-$10 473, 95%CI = −$17 to 827 to -$3491, $P < 0.001$) and schizophrenia related (-$8457, 95%CI = −$12 to 710 to -$3638, $P < 0.001$) medical costs PP compared with OAA had significantly fewer number of days in long-term care setting (4.3 ± 38.6 vs 5.2 ± 27.2, $P < 0.001$), but greater proportion with outpatient service visits (100.0% vs 99.9%,

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					$P = 0.040$) and mean number of outpatient service visits (68.5 ± 62.8 vs 68.0 ± 41.5, $P = 0.011$) PP compared with OAA had significantly greater mean number of mental health intensive case management visits (13.3 ± 38.9 vs 8.8 ± 19.4, $P < 0.001$) but significantly fewer mean number of other outpatient visits (52.6 ± 55.9 vs 56.5 ± 37.2, $P < 0.001$) PP compared with OAA had significantly fewer ED visits (2.6 ± 6.4 vs 2.7 ± 3.9, $P = 0.020$) PP compared with OAA had significantly lower proportion of patients with inpatient hospitalization (66.6% vs 74.3%, $P < 0.001$), longer time to first hospitalization (107.3 ± 131.8 days vs 86.1 ± 78.4 days, $P < 0.001$), fewer hospitalizations (1.6 ± 3.9 vs 2.0 ± 2.4, $P < 0.001$), fewer days in inpatient setting (25.8 ± 67.6 vs 34.8 ± 48.0, $P < 0.001$), and mental health setting (24.0 ± 64.4 vs 31.1 ± 44.7, $P < 0.001$)
38. Levitan *et al.* (2016), United States	Retrospective analysis of two RCTs Multicenter from various settings	Paliperidone Palmitate Once Month (PP1M) ($N = 193$), mean age (26.3 years) Placebo ($N = 192$) Paliperidone ER ($N = 104$), mean age (27.1 years) Placebo ($N = 101$)	Efficacy outcomes: relapse, psychiatric hospitalization Clinical Global Impression–Severity scale (CGI) Personal and Social Performance (PSP) scale Positive and Negative Syndrome Scale (PANSS) Proportion of patients with psychiatric hospitalization after intervention started	40 weeks	There were less time to Relapse (−55, 95%CI = −151 to - 40), PANSS (−53, 95%CI = −123 to −18), and hospitalization (−37, 95% CI = −86 to −12) per 1000 patients treated with PP1M CGI showed a consistent pattern favoring PP1M but were not significant (risk difference–25, 95% CI = 81 to −31) There were fewer PSP worsening events (PP1M = 64 vs Paliperidone ER = 204, risk difference = −165, 95% CI = −93, −237) per 1000 patients treated with PP1M, $P < 0.05$ There were significantly fewer psychiatric hospitalizations in the PP1M group compared with the Paliperidone group (risk

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					difference = −53, 95% CI = −98 to −7, P = n/a)
39. Lin *et al.* (2020), Taiwan	Retrospective Cohort Geriatric inpatients (>60 years old)	Long-Acting Injectable Antipsychotics (LAIs), (n = 151), male, (50.3%), mean age (65.2 years) Oral Antipsychotics (OAPs), (n = 1017), male (58.4%), mean age (66.0 years)	Rehospitalizations within 1 year of discharge Treatment discontinuation defined as lack of attendance to the outpatient clinic for more than 3 months during the 1-year follow-up period Discontinuation date: date of the last outpatient visit	12 months	LAIs group had a significantly lower rehospitalization rate (53.6% vs 66.1%, x^2 = 8.87, df = 1, P = 0.003) Among the two groups, there was no significant difference on the discontinuation rate (LAIs = 7.9% [12/151]; OAPs = 8.7% [88/1017]; P = 0.772) or time to discontinuation (LAIs APs, mean follow-up time = 341.1 days, 95% CI = 327.7 to 354.6; OAPs, mean follow-up time = 328.7 days, 95% CI = 321.3 to 336.1; P = 0.238)
40. Liu *et al.* (2015), Taiwan	Retrospective cohort Psychiatric acute ward of university medical center 2004 to 2008	Long-Acting Injectable Antipsychotic (LAIA), (n = 47), male (40.0%), mean age (37.8 years) Oral Antipsychotics, (n = 45), male (51.0%), mean age (37.4 years)	Rehospitalization rates	36 months	LAIA compared with Oral antipsychotics group had no significant differences in hospitalization in year 1 (17.8% vs 26.1%), in year 2 (34% vs 28.7%), and year 3 (42.6% vs 39.7%) The overall odds of rehospitalization, comparing the LAIA to the oral medication group during the 3-year follow-up period, were not significantly different (1.085 ± 0.373, 95%CI = 0.553 to 2.13, P = 0.813)
41. Lu *et al.* (2020), United States	Retrospective cohort Community-based outpatient psychiatric hospital	Long-Acting Injectable (LAI), (n = 23), male (60.9%), Caucasian (47.8%), mean age (49.6 years) Oral (n = 24), male (62.5%), African American (62.5%), mean age (56.0 years)	The number of hospitalizations/ED visits	12 months	Number of hospitalizations/ED visits significantly decreased in the LAI group after LAI treatment was initiated (t = 3.70, P = 0.002)
42. Macfadden *et al.* (2010), United States, South America, and India	Prospective RCT Between 2006 and 2009	N = 355 Risperidone LAT, (n = 177), Male = 59.3%, Cau casian = 24.3%, mean age (38.1 years) Oral Aripiprazole, Male = 61%, Caucasian = 18%, mean age (37.6 years)	Time to relapse (days) Time in remission (days) Positive and Negative Syndrome Scale (PANSS)	24 months	There was no significant difference between groups. The observed end points of time to relapse (45.8% in RLAT group and 43.6% in aripiprazole, P = 0.684), and time in remission (373.5 ± 282.6 days for the RLAT group and 356.7 ± 292.0 days for the Aripiprazole, P = 0.646)

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					Non-significant between groups (RLAT = −11.0 ± 1.1 points vs aripipra zole = −10.9 ± 1.1 points; $P = 0.968$)
43. Malla *et al.* (2016), Canada	RCT 12 sites across Canada 2004 to 2006	Risperidone Long-Acting Injections (RLAI; $n = 42$), male (78.6%), White (81%), age (22.5) Oral Second-Generation Antipsychotics (Oral; $n = 35$), male (91.4%), White (74.3%), age (23)	Psychotic symptoms: Positive and Negative Syndrome Scale (PANSS) Global clinical severity: CGI-S	24 months	Although mean PANSS scores significantly decreased between baseline and endpoint in both RLAI (−18.1 ± 22.48, $P < 0.05$) and oral group (−17.7 ± 16.45, $P < 0.05$), these scores were not significant between groups CGI-scores were non-significant between groups at the endpoint (RLAI = −1.2 ±0.82) and oral = −0.7 ±0.77, P = n/a)
44. Manjelievskaia *et al.* (2018), United States	Retrospective cohort IBM Watson Health MarketScan Medicaid Multi-State Database January 2010 to December 2014	Paliperidone Palmitate Once Monthly (PP1M), ($n = 7672$), male (48.8%), Black (52.4%), mean age (40.3 years) Oral Atypical Antipsychotics (OAA), ($n = 7926$), male (48.9%), Black (52.4%), mean age (40.0 years)	Proportion of days covered (PDC) for 80% or greater in the 1 year immediately post-index Duration of continuous exposure to index treatment Outpatient office visit All cause costs Outpatient pharmacy costs Proportion of patients with admission Number of admissions per patient Average length of stay per admission	12 months	LAI group compared with Oral group, there were significantly higher adherence (26.7% vs 22.3%, $P < 0.049$) and greater days of continuous exposure to treatment (176.8 vs 148.9, $P = 0.004$) PP1M compared with OAA had significantly lower outpatient visits (83.1% vs 84.5%, $P = 0.019$) PP1M compared with OAA had no difference in all-cause monthly costs ($225, 95% CI = -$31 to $573, P = n/a), but outpatient pharmacy costs were significantly higher in PP1M patients ($634, 95%CI = -$554 to $728, P = n/a) PP1M patients compared with OAA had significantly lower admissions (25.6% vs 33.9%, $P < 0.001$) and greater average length of stay per admission (7.3 vs 6.8, $P = 0.030$). However, there was no significant difference in number of admissions per patient (0.5 vs 0.8, $P = 0.109$)
45. Marchiaro *et al.* (2005), Italy	Retrospective cohort Outpatients July 2004 to September 2004	$N = 60$ Long-Acting Injectable (LAI), (Depot) Neuroleptics ($n = 30$), male (60%), mean age (40.7 years) Second Generation Antipsychotics ($n = 30$) male (53.3%), mean age (39.4 years)	Readmission Rates	24 months	There was no difference between groups on the readmission rate, (oral group = 30%, depot = 37%, $P = 0.784$)

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
46. Marcus *et al.* (2015), United States	Retrospective cohort Administrative claims data from Truven Health Analytics MarketScan Multi-State Medicaid claims database July 1, 2010 and December 31, 2012	Long-Acting Injectable (LAI), (n = 340), male (60.9%), African American (55.0%), mean age (37.5 years) FGA LAIs (n = 157), male (58.0%), African American (65.0%), mean age (38.7 years) SGA LAIs (n = 183), male (63.4%), African American (46.4%), mean age (36.5 years) Orals (n = 3428), male (48.8), African American (48.2), mean age (38 years)	Proportion of days covered (PDC) Discontinuation: Continuous medication gap ≥ 60 days Rehospitalization: Schizophrenia-related rehospitalization all in the 6 months after discharge	6 months	In LAI group compared with oral group, there were significantly higher adherence (48.2% vs 32.3%), lower odds of being nonadherent (adjusted OR = 0.35, 95% CI = 0.27 to 0.46, P < 0.001), and lower discontinuation (23.8% vs 39.4%), (adjusted OR = 0.45, 95%CI = 0.34 to 0.60, P < 0.001) Both the FGA (adjusted OR = 0.58, 95% CI = 0.40 to 0.85, P = 0.005), and SGA LAI users (adjusted OR = 0.34, 95% CI = 0.23 to 0.51, P < 0.001) had lower odds of nonadherence compared with patients using oral antipsychotics LAI compared with orals had significantly lower schizophrenia related hospitalizations (19.1 vs 25.3) and lower odds of hospitalizations (adjusted OR = 0.73, 95% CI = 0.54 to 0.99, P = 0.041)
47. Mohamed *et al.* (2009), United States	Retrospective cohort National administrative databases Fiscal year 2005	Long-Acting Injectable Risperidone (LAIR), (n = 280), male (92.5%), Black (25.7%), mean age between 50 and 64 (90%) Not Long-acting injectable risperidone (No LAIR), (n = 11 541), male (93.4%), Black (21.4%), mean age between 50 and 64 (48.9%)	Medication discontinuation	18 months	Patients who were initiated on LAIR were more likely to discontinue their medication than those who were initiated on oral first- or second-generation antipsychotics (SGAs) with the exception ziprasidone and aripiprazole after adjusting for potentially confounding factors (clozapine HR = 0.37, olanzapine HR = 0.83, risperidone HR = 0.83, or quetiapine HR = 0.78, P = 0.002) 54% of those initiated on LAIR continue for 1 year and 44% continue for 18 months
48. Moore *et al.* (1998), United States	Prospective cohort Spring Grove Hospital Center Between March 1994 and December 1995	Haloperidol Decanoate (n = 14) Fluphenazine Decanoate (n = 29) Risperidone (n = 75)	Rehospitalization rates Annual costs (both the outpatient medication and hospitalization costs)	12 months	Risperidone was associated with lower rehospitalization rates as compared with fluphenazine decanoate and haloperidol decanoate (17% vs 21% vs 36%, P = n/a). The annual costs was lower in Risperidone compared with fluphenazine and haloperidol ($12 137 vs $13 693 vs $23 649, P = n/a)

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
49. Offord *et al.* (2013), United States	Retrospective cohort Between January 2005 and 2010 Health care claims database from 100 companies	Commercial population Long-Acting Injectable (LAI), (N = 394) Oral (N = 2610) Medicare population Long-Acting Injectable (LAI), (N = 147) Oral, (N = 518)	Medication Possession Ratio (MPR) Mean Number of Hospitalizations Length of Stay (LOS)	12 months	Among the commercially insured and Medicare insured study populations, the LAI group showed greater medication adherence compared with the oral group (Commercial: 0.67 ± 0.34 vs 0.56 ± 0.35, $P < 0.001$; Medicare: 0.68 ± 0.34 vs 0.59 ± 0.36, $P < 0.005$) Compared with those treated with oral antipsychotics, patients treated with LAI had greater reductions in hospitalizations for any cause (- 0.90 ± 1.77 vs 0.02 ± 1.49, $P < 0.001$) and associated LOS (−10.29 ± 23.23 vs 0.70 ± 16.73, $P < 0.001$) between the baseline and follow-up periods. Compared with those treated with oral antipsychotics, the number of schizophrenia relapses requiring inpatient care (−0.60 ± 1.37 vs 0.05 ± 0.99, $P < 0.001$) and LOS (- 7.46 ± 20.68 vs 0.60 ± 12.49, $P < 0.001$) were more significantly reduced between the baseline and follow-up periods for patients treated with LAI
50. Olivares *et al.* (2009), Spain	Prospective cohort	Risperidone Long-Acting Injection (RLAI), (n = 1345), male (63.3%), mean age (38.4 years) Oral Antipsychotic (AP) (n = 277), male (63.2%), mean age (37.0 years)	Percent hospitalized Hospital stays (number/patient) Duration (days/patient)	24 months	RLAI group compared with oral group had a significantly greater intensity of hospitalization in terms of the percent of patients hospitalized (35.1% vs 27.1%, $P = 0.025$) and number of hospital stays (0.49 vs 0.32 per patient, $P = 0.019$) but not for the mean duration of stay (21.21 vs 15.27 days, $P = 0.357$)
51. Pesa *et al.* (2017), United States	Retrospective cohort California Medicaid Patients Database 2009 to 2013	Paliperidone Palmitate Once Monthly (PP1M), (n = 722) Oral Antipsychotic Therapy (OAT), (n = 722)	Discontinuation (30-day gap in index treatment therapy) Persistence (30-day gap between prescriptions) Proportion of Days Covered (PDC) Any inpatient visit Hospitalization days Any outpatient visits Number of Emergency room visits	12 months	PP1M compared with OAT had significantly lower discontinuation (30.6% vs 39.5%, $P < 0.001$) and significantly higher persistence (69.4% vs 60.5% $P < 0.001$) and mean PDC (0.7 vs 0.6, $P < 0.001$) PP1M compared with OAT had significantly lower inpatient visits (61.6% vs 77.4%, $P < 0.001$) and hospitalization days (15.0 vs 27.7, $P < 0.001$)

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					PP1M compared with OAT had significantly lower outpatient visit (49.0% vs 56.0%, $P = 0.008$) and ER visits (2.1 vs 2.9, $P = 0.016$)
52. Pesa *et al.* (2015), United States	Retrospective cohort MarketScan Medicaid Multi-State Database (Truven Health Analytics, Ann Arbor, MI, USA) 2009 to 2011	Paliperidone Palmitate (PP), ($n = 984$), male (58.2%), Black (51.9%), mean age (38.8 years) Oral Antipsychotic Therapy (OAT), ($n = 4199$), male (48.8%), Black (47.3%), mean age (41.6 years)	Inpatient hospital admission Mental health related Emergency room visits All-cause monthly cost differentials (inpatient, emergency, outpatient, pharmacy, total) Monthly mental-health related costs (inpatient, emergency, outpatient, pharmacy, total)	12 months	PP compared with OAT had significantly lower risks for any inpatient hospital admission (by 36%, 95%CI = 40 to 30, $P < 0.0001$) and mental health inpatient admission (by 38%, 95%CI = 43 to 32, $P < 0.0001$) PP compared with OAT had significantly lower risks for any ED visits (by 18%, 95% CI = 21 to 15, $P = 0.013$) In terms of all-cause costs, PP compared with OAT had significantly lower inpatient costs (−234.19, 95%CI = −361.70 to −106.67, $P = 0.0003$) and outpatient costs (−335.89, 95%CI = −382.11 to −289.67, $P < 0.0001$); but higher pharmacy costs (1003.65, 95%CI = 986.21 to 1021.09, $P<0.00001$) and total costs (433.58, 95% CI = 297.88 to 569.27, $P < 0.0001$) In terms of mental health–related costs, PP compared with OAT had significantly lower inpatient costs (−270.56, 95% CI = −354.67 to −186.45, $P = 0.0003$) and outpatient costs (−285.94, 95% CI = −317.70 to −254.17, $P < 0.0001$); but higher pharmacy costs (1019.30, 95% CI = 1004.50 to 1034.10, $P < 0.0001$) and total costs (462.80, 95%CI = 373.95 to 551.65, $P < 0.0001$)
53. Petrić *et al.* (2019), Croatia	Retrospective cohort Adolescent first episode schizophrenia Medical records 2014 to 2017	Long-Acting Paliperidone Palmitate Antipsychotic (LAIPP), ($n = 18$), male (55.6%), mean age (16.56) Oral antipsychotic	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression Improvement and Severity (CGI-I and CGI-S) Personal and Social Performance Scale (PSP)	12 months	LAIPP compared with oral had significantly greater reductions in PANSS scores (−43.9 vs −35.9, $P < 0.004$) and CGI (−3 vs −2.5, $P = 0.018$) Patients treated with paliperidone palmitate had significantly greater improvement in PSP 36.83 ± 6.09) compared with those

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
		Risperidone (n = 18), male (50%), mean age (16.2) Adolescents age 15-18 years (mean 16.6 for PP and mean 16.2 for OA group) Male (55.6% for PP group and 50.0 for OA group)	Hospitalizations		in the risperidone group (29 ± 4.31), P = 0.001 PP compared with oral risperidone group had significantly lower hospitalizations (11.1% vs 50.0%, P = 0.027)
54. Pilon *et al.* (2017), United States	Retrospective from two data sources	Long-acting injectable (LAI) antipsychotics (program group), (n = 102), female (37.3%), White (79.4%), age (40.6) Oral antipsychotics (OAs), (nonprogram group), (n = 408), female (39.0%), White (78.7%), age (40.7)	Persistence (program group): no documentation of discontinuation from their index medication within the chart Persistence (nonprogram group): a gap of 60 days between prescription claims or between the last prescription and 6 months post-index Hospitalization rate: the proportion of patients with one or more all-cause hospitalization during the 6-month post-index period	6 months	Adjusted ORs indicated that the persistence rate at 6 months was significantly higher for the program group (88.2%) vs the nonprogram group (43.9%, OR = 9.70; P < 0.0001) The 6-month post-index hospitalization rate for the program group (14.7%) was significantly lower vs the nonprogram group after adjustments (22.5%, OR = 0.55, P < 0.0001) Numerically lower (not statistically significant) for the program cohort at 14.7% compared with the nonprogram cohort at 22.5% (P = 0.819)
55. Pilon *et al.* (2017), United States	Retrospective cohort Medicaid data from 5 states 09/2008 to 03/2015	Once Monthly Paliperidone Palmitate (PP1M), (n = 227), male (75.3%), White (43.2%), mean age (22.3 years) Oral Atypical Antipsychotics (OAAs), (n = 2168), male (58.9%), White (52.9%), mean age (21.6 years)	Proportion of days covered (PDC) for 80% or greater in the 1 year immediately post-index Persistence: no gap 90 days Outpatient visits Medical costs Pharmacy costs Total health care costs	12 months	PP1M compared with OAAs had non-significant higher rate of PDC (39.3% vs 38.4%, P = 0.1534) but significantly higher persistence (43.8% vs 36.1%, P < 0.0001) PP1M compared with OAAs had non-significant lower outpatient visits (0.91, 95%CI = 0.83 to 1.01, P = 0.072) PP1M compared with OAAs had significantly lower medical costs (-$286, 95% CI = −412 to −150, P < 0.0001), but higher pharmacy costs (323, 95%CI = 250 to 392, P < 0.0001), but non-significant total health care costs ($37, 95%CI = −117 to 212, P = 0.709)
56. Pilon *et al.* (2017), United States	Retrospective cohort Medicaid data from 6 states 2010 to 2015	Second-Generation Long-Acting Injectable Therapies (SGA-LAIs), (n = 3307), male (59.5%), mean age (41.8 years)	Inpatient visits Mental health institute admission Proportion of days covered (PDC) ≥80%	12 months	SGA-LAI compared with OAA had no significant difference in inpatient visits (adjusted IRR = 1.05, 95%CI = 0.95 to 1.16, P = 0.377)

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
		Oral Atypical Antipsychotics (OAAs), (n = 21 355), male (50.0%), mean age (44.2 years)	Persistence: no gap ≥30, 60, or 90 days to index treatment Outpatient visits Emergency department visits Medical costs 1-day mental health institute visit costs		However, SGA-LAI compared with OAA had significantly higher mental health institute admission (adjusted IRR = 1.16, 95% CI = 1.10 to 1.23, $P < 0.001$) SGA-LAI compared with OAA had higher PDC (31.1% vs 28.1%, $P < 0.0001$) and persistence of no gap for 30 days (26.2% vs 24.0%, $P < 0.001$), 60 days (40.4% vs 34.3%, $P < 0.001$), and 90days (46.5% vs 41.0%, $P < 0.0001$) SGA-LAI compared with OAA non-significantly lower outpatient visits (IRR = 0.97, 95%CI = 0.92 to 1.02, $P = 0.204$). However, likelihood of PP-LAI vs OAA was significantly lower (IRR = 0.92, 95%CI = 0.87 to 0.97, $P = 0.004$), but not A-LAI vs OAA, $P = 0.056$ SGA-LAI compared with OAA had no significant difference in ED visits (Adjusted IRR = 0.94, 95%CI = 0.82 to 1.08, $P = 0.389$) SGA-LAI compared with OAA had significantly lower medical costs (-$168, 95% CI = −238 to −94, $P < 0.001$), lower inpatient costs (-$107, 95%CI = −145 to −64, $P < 0.001$), and lower home care costs (-$100, 95%CI = −139 to −60, $P < 0.001$) SGA-LAI compared with OAA had higher 1-day mental institute visit costs ($33, 95% CI = 25 to 41, $P < 0.001$)
57. Remington and Khramov (2001), Canada	Retrospective cohort Schizophrenia and Continuing Care Program Between 1993 and 1995	Clozapine (N = 15) Risperidone (N = 15) Depot Conventional (N = 18) Oral Conventional (N = 18)	Number of hospitalizations Rehospitalization days Emergency room visits Outpatient visits with physicians and non-physician caretakers Clinical Global Impression scale (CGI)	18 months	There was no significant difference between depot conventional and oral conventional, clozapine, or risperidone groups in the mean number of hospitalizations (1.1 vs 0.7 vs 0.9 vs 0.9, P = n/a), days in the hospital at rehospitalization (20.8 vs 31.8 vs 35.1 vs

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					28.6, P = n/a), or mean number of ED visits (2.1 vs 1.6 vs 1.5 vs 1.4, P = n/a) However, there were significant differences between depot conventional and oral conventional, clozapine, or risperidone groups in the number of physicians (23.7 vs 15.4 vs 58.9 vs 40.9, $P = 0.0001$) and non-physician visits (27.3 vs 8.4 vs 32.2 vs 17.1, $P = 0.004$) There were significant differences between depot conventional and oral conventional, clozapine, or risperidone groups in CGI (3.7 vs 3.4 vs 4.1 vs 3.7, $P = 0.0001$)
58. Rosenheck *et al.* (2011), United States	RCT	Oral Antipsychotic (n = 182) Injectable Risperidone (n = 187)	Total days of psychiatric hospitalization Proportion of patients with psychiatric hospitalization Heinrichs–Carpenter Quality of Life Scale Personal and Social Performance scale (PSP)	24 months	Injectable Risperidone compared with oral antipsychotic had no significant differences in total days of psychiatric hospitalization (19.2 ± 59.7 vs 20.3 ± 43.4, $P = 0.80$) or proportion of patients hospitalized (64.7 vs 62.1, $P = 0.60$) There was no significant difference in the quality of life scores (2.86 ± 0.06 vs 2.78 ± 0.06, $P = 0.28$) and the PSP between two groups (0.66 ± 0.02 vs 0.67 ± 0.02, $P = 0.63$).
59. San *et al.* (2013), Spain	Prospective cohort (with retrospective component) Spanish National Health Care System	N = 1646 Long-Acting Injectable (LAI), (N = 827) Oral Atypical route (N = 645) Depot Typical injection (N = 120) Oral Typical route (N = 51)	Psychiatrist's Opinion on Adherence to Pharmacological Treatment Scale Relapse/Readmission at 6 and 12 months	12 months	There were statistically significant differences in medication adherence between patients treated with LAI compared with depot typical antipsychotics, oral atypical, and oral typical antipsychotics (41.9% vs 34.7% vs 25.8% vs 22.4%, $P < 0.0001$) The mean time until the first relapse at follow-up was 10.2 ± 0.2 months for patients treated with LAI, 10.3 ± 0.6 for oral typical antipsychotics, 10.1 ± 0.2 for oral atypical antipsychotics, and 8.9 ± 0.4 for oral typical antipsychotics. No difference observed between groups, log-rank test 2.49, $P = 0.476$

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
60. Schreiner *et al.*, (2014), Europe, Middle East, Africa	6-month retrospective and 12-month prospective Various treatment centers	Risperidone Long-Acting Treatment (RLAT), (n = 561) Oral Antipsychotics (OAP), (n = 522)	Clinical Global Impression of Schizophrenia (CGI-SCH) Global Assessment of Functioning (GAF) Compliance Rating Scale (CRS) Mean number of hospitalizations Duration of hospitalizations	12 months	RLAT compared with OAP had significantly better mean change of CGI-SCH scores (overall = −1.10 vs −0.80, positive = −1.16 vs −0.86, and negative = −0.98 vs −0.75, P = n/a) and GAF scores (13.5 ± 14.7 vs 8.8 ± 13.0; $P < 0.001$) Mean improvements in CRS scores better in RLAT (1.3 ± 2.0) vs OAP (0.5 ± 1.6, $P < 0.0001$) patients during treatment, but at end of treatment similar adherence between groups (5.7 ± 1.4 and 5.8 ± 1.3) RLAT compared with OAP had no difference in hospitalization rate (0.5 ± 7.8 vs 0.3 ± 2.1, P = n/a), but had significantly lower durations of days per hospitalizations prospectively (8.2 ± 21.6 vs 16.2 ± 38.6, P = 0.002)
61. Song *et al.* (2019), United States	Retrospective cohort IBM Watson Health MarketScan Multi-State Medicaid Database January 1, 2010 through June 30, 2016	Oral Atypical Antipsychotics (OAA), (n = 7029), male (56.0%), Black (52.7%), mean age (40.6 years) Paliperidone Palmitate Long Antipsychotics Injectable (PPLAI), (n = 4302), male (59.3%), Black (50.6%), mean age (39.6 years) Aripiprazole Long Antipsychotics injectable (ALAI), (n = 586), male (53.4%), Black (43.7%), mean age (38 years) Risperidone Long-Acting Injectable (RLAI), (n = 1456), male (56%), Black (51.1%), mean age (41 years)	Discontinuation: lack of subsequent claims for the index medication for 60 and 90 days following the exhaustion of the previous claim's "days' supply"	12-month	Adjusted hazard ratios for discontinuation were HR = 0.60; 95%CI = 0.56 to 0.64) for PPLAI, 0.69 HR = 0.69; 95%CI = 0.60 to 0.79) for ALAI, and HR = 0.70, 95% CI = 0.64 to 0.77) for RLAI vs OAA, $P < 0.05$)
62. Stanković and Ille (2013), Serbia	Retrospective cohort Outpatient setting	Depot administration (n = 19), male (47.3%), mean age (44.4 years) Oral administration (n = 37), male (62.2%), mean age (34.9 years)	Positive and Negative Syndrome Scale (PANSS) Medication Adherence Rating Scale (MARS) Medication Adherence Questionnaire (MAQ)	N/A	Depot compared with oral group had significantly lower mean scores on PANSS (70.0 vs 84.6, P = 0.006) and in all subscale scores for positive symptoms (12.4 vs 15.2, P = 0.045), negative symptoms

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					(22.5 vs 27.1, $P = 0.016$), and general psychopathology (34.9 vs 42.2, $P = 0.007$) No significant difference in mean MARS (8.5 ± 1.4 vs 7.7 ± 2.4, $P = 0.113$) or MAQ scores (3.0 ± 0.7 vs 2.8 ± 1.1, $P = 0.544$) by depot vs oral groups
63. Subotnik *et al.* (2015), United States	RCT University-based research clinic First episode schizophrenia	Long-Acting Injectable Risperidone ($n = 43$), male (78%), White (45%), mean age (21.9 years) Oral Risperidone ($n = 43$), male (79%), White (54%), mean age (21.1 years)	Psychiatric hospitalizations Hospital days Brief Psychiatric Rating Scale (BPRS) Psychotic Symptom Control: proportion of the follow-up period during which BPRS hallucinations and unusual thought content rated less than 4 on the BPRS Psychiatric hospitalizations Hospital days	12 months	Long-Acting Risperidone group had lower psychiatric hospitalizations compared with oral group (5.0% vs 18.6%) and fewer mean hospital days (0.5 vs 1.8, $P = 0.07$) BPRS scores were lower for the long-acting risperidone group (2/40, 5%) compared with the oral group (14/43, 33%), $P < 0.001$, RR = 84.7% Long-acting injectable risperidone better controlled mean levels of hallucinations and delusions throughout follow-up ($\beta = -0.30$; $t = -2.6$; $P = 0.01$)
64. Taipale *et al.* (2018), Finland	Retrospective Cohort Inpatient hospital care from 1974 to 2014 First episode schizophrenia	Prevalent Cohort ($n = 62250$), male (50.2%), median age (45.6 years) Incident Cohort ($n = 8719$, male (56.2%), median age (36.2 years)	Psychiatric rehospitalization All cause hospitalization	Up to 240 months	LAI use compared with oral medications use resulted in significantly lower risk for psychiatric rehospitalization (first generation LAIs = 0.46, 95%CI = 0.40 to 0.54: second generation LAIs = 0.45, 95% CI = 0.39 to 0.52) vs (first generation orals HR = 0.67, 95%CI = 0.60 to 0.74; second generation orals HR = 0.57, 95%CI = 0.53 to 0.61), P = n/a LAI use compared with oral medications use resulted in significantly lower risk for all cause hospitalization (first generation LAIs HR = 0.58, 95%CI = 0.51–0.66; second generation LAIs HR = 0.56, 95% CI = 0.50 to 0.63) vs (first generation orals HR = 0.80, 95% CI = 0.74 to 0.87; second generation orals HR = 0.69, 95%CI = 0.66 to 0.73), P = n/a
65. Tavcar *et al.* (2000), Slovenia	Prospective study Slovenian Registry of psychiatric inpatients	$N = (447)$ Oral, $N = 82$, male (50.0%), mean age (40.1 years)	Rehospitalization Rates	NA	There were no differences between depot (5.7, 5.6%) and oral (6.5, 7.1%) or atypical

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
		Depot, $N = 332$, male (45.3%), mean age (36.6 years) Atypical, $N = 43$, male (34.9%), mean age (40.6 years)			(6.9, 5.3%) groups on rehospitalization rates number P = n/a
66. Tiihonen *et al.* (2011), Finland	Retrospective cohort National Hospital Discharge Register Between 2000 and 2007	$N = 2588$	All-cause discontinuation First rehospitalization	24 months	Depot antipsychotics were associated with a 59% lower risk of discontinuation than oral antipsychotics (HR = 0.41, 95% CI = 0.27 to 0.61, $P < 0.0001$) Depot antipsychotics were not associated with risk of rehospitalization as compared with oral antipsychotics (HR = 0.36, 95% CI = 0.17 to 0.75, $P = 0.007$)
67. Tomko *et al.* 2016, United States	Retrospective cohort Patients with concurrent tobacco use 2012 to 2015	Paliperidone Palmitate (PP), ($n = 108$), male ($n = 68$), mean age (41.88 years) Oral Clozapine, ($n = 18$), male ($n = 13$), mean age (48.12 years)	Readmissions Time until readmission (in months)	36 months	PP compared with Oral Clozapine had significantly lower readmission rates (16.7% vs 50.0%, $P = 0.004$) but no difference in time to readmission (6.14months vs 5.85 months, $P = 0.425$)
68. Valevski *et al.* (2012), Israel	Retrospective cohort Geha Mental Health Center affiliated Between 1991 and 2005	Long-Acting First-Generation Antipsychotic (FGA-LAI), ($N = 293$) Clozapine ($N = 74$)	Readmission Rate	12 months	Patients treated with clozapine had significant lower readmission rate compared with long-acting FGA medications (HR = 1.646, 95% CI = 1.039 2.610, $P = 0.034$)
69. Varner *et al.* (2001), United States	Retrospective cohort Harris County Psychiatric Hospital, Houston	$N = 153$ Oral haloperidol ($n = 58$) Depot haloperidol ($n = 95$)	Rehospitalization Outpatient visits	96 months 48 Months	No difference between groups in subsequent rehospitalization (oral = 3.0 ± 2.7 vs depot = 4.3 ± 4.6) No significant difference between the two groups on the outpatient visit ($x^2 = 0.00$, P = n/a) No difference in number of outpatient days before readmission between depot group and oral group (354 days vs 392 days, $t = -0.44$, P = n/a)
70. Weiden *et al.* (2009), United States	Prospective RCT Academic Medical Center and Hospital	Long-Acting Injectable Risperidone (LAIR), ($n = 26$) Oral Risperidone Therapy (ORAL), ($n = 11$)	Adherence behaviors based on gap of not taking antipsychotic medication for more than 14 days	3 months	RLAIR compared with Oral group had significantly higher proportion of adherent participants (89%, 95%CI = 64% to 97% vs 59%, 95%CI = 32% to 78%, $P = 0.035$)
71. Weiden *et al.* (2012), United States	Prospective RCT	Risperidone Long-Acting Injectable (RLAI), ($n = 19$) Oral Risperidone Therapy (ORAL), ($n = 18$)	Adherence behaviors based on gap of not taking antipsychotic medication for more than 14 days	24 months	No differences in proportion of nonadherent days between groups, the median time to gap event was 42 weeks (95% CI = 15-50) for the RLAI group and

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TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					12 weeks (95% CI = 2 to 45) for the ORAL group (P = 0.188)
72. Xiao *et al.* (2015), United States	Retrospective study Medicaid beneficiaries (New Jersey, Iowa, Missouri, and Kansas) between 2009 and 2012	Paliperidone Palmitate (PP), (n = 952), male (63.1%), White (46.7%), mean age (40.3 years) Oral Atypical Antipsychotics (OAAs), (n = 12 174), male (57.6%), White (58.3%), mean age (45.3 years)	Medical Costs Pharmacy Costs All-Cause Healthcare Resource Utilization (Emergency room visits and outpatient visits)	36 months	Compared with OAAs, PP group had lower medical costs (MMCD = −$136.15; P = 0.0001) and higher pharmacy costs (MMCD = $232.88; P < 0.001) Patients treated with PP had fewer inpatient visits (RR: 0.91, 95% CI = 0.90 to 0.92, P < 0.0001), less frequent visits for ED visits (RR = 0.58, 95% CI = 0.57 to 0.60, P < 0.0001), and more outpatient visits (RR = 1.15, 95% CI = 1.15 to 1.16, P < 0.0001) compared with those treated with OAAs
73. Xiao *et al.* (2016), United States	Retrospective study Medicaid databases for Florida, Iowa, Kansas, Mississippi, Missouri, and New Jersey	Paliperidone Palmitate (PP), (n = 876), male (54.7%), White (53.2%), mean age (40.8 years) Oral Atypical Antipsychotics (OAAs), (n = 10 778), male (45.2%), White (57.6%), mean age (43.2 years)	Hospitalizations Hospitalization days All-Cause Healthcare Resource Utilization (Emergency room visits and outpatient visits) Medical Costs Pharmacy Costs	12 months	PP compared with OAA had significantly lower risk for hospitalization (IRR = 0.96, 95% CI = 0.94 to 0.99, P = 0.004) and hospitalization days (IRR = 0.85, 95% CI = 0.84 to 0.86, P < 0.001) Patients treated with PP had less frequent visits for ED (RR = 0.71, 95% CI = 0.70 to 0.73, P < 0.001) compared with those treated with OAAs No difference was found on outpatient visits between two groups on outpatient visits (IRR = 1.00, 95% CI = 0.99 to 1.02, P = 0.832) Compared with OAAs, PP was associated with significantly lower medical costs (MMCD= -$383, P < 0.001) and higher pharmacy costs (MMCD= $270, P < 0.001)
74. Yan *et al.* (2018), United States	Retrospective cohort The Truven Health MarketScan® Medicaid, commercial, and supplemental Medicare databases January 2012 to June 2016	Schizophrenia: Aripiprazole once-monthly AOM (n = 408), female (42.2%), African American (31%), age (37.3 years) Oral antipsychotics (n = 3361), female (52.1%), African American (44.6%), mean age (43.6 years)	Proportion of days covered (PDC) for 80% or greater in the 1 year immediately post-index Discontinuation: lack of subsequent claims for the index medication for 60 days following the exhaustion of the previous claim's "days' supply" Median time to discontinuation in days	12 months	AOM compared with oral had significantly higher PDC (0.56 ± 0.32 vs 0.45 ± 0.33, P < 0.001) and lower discontinuation (307 ± 75.2 vs 2857 ± 85.0, P < 0.001) and higher median time to discontinuation (193 days vs 89 days, P < 0.001)

(*Continued*)

TABLE 1 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
75. Young-Xu *et al.* (2016), United States	Retrospective cohort VHA Corporate Data Warehouse Between January 2010 and October 2014	Paliperidone Palmitate (PP), (n = 2285), male (89.9%), White (36%), mean age (50.2) years Oral Atypical Antipsychotics (OAAs), (n = 8005), male (90.7%), White (39.9%), mean age (53.7 years)	Number of patients with inpatient stays (%) Time to first hospital admission (days) Number of stays per patient Number of days in inpatient setting Number of mental health stays per patient Number of days in mental health setting Proportion of Days Covered by index drug Mean duration of treatment Proportion of patients with treatment gap of > 30 days Proportion of patients with treatment gap of > 60 days Number of outpatient visits Number of emergency room visits Outpatients visit costs Pharmacy costs Inpatient costs	18 months	PP compared with OAA had significantly lower proportion of patients with inpatient stays (83.3% vs 89.1%, $P < 0.001$), greater time to first hospital admission (116.2 ± 149.0 vs 90.6 ± 78.9, $P < 0.001$), lower stays per patient (2.3 ± 5.4 vs 2.6 ± 3.0, $P < 0.001$) and days in inpatient setting (43.7 ± 104.0 vs 53.4 ± 65.2, $P < 0.001$), lower number of mental health stays per patient (1.8 ± 4.2 vs 2.0 ± 2.1, $P < 0.001$), and days in mental health setting (35.9 ± 90.3 vs 40.6 ± 51.9, $P < 0.001$) PP compared with OAA had significantly greater PDC (35.8% vs 23.3%, $P < 0.001$) and duration of treatment (209.6 ± 182.5 vs 165.0 ± 91.9, $P < 0.001$), and lower 30-day (71.2% vs 83.0%, $P < 0.001$) and 60-day (60.6% vs 74.0%, $P < 0.001$) treatment gap PP compared with OAA had significantly lower outpatient visits per patients (69.1 ± 68.4 vs 67.4 ± 41.1, $P < 0.001$) No significant difference between the two groups on the number of ED visits per patients (2.3 ± 6.1 vs 2.4 ± 3.5, $P = 0.062$) PP compared with OAA had significantly lower total outpatient costs ($8511.36, $P = 0.012$). PP treatment had greater outpatient visit ($2527.44, $P < 0.0001$) and pharmacy ($3416.96, $P < 0.0001$), but lower inpatient stay costs (-$14 455.76, $P < 0.0001$)

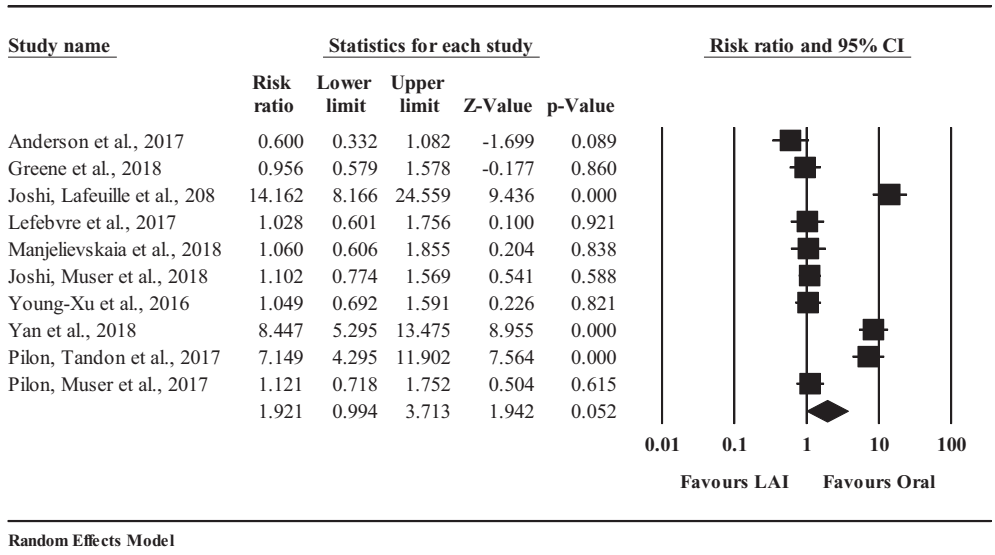

FIG. 2 Forest plot of studies assessing the differences between long-acting injectable (LAI) and oral antipsychotics in the proportion of patients that had 80% or more proportion of days covered (PDC).

Subotnik *et al*. 2015) assessed symptom remission and relapse (Table 2). Eleven studies (Anderson *et al*. 2017; Barrio *et al*. 2013; Bellido *et al*. 2008; Emsley *et al*. 2008; Joshi *et al*. 2018b; Keks *et al*. 2007; Petrić *et al*. 2019; Remington & Khramov 2001; Schreiner *et al*. 2014; Stanković & Ille 2013; Subotnik *et al*. 2015) reported that compared with orals, LAIs were associated with improvements in PANSS scores and GAF, greater symptom remission, and lower relapse. However, pooled analysis of nine studies (Bai *et al*. 2007; Barrio *et al*. 2013; Emsley *et al*. 2008; Keks *et al*. 2007; Kim *et al*. 2008; Macfadden *et al*. 2010; Petrić *et al*. 2019; Rosenheck *et al*. 2011; Stanković & Ille 2013) found no statistically significant differences between LAIs and orals in mean PANSS scores (n = 1323, 95% CI = −0.579 to 0.016, P = 0.064; τ^2 = 0.154, I^2 = 82.993%, Q = 47.039, df = 8, P < 0.001) (Figure 3). The true effect in 95% of all comparable populations fell within the prediction interval −1.23 to 0.61 (see supplemental material). Furthermore, five studies (Bai *et al*. 2007; Bozzatello *et al*. 2019; Kim *et al*. 2008; Olivares *et al*. 2009; Remington & Khramov 2001) reported no difference in the mean CGI scores (n = 861, 95%CI = −0.234 to 0.566, P = 0.416; τ^2 = 0.142, I^2 = 73.24%, Q = 14.950, df = 4, P = 0.005). Too few studies were available to calculate the true effect of the predication interval of the dispersion in LAIs compared with orals on GAF.

Rehospitalization

Among the selected studies, 50 (Alphs *et al*. 2016; Ascher-Svanum *et al*. 2013; Barnett *et al*. 2012; Barrio *et al*. 2013; Baser *et al*. 2015; Bellido *et al*. 2008; Chan *et al*. 2015; Conley *et al*. 2003; Detke *et al*. 2014; Devito *et al*. 1978; Fan *et al*. 2018; Grimaldi-Bensouda *et al*. 2012; Haro *et al*. 2007; Høiberg & Nielsen 2006; Huang *et al*. 2013; Joshi *et al*. 2018b, 2018c; Ju *et al*. 2014; Lafeuille *et al*. 2013, 2015, 2018; Leatherman *et al*. 2014; Lefebvre *et al*. 2017; Levitan *et al*. 2016; Lin *et al*. 2020; Liu *et al*. 2015; Manjelievskaia *et al*. 2018; Marchiaro *et al*. 2005; Marcus *et al*. 2015; Moore *et al*. 1998; Offord *et al*. 2013; Olivares *et al*. 2009; Pesa *et al*. 2015, 2017; Petrić *et al*. 2019; Pilon *et al*. 2017c; Remington & Khramov 2001; Rosenheck *et al*. 2011; San *et al*. 2013; Schreiner *et al*. 2014; Subotnik *et al*. 2015; Taipale *et al*. 2018; Tavcar *et al*. 2000; Tiihonen *et al*. 2011; Tomko *et al*. 2016; Valevski *et al*. 2012; Varner *et al*. 2001; Xiao *et al*. 2015, 2016; Young-Xu *et al*. 2016) assessed the number and rates of rehospitalizations and days spent in the hospital among patients taking LAIs compared with orals (Table 3). Of these studies, 27 reported that LAI users had statistically significantly lower mean number of rehospitalizations (Baser *et al*. 2015; Bellido *et al*. 2008; Detke *et al*. 2014; Devito *et al*. 1978; Grimaldi-Bensouda *et al*. 2012; Haro *et al*. 2007; Joshi *et al*. 2018c; Lafeuille *et al*. 2013, 2015; Lefebvre *et al*. 2017; Levitan *et al*. 2016; Lin *et al*. 2020; Manjelievskaia *et al*. 2018; Marcus *et al*. 2015; Offord *et al*. 2013; Olivares *et al*. 2009; Pesa *et al*. 2015, 2017; Petrić *et al*. 2019; Subotnik *et al*. 2015; Taipale *et al*. 2018; Tomko *et al*. 2016; Xiao *et al*. 2016; Young-Xu *et al*. 2016) and rehospitalization rates (Ju *et al*. 2014; Valevski *et al*. 2012; Xiao *et al*. 2015) compared with oral users. Also, ten studies (Baser *et al*.

TABLE 2 *Characteristics of studies assessing symptom remission/relapse*

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
1. Anderson *et al.* (2017), United States	Retrospective cohort Data from 46 Community Behavioral Health Organizations	Paliperidone Palmitate (PP) All: N = 482, male (72.0%), White (50.0%), mean age (41.1 years) PP-N (new user): n = 174, male (74.0%), White (42.0%), mean age (39.6 years) PP-C (continuous): n = 308, male (72.0%), White (57.0%), mean age (42.0 years) Oral Antipsychotic Therapy (OAT) users: n = 281, male (66.0%), White (49.0%), mean age (42.1 years)	Remission status: Structured Clinical Interview for Symptoms of Remission (SCI-SR) using the Positive and Negative Syndrome Scale (PANSS) items	12 months	Paliperidone Palmitate users were significantly more likely to achieve remission in follow-up than OAT users (PP-N vs OAT: OR=2.65, 95%CI=1.39 to 5.05; PP-C vs OAT: OR=1.83, 95% CI=1.03 to 3.25) PP-N and PP-C group compared with OAT group had significantly higher remission rates (45% vs 39% vs 23%, $P < 0.001$). PP-N users in remission represented a 25% increase relative to 14% increase in OAT group
2. Aykut (2019), Turkey	Controlled Trial Patients at outpatient psychiatric clinics Jan to July 2014	Paliperidone Palmitate (PP), (n = 33), male (72.7%), mean age (36.9 years) Second-generation oral antipsychotic (n = 51), male (64.7%), mean age (37.2 years)	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression (CGI)	6 Months	PP compared with oral had no significant difference in PANSS scores (16 vs 16, P = 0.902) but had significant differences in CGI improvement (2 vs 1, P = 0.023)
3. Bai *et al.* (2007), Taiwan	RCT Between 2004 and 2005	Risperidone Long-Acting Injectable (RLAI), (n = 25), male (48.0%), mean age (44.7 years) Oral Risperidone, (n = 25), male (52.0%), mean age (48.1 years)	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression–Severity (CGI–S) Global Assessment of Functioning (GAF)	12 months	There were no differences between groups on the PANSS (RLAI = 2.32 ± 11.3 vs Oral= −0.52 ± 11.3, P = 0.058), CGI (RLAI = 0.04 ± 0.35 vs Oral = 0.04 ± 0.35, P = n/a), or GAF (RLAI= −16.4 ± 18.5 vs Oral= −9.2 ± 20.4, P = n/a)
4. Barnett *et al.* (2012), United States	Comparative Effectiveness RCT VA patients	LAI Risperidone, (n = 187), male (92.0%), White (46.5%), mean age (50.7 years) Standard Care (Oral Antipsychotic), (n = 182), male (91.2%), Black (47.8%), mean age (51.3 years)	Positive and Negative Syndrome Scale (PANSS)	24 months	LAI compared with oral did not have any significant difference in mean PANSS score (74.1 ± 0.91 vs 74.7 ± 0.92, P = 0.65)
5. Barrio *et al.* (2013), Spain	Case–control study Patients with schizophrenia from a psychiatry unit	Risperidone Long-Acting Injectable (RLAI), (n = 26),	Positive and Negative Syndrome Scale (PANSS)	24 months	RLAI compared with oral showed a significantly greater reduction in mean PANSS scores (47.7 ± 12.0 vs

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TABLE 2 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
	2004 to 2008	male (61.5%), White (84.6%), mean age (26.9 years) Oral Antipsychotics, (n = 26), male (57.7%), White (92.3%), mean age (27.4 years)	Negative and general psychopathology		66.2 ± 18.5, $P < 0.001$), negative (14.3 ± 6.1 vs 19.4 ± 6.4, $P = 005$) and general (23.4 ± 6.3 vs 32.7 ± 8.1, $P < 0.001$) psychopathology
6. Bellido *et al.* (2008), Spain	Prospective cohort	$N = 60$ Long-Acting Injectable (LAI; e.g., depot) (n = 35) Oral (n = 25)	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression– Severity (CGI)	12 months	LAI had lower PANSS total score compared with Oral ($P < 0.01$) LAI had lower CGI score compared with Oral ($P < 0.01$)
7. Bozzatello *et al.* (2019), Italy	Open label RCT	Long-Acting Paliperidone Palmitate Once Monthly (PP1M) (n = 36) Oral Paliperidone Extended Release (ER), (n = 36)	Severity of illness: Clinical Global Impression–Schizophrenia (CGI–SCH)	6 months	PP1M compared with oral had significant improvements in negative symptoms (CGI-S negative; PP1M = 2.91 ± 1.06 vs Paliperidone ER = 3.87 ± 1.48, $P = 0.012$) There was no significant difference between the two groups on the total CGI-S (PP1M = 4.18 ± 1.24 vs Paliperidone ER = 3.7 ± 1.32, $P = 0.136$)
8. Emsley *et al.* (2008), South Africa	Secondary data analysis	Risperidone Long-Acting Injection (RLAI), (n = 50), male (64.0%) mixed (White and Black; 78.0%), mean age (25.4 years) Oral antipsychotics (n = 47), male (57.4%) mixed (White and Black; 40%), mean age (25.9 years)	Clinical response: a 20% decrease in the PANSS total score	24 months	The RLAI group compared with the oral group had a greater proportion of those with a clinical response (84.0% vs 80.9%, $P = 0.790$), although non-significant There was a greater reduction on the PANSS total score (−39.7 ± 21.1 vs −25.7 ± 30.2, $P = 0.009$)
9. Foster *et al.* (2017), United States	Secondary analysis	Long-Acting Injectable (n = 20) Oral Antipsychotic medications (OA) (n = 206) Combination of two or more antipsychotics (CA) (n = 50)	Time to first relapse	30 months	No significant difference in the relapse rate among groups ($\chi^2 = 3.85$, $P = 0.146$) LAI group's mean time (594 days) to first relapse was not significantly different from the other groups (OA=562 days, CA=409 days, log-rank $\chi^2 = 6.81$, df. = 2, $P = 0.033$)
10. Joshi *et al.* (2018), United States	Prospective cohort study 46 CBHOs outpatient services	Long-Acting Injection Antipsychotics Therapy (LAI-APT), (n = 599 for schizophrenia), male (72.5%),	Structured Clinical Interview for Symptoms of Remission (SCI-SR)	12 months	LAI APT compared with oral APT had significantly higher remission (40.0% vs 23.6%), P = n/a

(*Continued*)

TABLE 2 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
		White (50.6%), mean age (41.1 years) Oral Antipsychotics Therapy (APT), (n = 281 for schizophrenia), male (65.8%), white (49.1%), mean age (42.1 years)			
11. Keks *et al.* (2007), Australia, Belgium, France, Germany, Greece, Luxembourg, Poland, Russia, Spain, Netherlands and UK	Prospective cohort 48 centers (Australia, Belgium, France, Germany, Greece, Luxembourg, Poland, Russia, Spain, Netherlands and UK)	Long-Acting Injectable Risperidone (n = 247), Male=56.0%, White=96.0%, mean age (35.1 years) Oral Olanzapine, (n = 300), Male=58.0%, White=97.0%, mean age (35.2 years)	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression–Severity (CGI–S)	12 months	Patients treated LAI Risperidone had significant improvements on the total PANSS score than in those treated with oral Olanzapine (91 vs 79%, $P < 0.001$) There were reductions in the overall severity CGI score in the LAI Risperidone and Olanzapine groups (-1.1 ± 1.2 and -1.3 ± 1.2, P = n/a)
12. Macfadden *et al.* (2010), United States, South America, and India	RCT Between 2006 and 2009	N = 355 Risperidone LAT, (n = 177), Male=59.3%, Cau casian = 24.3%, mean age (38.1 years) Oral Aripiprazole, Male = 61%, Cau casian = 18%, mean age (37.6 years)	Time to relapse (days) Time in remission (days) Positive and Negative Syndrome Scale (PANSS)	24 months	There was no significant difference between groups. The observed end points of time to relapse (45.8% in RLAT group and 43.6% in aripiprazole, $P = 0.684$), and time in remission (373.5 ± 282.6 days for the RLAT group and 356.7 ± 292.0 days for the Aripiprazole, $P = 0.646$) Non-significant between groups (RLAT= -11.0 ± 1.1 points vs aripiprazole= -10.9 ± 1.1 points; $P = 0.968$)
13. Malla *et al.* (2016), Canada	RCT 12 sites across Canada 2004 to 2006	Risperidone Long-Acting Injections (RLAI; n = 42), male (78.6%), White (81.0%), mean age (22.5 years) Oral Second-Generation Antipsychotics (Oral; n = 35), male (91.4%), White (74.3%), mean age (23.0 years)	Psychotic symptoms: Positive and Negative Syndrome Scale (PANSS) Global clinical severity: CGI-S	24 months	Although mean PANSS scores significantly decreased between baseline and endpoint in both RLAI (-18.1 ± 22.48, $P < 0.05$) and oral group (-17.7 ± 16.45, $P < 0.05$), these scores were not significant between groups CGI-scores were non-significant between groups at the endpoint (RLAI= -1.2 ± 0.82) and oral= -0.7 ± 0.77, P = n/a)
14. Petrić *et al.* (2019), Croatia	Retrospective Cohort Adolescent first episode schizophrenia	Long-Acting Paliperidone Palmitate (LAIPP) Antipsychotic (n = 18)	Positive and Negative Syndrome Scale (PANSS) Clinical Global Impression	12 months	LAIPP compared with oral had significantly greater reductions in PANSS

(*Continued*)

TABLE 2 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
	Medical records 2014 to 2017	Oral Antipsychotic Risperidone (n = 18)	Improvement and Severity (CGI-I and CGI-S)		scores (−43.9 vs −35.9, $P < 0.004$) and CGI (−3 vs −2.5, $P = 0.018$)
15. Remington and Khramov (2001), Canada	Retrospective cohort Schizophrenia and Continuing Care Program Between 1993 and 1995	Clozapine (n = 15) Risperidone (n = 15) Depot Conventional (n = 18) Oral Conventional (n = 18)	Clinical Global Impression scale (CGI)	18 months	There were significant differences between depot conventional and oral conventional, clozapine, or risperidone groups in CGI (3.7 vs 3.4 vs 4.1 vs 3.7, $P = 0.0001$)
16. Schreiner *et al*. (2014), Europe, Middle East, Africa	6-month retrospective and 12-month prospective Various treatment centers	Risperidone Long-Acting Treatment (RLAT), (n = 561) Oral Antipsychotics (OAP), (n = 522),	Clinical Global Impression of Schizophrenia (CGI-SCH) Global Assessment of Functioning (GAF)	12 months	RLAT compared with OAP had significantly better mean change of CGI-SCH scores (overall= −1.10 vs −0.80, positive= −1.16 vs −0.86, and negative= −0.98 vs −0.75, P = n/a) and GAF scores (13.5 ± 14.7 vs 8.8 ± 13.0; $P < 0.001$)
17. Stanković and Ille (2013), Serbia	Retrospective chart review Outpatient setting	Depot administration (n = 19), male (47.3%), mean age (44.4 years) Oral administration (n = 37), male (62.2%), mean age (34.9 years)	Positive and Negative Syndrome Scale (PANSS)	*N*/A	Depot compared with oral group had significantly lower mean scores on PANSS (70.0 vs 84.6, $P = 0.006$) and in all subscale scores for positive symptoms (12.4 vs 15.2, $P = 0.045$), negative symptoms (22.5 vs 27.1, $P = 0.016$), and general psychopathology (34.9 vs 42.2, $P = 0.007$).
18. Subotnik *et al*. (2015), United States	RCT University-based research clinic First episode schizophrenia	Long-Acting Injectable Risperidone (n = 43), male (78.0%), White (45.0%), mean age (21.9 years) Oral Risperidone (n = 43), male (79.0%), White (54.0%), mean age (21.1 years)	Brief Psychiatric Rating Scale (BPRS) Psychotic Symptom Control: proportion of the follow-up period during which BPRS hallucinations and unusual thought content rated less than 4 on the BPRS	12 months	BPRS scores were lower for the long-acting risperidone group (2/40, 5%) compared with the oral group (14/43, 33%), $P < 0.001$, RR=84.7% Long-acting injectable risperidone group had better controlled mean levels of hallucinations and delusions throughout follow-up ($\beta = -0.30$; $t = -2.6$; $P = 0.01$)

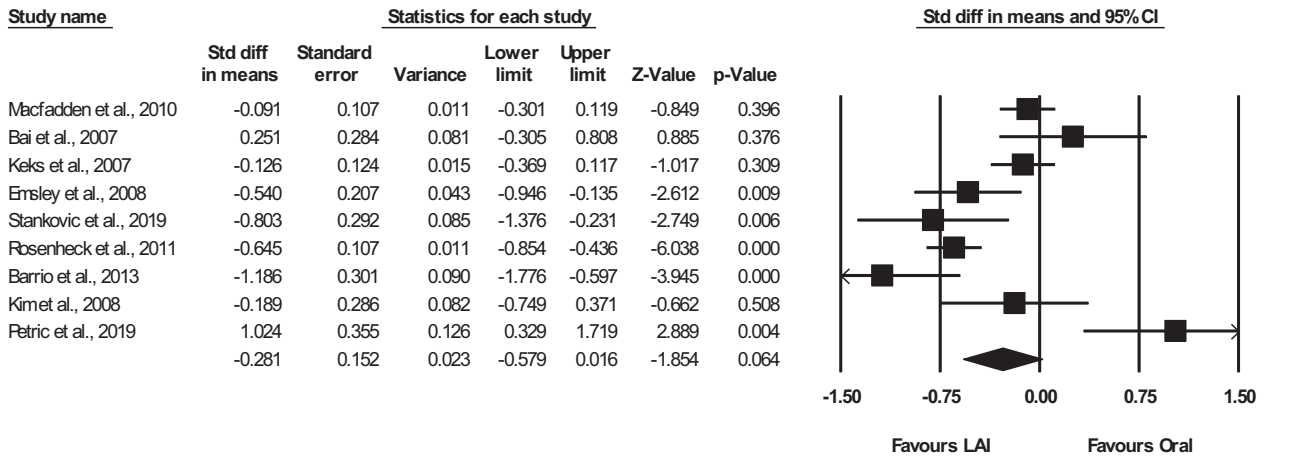

FIG. 3 Forest plot of studies assessing the differences between long-acting injectable (LAI) and oral antipsychotics using the Positive and Negative Syndrome Scale (PANSS).

2015; Detke *et al*. 2014; Fan *et al*. 2018; Lafeuille *et al*. 2013; Lefebvre *et al*. 2017; Offord *et al*. 2013; Schreiner *et al*. 2014; Subotnik *et al*. 2015; Xiao *et al*. 2016; Young-Xu *et al*. 2016) found that LAI use resulted in statistically significantly fewer days in the hospital compared with orals. However, 22 studies reported that LAI and oral users were no different in rehospitalization rates (Alphs *et al*. 2016; Ascher-Svanum *et al*. 2013; Barrio *et al*. 2013; Chan *et al*. 2015; Høiberg & Nielsen 2006; Huang *et al*. 2013; Joshi *et al*. 2018b; Lafeuille *et al*. 2018; Leatherman *et al*. 2014; Liu *et al*. 2015; Marchiaro *et al*. 2005; Moore *et al*. 1998; Pilon *et al*. 2017c; Remington & Khramov 2001; Rosenheck *et al*. 2011; San *et al*. 2013; Schreiner *et al*. 2014; Tavcar *et al*. 2000; Tiihonen *et al*. 2011; Varner *et al*. 2001) and length of hospital stay (Ascher-Svanum *et al*. 2013; Barnett *et al*. 2012; Chan *et al*. 2015; Remington & Khramov 2001). One study (Conley *et al*. 2003) reported that 1-year readmission risk among an oral group was statistically significantly lower than haloperidol decanoate, but not fluphenazine decanoate. Between the two decanoate groups, there were no differences. Thirteen pooled studies (Ascher-Svanum *et al*. 2013; Baser *et al*. 2015; Detke *et al*. 2014; Fan *et al*. 2018; Joshi *et al*. 2018c; Lafeuille *et al*. 2013; Manjelievskaia *et al*. 2018; Offord *et al*. 2013; Olivares *et al*. 2009; Pesa *et al*. 2017; Remington & Khramov 2001; Schreiner *et al*. 2014; Young-Xu *et al*. 2016) found no differences in mean number of rehospitalizations between LAI and oral users (n = 39139, 95%CI = −0.144 to 0.023, P = 0.158; τ^2 = 0.018, I^2 = 91.25%, Q = 137.251, df = 12, P < 0.001). The true effect in 95% of all comparable populations fell within the prediction interval −0.37 to 0.25 (see supplementary material), indicating that the observed effect is inconsistent among the included populations.

Outpatient/emergency department visits

Twenty-one studies (Baser *et al*. 2015; Chan *et al*. 2015; Fan *et al*. 2018; Joshi *et al*. 2018a, 2018b, 2018c; Lafeuille *et al*. 2013, 2015, 2018; Lefebvre *et al*. 2017; Lu *et al*. 2020; Manjelievskaia *et al*. 2018; Pesa *et al*. 2015, 2017; Pilon *et al*. 2017b, 2017c; Remington & Khramov 2001; Varner *et al*. 2001; Xiao *et al*. 2015, 2016; Young-Xu *et al*. 2016) examined changes in outpatient and ED visits (Table 4). Of 16 studies examining outpatient visits, six reported significantly lower (Baser *et al*. 2015; Joshi *et al*. 2018a; Manjelievskaia *et al*. 2018; Pesa *et al*. 2017; Pilon *et al*. 2017c; Young-Xu *et al*. 2016) and five reported higher (Joshi *et al*. 2018b; Lafeuille *et al*. 2018; Lefebvre *et al*. 2017; Remington & Khramov 2001; Xiao *et al*. 2015) visits among LAI compared with oral users. Of 17 studies examining ED visits, nine reported lower (Lafeuille *et al*. 2013, 2015; Lefebvre *et al*. 2017; Lu *et al*. 2020; Pesa *et al*. 2015, 2017; Xiao *et al*. 2015, 2016) and two higher (Chan *et al*. 2015; Fan *et al*. 2018) visits among LAI compared with oral users. But 12 studies found no difference in numbers of outpatient (Fan *et al*. 2018;

TABLE 3 *Characteristics of studies assessing readmission/rehospitalization*

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
1. Alphs *et al.* (2016), United States	RCT Patients with prior incarcerations	Paliperidone Palmitate (PP), (n = 93) Oral antipsychotics (OAs), (n = 88)	Number of institutionalizations Number of psychiatric hospitalizations	15 months	PP compared with OA had significantly lower number of institutionalizations (1.27 ± 0.132 vs 0.82 ± 0.095, P = 0.011) but not psychiatric hospitalizations (0.29 ± 0.075 vs 0.15 ± 0.037, P = 0.074)
2. Ascher-Svanum *et al.* (2013), United States	Post hoc analysis of RCT Multicenter from various settings	Olanzapine-LAI (n = 598), male (65.5%), mean age (38.8 years) Oral olanzapine (n = 322), male (64.9%), mean age (39.0 years) Sub-therapeutic olanzapine-LAI (n = 144), male (66.7%), mean age (39.5 years)	Hospitalization rate Number of hospitalizations Number of days hospitalized	6 months	No difference between Olanzapine-LAI and Oral Olanzapine in hospitalization rate (5.2% vs 4.0%, P = 0.436), average number of hospitalizations (0.1 ± 0.4 vs 0.1 ± 0.5, P = 0.438), and number of days hospitalized (1.5 ± 12.26 vs 2.3 ± 17.2, P = 0.463)
3. Barnett *et al.* (2012), United States	Comparative effectiveness RCT VA patients	LAI Risperidone, (n = 187), male (92.0%), White (46.5%), mean age (50.7 years) Standard care (oral antipsychotic), (n = 182), male (92.2%), Black (47.8%), mean age (51.3 years)	Acute medical/surgical hospital stays (mean total days) Acute psychiatric hospital stays (mean days)	24 months	LAI compared with oral did not have any significant difference in total acute medical/surgical stays (0.2 ± 0.05 vs 0.2 ± 0.08, P = 0.764) or psychiatric hospital stays (2.8 ± 0.6 vs 3.2 ± 0.9, P = 0.730)
4. Barrio *et al.* (2013), Spain	Case–control study Patients with schizophrenia from a psychiatry unit 2004 to 2008	Risperidone Long-Acting Injectable (RLAI), (n = 26), male (61.5%), White (84.6%), mean age (26.9 years) Oral Antipsychotics, (n = 26), male (57.7%), White (92.3%), mean age (27.4 years)	Number of hospital admissions	24 months	No significant difference in readmission between the RLAI and OA group (19.2% vs 42.3%, P = 0.136)
5. Baser *et al.* 2015, United States	Retrospective cohort VA Medical records July 2007 to May 2012	Paliperidone Palmitate Long-Acting Injection (PP), (n = 381), male (92%), mean age (50.2 years) Oral Atypical Antipsychotics (OAT), (n = 3537), male (92%), mean age (52.2 years)	Any hospitalization Number of hospitalizations Number of inpatient days per patient	12 months	PP compared with OAT had significantly lower hospitalizations (34% vs 53%, P < 0.001), number of hospitalizations (0.81 vs 1.30, P < 0.001), and number of inpatient days (13.24 vs 24.18, P = 0.002)
6. Bellido (2008), Spain	Prospective cohort	N = 60 Long-Acting Injection (LAI), (e.g., depot) = 35 (58.3%) Oral = 25 (41.7%)	Rehospitalization	12 months	LAI had lower proportion of those re-hospitalized compared with Oral (4.0% vs 48.6%, P = n/a)
7. Chan *et al.* (2015), Taiwan	Retrospective cohort Regional hospital with outpatient department or psychiatric wards	Long-Acting Injection Risperidone (RLAI), (n = 43), male (n = 23), mean age (33.8 years)	Rehospitalization rate Lengths of hospital stay	12 months	All three groups were similar in rehospitalization rates (all oral anti-psychotic=28.9%, oral risperidone=30.1%, RLAI=30.2%, P > 0.999)

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TABLE 3 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
		All oral antipsychotic (n = 336), male (n = 178), mean age (39.4 years) Oral risperidone (n = 103), male (n = 58), mean age (39.0 years)			There was no significant difference in average hospital length of stay (in days) between RLAI, all-oral antipsychotic, and oral risperidone groups (34.5 vs 28.7 vs 31.8%, P = 0.621)
8. Conley *et al.* (2003), United States	Prospective cohort Inpatient records from 6 public psychiatric hospitals in Maryland 1997	Second-generation antipsychotics (SGAs): Clozapine (n = 41), male (61.0%), White (64.0%), mean age (36.9 years) Risperidone (n = 149), male (63.0%), White (67.0%), mean age (38 years) Olanzapine (n = 103), male (58.0%), White (74.0%), mean age (39.7 years) Depot group: Fluphenazine decanoate (n = 59), male (72.0%), White (44.0%), mean age (39.9 years) Haloperidol decanoate (n = 59), male (68.0%), White (36.0%), mean age (35.1 years)	Rehospitalization in any public hospital for a psychiatric condition	Between January 1, 1997 and December 31, 1997	One-year readmission risks were 10%, 95% CI=1 to 19 for clozapine, 12%, 95% CI=7 to 18 for risperidone, 13%, 95% CI=6 to 20 for olanzapine, 21%, 95% CI=10 to 31 for Fluphenazine decanoate, and 35%, 95% CI=22 to 47 These risks were not significantly lower than the readmission risk for fluphenazine decanoate (21%, P value not reported) but were significantly lower than haloperidol decanoate (35%, $P < 0.05$) for all three SGAs
9. Detke *et al.* (2014), United States	RCT	Olanzapine long-acting injection (LAI), (n = 264), male (66.3%), White (61.0%), mean age (41.7 years) Oral olanzapine, (n = 260), male (68.1%), White (63.1%), mean age (40.1 years)	Hospitalization rate Mean duration of hospitalization days Mean number of hospitalizations days	24 months	Olanzapine LAI group compared with the oral group did not have significantly fewer hospitalization because of psychiatric reasons (7.6%, 95%CI=4.7 to 11.5 vs 9.2%, 95%CI=6.0 to 13.4) However, mean duration of hospitalization was lower for Olanzapine LAI compared with oral (6 vs 20, P = 0.02) LAI had significant lower mean number of hospitalization day (0.43 ± 2.0 compared with oral group (1.80 ± 9.3), P = 0.020
10. Devito *et al.* (1978), United States	Quasi-experimental design	Fluphenazine Decanoate, (n = 61), male (n = 31), White (n = 60) Oral Antipsychotics (comparison group), (n = 61), male (n = 23), White (n = 60)	Readmissions	12 months	Fluphenazine decanoate had significantly fewer readmissions (n = 25) during the one-year study period compared with the oral antipsychotics group (n = 34), P = n/a.
11. Fan *et al.* (2018), Taiwan	Retrospective matched cohort	Long-Acting Injectable (LAI) Risperidone (n = 691), male	Hospital admissions Length of stay	12 months	LAI compared with oral had significantly more hospital admissions (2.67 ± 2.23 vs 2.41 ± 2.59, $P < 0.01$) and shorter lengths of stay

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TABLE 3 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
	National Health Research Institute Database- Psychiatric Inpatient Medical Claim Dataset	(45.88%), age: 16–30 (36.90%), and 31–45 (37.05%) Oral Risperidone (n = 1382), male (45.88%), age: 16–30 (37.12%), and 31–45 (37.05%)			(179.83 ± 110.08 days vs 214.4 ± 117.46 days, $P < 0.01$).
12. Grimaldi-Bensouda *et al.* (2012), France	Retrospective cohort Patients from 15 regions in France from psychiatric centers	Risperidone Long-Acting Injectable (RLAI; n = 489), male (67.3%), mean age (36.7 years) Non-R-LAI group (n = 1370), male (69%), mean age (38.6 years)	Full-time hospital stays in a psychiatric ward or for psychiatric reasons	12 months	R-LAI compared with Non-R-LAI were 34% significantly less likely to be hospitalized (R-LAI: adjusted rate ratio=0.66, 95% CI=0.46 to 0.96, vs non- R-LAI; adjusted rate ratio=0.66, 95% CI=0.32 to 0.0.88).
13. Haro *et al.* (2007), 10 European Countries	Prospective cohort Schizophrenia Outpatient Health Outcomes study data	N = 7728 Long-Acting Injectable (LAI) Typicals (n = 348) Oral Typicals (n = 471) Olanzapine (n = 4247) Risperidone (n = 1549) Quetiapine (n = 583) Amisulpride (n = 256) Clozapine (n = 274)	Rehospitalization	36 months	Between LAI (depot) typicals and other groups, depot typicals (9.9%, HR=0.89, 95% CI=0.57 to 1.38) had a lower proportion of discontinuation rates for lack of compliance than oral typicals (12.8%, HR=2.15. 95% CI=1.54 to 3.01, $P < 0.01$), Risperidone (12.4%, HR=2.15. 95% CI=1.54 to 3.01, $P < 0.05$), Quetiapine (17.8%, HR=2.15. 95%CI=1.54 to 3.01, $P < 0.001$), and Amisulpride (15.6%, HR=2.15. 95%CI=1.54 to 3.01, $P < 0.05$), but not Olanzapine (9.0%, HR=1) and clozapine (8.9%, HR=0.92, 95%CI=0.58 to 1.46, P value not reported). This discontinuation rate was not significantly lower than olanzapine Between LAI (depot) typicals and other groups, depot typicals (RR = 1.44, 95% CI=1.10 to 1.88, $P < 0.01$) had significantly higher rehospitalization because of exacerbation of schizophrenia as compared with oral typicals (RR=1.39, 95% CI=1.08 to 1.79, $P < 0.01$)
14. Høiberg and Nielsen (2006), Norway	Retrospective cohort Between 1999 and 2000 Patients from a University Hospital	N = 123 Typical oral antipsychotic (n = 17) Typical depot antipsychotic (n = 47) Atypical oral antipsychotic (n = 59	Rehospitalization	12 months	Compared with those receiving typical depot antipsychotic, there were no differences in days to rehospitalization for those receiving typical oral or atypical antipsychotics (56 days vs 20 days vs 66 days, P = 0.148)
15. Huang *et al.* (2013), Taiwan	Retrospective cohort Taiwan National Health Research Institutes data	Long-Acting Injectable (LAI) antipsychotics (risperidone, haloperidol, or flupenthixol), (n = 726) Oral antipsychotics (risperidone, a different second-generation antipsychotic, or first-generation antipsychotic), (n = 6943)	Rehospitalization rates	12 months	There was no difference between patients treated with LAI and oral antipsychotics in reducing rehospitalization rates (27.3% vs 27.3%, P = n/a)

(*Continued*)

TABLE 3 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
16. Joshi *et al.* (2018), United States	Prospective cohort 46 CBHOs outpatient services	Long-Acting Injection Antipsychotics Therapy (LAI-APT), (n = 599 for schizophrenia), male (72.5%), White (50.6%), mean age (41.1 years) Oral Antipsychotics Therapy (APT), (n = 281 for schizophrenia), male (65.8%), White (49.1%), mean age (42.1 years)	Hospitalizations	12 months	LAI APT compared with oral had no significant difference in hospitalizations (13.4% vs 17.0%), P = n/a
17. Joshi *et al.* (2018), United States	Retrospective cohort Medicare Advantage Claims Data	Long-Acting Injectable Paliperidone Palmitate (PP), (n = 295), male (50.8%), White (65.8%), mean age (48.7 years) Oral Atypical Antipsychotics (OAA), (n = 2296), male (45.5%), White (72.3%), mean age (55.9 years)	Hospitalizations	12 months	Significant difference between PP and OAA groups in mean number of hospitalizations (0.62 ± 2.1 vs 0.85 ± 1.3, P = 0.002) PP group had lower odds of hospitalization compared with oral antipsychotics group (OR = 0.81, 95%CI=0.68-0.96)
18. Ju *et al.* (2014), Taiwan	Retrospective cohort Psychiatric Inpatient Medical Claims Data Between 2004 and 2009	Long-Acting Injection (LAI), n = 810 Oral Antipsychotic Medications, n = 945	Rehospitalization risk	12 months	Patients treated with LAIs were at a significantly lower risk for psychiatric rehospitalization than those treated with oral antipsychotics (28.2% vs 32.9%; OR=0.80, 95%CI=0.65-0.98, P = n/a)
19. Lafeuille *et al.* (2015), United States	Retrospective cohort Premier Perspective Comparative Hospital Database	Paliperidone Palmitate Cohort (n = 374), male (67.9%), White (47.6%), mean age (41.1 years) Oral Antipsychotic Cohort (n = 45 251), male (61.5%), White (45.1%), mean age (45.6 years)	All-cause rehospitalization	12 months	Paliperidone palmitate cohort compared with oral antipsychotic significantly less likely to be hospitalized (HR, 0.64; P < 0.0001)
20. Lafeuille *et al.* (2013), United States	Retrospective cohort Premier Hospital Database 2006 to 2010	Atypical Long-Acting treatment (LAT), (N = 1032), male (56.4%), White (46.8%), mean age (42.1 years) Oral Antipsychotic (Oral-AP), (N = 2796), male (55.4%), White (46.6%), mean age (42.4 years)	Number of rehospitalizations Frequency of rehospitalizations (all cause, mental disorder related, schizophrenia related) Mean days in hospital after rehospitalization	30 months	Atypical LAT patients compared with oral AP patients had significantly lower mean rehospitalizations related to all-cause (1.25 ± 2.09 vs 1.61 ± 2.82, P < 0.0001), mental-disorder-related (1.24 ± 2.08 vs 1.59 ± 2.79, P < 0.0001), schizophrenia related (1.15 ± 2.00 vs 1.41 ± 2.54, P < 0.0005) Atypical LAT patients compared with oral AP patients had significantly lower mean frequency of rehospitalizations related to all-cause (within 1-month=0.15 ± 0.41 vs 0.20 ± 0.49, P = 0.0286, 3-month = 0.30 ± 0.62 vs 0.38 ± 0.76, P = 0.0288, 6 months = 0.48 ± 0.84 vs 0.58 ± 1.05, P = 0.0029)

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TABLE 3 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
					Atypical LAT patients compared with oral AP patients had significantly lower mean frequency of mental disorder–related rehospitalizations (within 1-month=0.15 ± 0.41 vs 0.20 ± 0.49, $P = 0.0360$, 3-month=0.30 ± 0.62 vs 0.37 ± 0.76, $P = 0.0333$, 6 months=0.48 ± 0.84 vs 0.58 ± 1.05, $P = 0.0032$) Atypical LAT patients compared with Oral AP patients had significantly lower mean number of days in hospital after rehospitalization related to all-cause (13.46 ± 27.48 vs 15.69 ± 30.49, $P = 0.008$) and mental-disorder-related (13.44 ± 27.46 vs 15.62 ± 30.41, $P = 0.009$), but not schizophrenia related (12.79 ± 27.07 vs 14.28 ± 29.14, $P = 0.089$)
21. Lafeuille *et al.* (2018), United States	Retrospective cohort Medicaid databases from 6 states (Iowa, Kansas, Mississippi, Missouri, New Jersey, Wisconsin) July 2009 to 2015	Paliperidone Palmitate Once Monthly (PP1M), (n = 371), mean age (45.0 years) Oral Atypical Antipsychotics (n = 8296), mean age (47.5 years)	All-cause and schizophrenia-related inpatient admissions	12 months	PP1M compared with OAA had no difference in rates of all cause (IRR=0.89, 95%CI=0.72 to 1.08, $P = 0.156$) and schizophrenia related (IRR=1.07, 95%CI=0.83 to 1.34, $P = 0.658$) inpatient visits
22. Leatherman *et al.* (2014), United States	RCT VA patients	Long-Acting Injectable (LAI) Risperidone, (n = 187), male (91.98%), White (46.52%), age ≥ 53 (53.4%) Oral (n = 182), male (90.66%), White (43.41%), age ≥ 53 (54.95%)	Time to hospitalization	24 months	There was a significant difference between groups on the mean of HCQT who were hospitalized at randomization (2.72 vs 2.58, $P = 0.05$
23. Lefebvre *et al.* (2017), United States	Retrospective cohort The VHA's Corporate Data Warehouse January 2010 to June 2015	Paliperidone Palmitate (PP), (n = 1684), male (93.3%), mean age (49.0 years) Oral Antipsychotic (OAA), (n = 5188), male (93.5%), mean age (52.4 years)	Proportion of patients with inpatient hospitalization Mean time to first admission in days Median number of hospitalizations Mean days in inpatient setting Number of days in mental health setting	18 months	PP compared with OAA had significantly lower proportion of patients with inpatient hospitalization (66.6% vs 74.3%, $P < 0.001$), longer time to first hospitalization (107.3 ± 131.8 days vs 86.1 ± 78.4 days, $P < 0.001$), fewer hospitalizations (1.6 ± 3.9 vs 2.0 ± 2.4, $P < 0.001$), fewer days in inpatient setting (25.8 ± 67.6 vs 34.8 ± 48.0, $P < 0.001$), and mental health setting (24.0 ± 64.4 vs 31.1 ± 44.7, $P < 0.001$)

(*Continued*)

TABLE 3 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
24. Levitan *et al.* (2016), United States	Post-hoc Assessment of two RCTs Multicenter from various settings	Paliperidone ER (n = 104), mean age (27.1 years) Placebo (n = 101) Paliperidone Palmitate Once Month (PP1M), (n = 193), mean age (26.3 years) Placebo (n = 192)	Proportion of patients with psychiatric hospitalization after intervention started	10 months	There were significantly fewer psychiatric hospitalizations in the PP1M group compared with the Paliperidone group (risk difference= −53, 95% CI= −98 to −7, P = n/a)
25. Lin *et al.* (2020), Taiwan	Retrospective cohort Geriatric inpatients (>60 years old)	Long-Acting Injectable Antipsychotics (LAIs), (n = 151), male, (50.3%), mean age (65.2 years) Oral Antipsychotics (OAPs), (n = 1017), male (58.4%), mean age (66.0 years)	Rehospitalizations within 1 year of discharge	12 months	LAIs group had a significantly lower rehospitalization rate (53.6% vs 66.1%, x^2 = 8.87, df=1, P = 0.003)
26. Liu *et al.* (2015), Taiwan	Retrospective cohort Psychiatric acute ward of university medical center 2004 to 2008	Long-Acting Injectable Antipsychotic (LAIA), (n = 47), male (40.0%), mean age (37.8 years) Oral Antipsychotics, (n = 45), male (51.0%), mean age (37.4 years)	Rehospitalization rates	36 months	LAIA compared with Oral antipsychotics group had no significant differences in hospitalization in year 1 (17.8% vs 26.1%), in year 2 (34% vs 28.7%), and year 3 (42.6% vs 39.7%) The overall odds of rehospitalization, comparing the LAIA to the oral medication group during the 3-year follow-up period, were not significantly different (1.085 ± 0.373, 95%CI=0.553 to 2.13, P = 0.813)
27. Manjelievskaia *et al.* (2018), United States	Retrospective cohort IBM Watson Health MarketScan Medicaid Multi-State Database January 2010 to December 2014	Paliperidone Palmitate Once Monthly (PP1M), (n = 7672), male (48.8%), Black (52.4%), mean age (40.3 years) Oral Atypical Antipsychotics (OAA), (n = 7926), male (48.9%), Black (52.4%), mean age (40.0 years)	Proportion of patients with hospital admission Number of admissions per patient Average length of stay per admission	12 months	PP1M patients compared with OAA had significantly lower admissions (25.6% vs 33.9%, P < 0.001) and greater average length of stay per admission (7.3 vs 6.8, P = 0.030). However, there was no significant difference in number of admissions per patient (0.5 vs 0.8, P = 0.109)
28. Marcus *et al.* (2015), United States	Retrospective cohort Administrative claims data from Truven Health Analytics MarketScan Multi-State Medicaid claims database July 1, 2010 and December 31, 2012	Long-Acting Injectable (LAI), (n = 340), male (60.9%), African American (55.0%), mean age (37.5 years) FGA LAIs (n = 157), male (58.0%), African American (65.0%), mean age (38.7 years) SGA LAIs (n = 183), male (63.4%), African American (46.4%), mean age (36.5 years) Orals (n = 3428), female (51.2), African American (48.2), age (38)	Rehospitalization: Schizophrenia-related rehospitalization in the 6 months after discharge	6 months	LAI compared with orals had significantly lower schizophrenia-related hospitalizations (19.1 vs 25.3) and lower odds of hospitalizations (adjusted OR=0.73, 95%CI = 0.54 to 0.99, P = 0.041)

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TABLE 3 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
29. Marchiaro *et al.* (2005), Italy	Retrospective cohort Outpatients July 2004 to September 2004	$N = 60$ Long-Acting Injectable (LAI), (Depot) Neuroleptics ($n = 30$), male (60.0%), mean age (40.7 years) Second-Generation Antipsychotics ($n = 30$) male (53.3%), mean age (39.4 years)	Readmission Rates	24 months	There was no difference between groups on the readmission rate (oral group=30%, depot = 37%, $P = 0.784$)
30. Moore *et al.* (1998), United States	Prospective cohort Spring Grove Hospital Center Between March 1994 and December 1995	Haloperidol Decanoate ($n = 14$) Fluphenazine Decanoate ($n = 29$) Risperidone ($n = 75$)	Rehospitalization rates	12 months	Risperidone was associated with lower rehospitalization rates as compared with fluphenazine decanoate and haloperidol decanoate (17.0% vs 21.0% vs 36.0%, P = n/a)
31. Olivares *et al.* (2009), Spain	Prospective cohort Multisite various settings	Risperidone Long-Acting Injection (RLAI), ($n = 1345$), male (63.3%), mean age (38.4 years) Oral Antipsychotic (AP) ($n = 277$), male (63.2%), mean age (37.0 years)	Hospital stays (number/patient) Duration (days/patient) Percent hospitalized	24 months	RLAI group compared with oral group had a significantly greater intensity of hospitalization in terms of the percent of patients hospitalized (35.1% vs 27.1%, $P = 0.025$) and number of hospital stays (0.49 vs 0.32 per patient, $P = 0.019$) but not for the mean duration of stay (21.21 vs 15.27 days, $P = 0.357$)
32. Offord *et al.* (2013), United States	Retrospective cohort Between January 2005 and 2010 Health care claims database from 100 companies	Commercial population LAI ($N = 394$) Oral ($N = 2610$) Medicare population LAI ($N = 147$) Oral ($N = 518$)	Mean Number of Hospitalizations Length of Stay (LOS)	12 months	Compared with those treated with oral antipsychotics, patients treated with LAI had greater reductions in hospitalizations for any cause (- 0.90 ± 1.77 vs 0.02 ± 1.49, $P < 0.001$) and associated LOS (−10.29 ± 23.23 vs 0.70 ± 16.73, $P < 0.001$) between the baseline and follow-up periods Compared with those treated with oral antipsychotics, the number of relapses because of schizophrenia requiring inpatient care (−0.60 ± 1.37 vs 0.05 ± 0.99, $P < 0.001$) and LOS (- 7.46 ± 20.68 vs 0.60 ± 12.49, $P < 0.001$) were significantly reduced between the baseline and follow-up periods for patients treated with LAI
33. Pesa *et al.* (2017), United States	Retrospective cohort California Medicaid Patients Database 2009 to 2013	Paliperidone Palmitate Once Monthly (PP1M), ($n = 722$) Oral Antipsychotic Therapy (OAT), ($n = 722$)	Any inpatient visit Hospitalization days	12 months	PP1M compared with OAT had significantly lower inpatient visits (61.6% vs 77.4%, $P < 0.001$) and hospitalization days (15.0 vs 27.7, $P < 0.001$)

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TABLE 3 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
34. Pesa *et al.* (2015), United States	Retrospective Cohort MarketScan Medicaid Multi-State Database (Truven Health Analytics, Ann Arbor, MI, USA) 2009 to 2011	Paliperidone Palmitate (PP), (n = 984), male (58.2%), Black (51.9%), mean age (38.8 years) Oral Antipsychotic Therapy (OAT), (n = 4199), male (48.8%), Black (47.3%), mean age (41.6 years)	Inpatient hospital admission Mental health related	12 months	PP compared with OAT had significantly lower risks for any inpatient hospital admission (by 36%, 95%CI=40 to 30, $P < 0.0001$) and mental health inpatient admission (by 38%, 95%CI=43 to 32, $P < 0.0001$)
35. Petrić *et al.* (2019), Croatia	Retrospective cohort Adolescent first episode schizophrenia Medical records 2014 to 2017	Long Acting Paliperidone Palmitate Antipsychotic (LAIPP), (n = 18), male (55.6%), mean age (16.7 years) Oral antipsychotic Risperidone (n = 18), male (50%), mean age (16.2 years)	Hospitalizations	12 months	PP compared with oral risperidone group had significantly lower hospitalizations (11.1% vs 50.0%, P = 0.027)
36. Pilon *et al.* (2017), United States	Retrospective cohort Medicaid data from 6 states 2010 to 2015	Second-Generation Long-Acting Injectable Therapies (SGA-LAIs), (n = 3307), male (59.5%), mean age (41.8 years) Oral Atypical Antipsychotics (OAAs), (n = 21 355), male (50.0%), mean age (44.2 years)	Inpatient visits Mental health institute admission	12 months	SGA-LAI compared with OAA had no significant difference in inpatient visits (Adjusted IRR=1.05, 95%CI=0.95 to 1.16, P = 0.377) However, SGA-LAI compared with OAA had significantly higher mental health institute admission (Adjusted IRR=1.16, 95%CI=1.10 to 1.23, $P < 0.001$)
37. Remington and Khramov (2001), Canada	Retrospective cohort Schizophrenia and Continuing Care Program Between 1993 and 1995,	Clozapine (N = 15) Risperidone (N = 15) Depot Conventional (N = 18) Oral Conventional (N = 18)	Number of hospitalizations Rehospitalization	18 months	There was no significant difference between depot conventional and oral conventional, clozapine, or risperidone groups in the mean number of hospitalizations (1.1 vs 0.7 vs 0.9 vs 0.9, P = n/a), days in the hospital at rehospitalization (20.8 vs 31.8 vs 35.1 vs 28.6, P = n/a), or mean number of ED visits (2.1 vs 1.6 vs 1.5 vs 1.4, P = n/a)
38. Rosenheck *et al.* (2011), United States	RCT	Oral Antipsychotic (n = 183) Injectable Risperidone (n = 187),	Total days of psychiatric hospitalization Proportion of patients with psychiatric hospitalization	24 months	Injectable Risperidone compared with oral antipsychotic had no significant differences in total days of psychiatric hospitalization (19.2 ± 59.7 vs 20.3 ± 43.4, P = 0.80) or proportion of patients hospitalized (64.7 vs 62.1, P = 0.60)
39. San *et al.* (2013), Spain	Retrospective and prospective cohort Spanish National Health Care System	N = 1646 Long-Acting Injectable (LAI), (n = 827) Oral Atypical route (n = 645) Depot Typical injection (n = 120) Oral Typical route (n = 51)	Relapse/readmission at 6 and 12 months	12 months	The mean time until the first relapse at follow-up was 10.2 ± 0.2 months for patients treated with LAI, 10.3 ± 0.6 for oral typical antipsychotics, 10.1 ± 0.2 for oral atypical antipsychotics, and 8.9 ± 0.4 for oral typical antipsychotics. No difference observed between groups, log-rank test 2.49, P = 0.476

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Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
40. Schreiner *et al.* (2014), Europe, Middle East, Africa	Six-month retrospective and 12-month prospective Various treatment centers	Risperidone long-acting treatment (RLAT), (n = 561), Oral antipsychotics (OAP), (n = 522)	Mean number of hospitalizations Duration of hospitalizations	12 months	RLAT compared with OAP had no difference in hospitalization rate (0.5 ± 7.8 vs 0.3 ± 2.1, P = n/a) but had significantly lower durations of days per hospitalizations prospectively (8.2 ± 21.6 vs 16.2 ± 38.6, P = 0.002)
41. Subotnik *et al.* (2015), United States	RCT University-based research clinic First episode schizophrenia	Long-Acting Injectable Risperidone (n = 43), male (78%), White (45%), mean age (21.9 years) Oral Risperidone (n = 43), male (79%), White (54%), mean age (21.1 years)	Psychiatric hospitalizations Hospital days	12 months	Long-Acting Risperidone group had lower psychiatric hospitalizations compared with oral group (5.0% vs 18.6%) and fewer mean hospital days (0.5 vs 1.8, P = 0.07)
42. Taipale *et al.* (2018), Finland	Retrospective cohort Inpatient hospital care from 1974 to 2014 First episode schizophrenia	Prevalent Cohort (n = 62250), male (50.2%), median age (45.6 years) Incident Cohort (n = 8719, male (56.2%), median age (36.2 years)	Psychiatric rehospitalization All-cause hospitalization	Up to 240 months	LAI use compared with oral medications use resulted in significantly lower risk for psychiatric rehospitalization (first generation LAIs=0.46, 95% CI=0.40 to 0.54: second generation LAIs=0.45, 95%CI=0.39 to 0.52) vs (first-generation orals HR = 0.67, 95% CI=0.60 to 0.74; second-generation orals HR=0.57, 95%CI=0.53 to 0.61), P = n/a LAI use compared with oral medications use resulted in significantly lower risk for all-cause hospitalization (first generation LAIs HR = 0.58, 95%CI = 0.51–0.66; second generation LAIs HR = 0.56, 95%CI = 0.50 to 0.63) vs (first generation orals HR = 0.80, 95% CI = 0.74 to 0.87; second generation orals HR = 0.69, 95%CI = 0.66 to 0.73), P = n/a
43. Tavcar *et al.* (2000), Slovenia	Prospective study Slovenian Registry of psychiatric inpatients	N= (447) Oral, N = 82, male (50.0%), mean age (40.1 years) Depot, N = 332, male (45.3%), mean age (36.6 years) Atypical, N = 43, male (34.9%), mean age (40.6 years)	Rehospitalization rates	NA	There were no differences between depot (5.7, 5.6%) and oral (6.5, 7.1%) or atypical (6.9, 5.3%) groups on rehospitalization rates number P = n/a
44. Tiihonen *et al.* (2011), Finland	Prospective cohort National Hospital Discharge Register Between 2000 and 2007	N = 2588	First rehospitalization	24 months	Depot antipsychotics were not associated with risk of rehospitalization as compared with oral antipsychotics (HR=0.36, 95%CI=0.17 to 0.75, P = 0.007)
	Retrospective cohort		Readmissions	36 months	PP compared with Oral Clozapine had significantly lower readmission rates (16.7% vs

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TABLE 3 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
45. Tomko *et al.* (2016), United States	Patients with concurrent tobacco use 2012 to 2015	Paliperidone Palmitate (PP), (n = 108), male (n = 68), mean age (41.9 years) Oral Clozapine, (n = 18), male (n = 13), mean age (48.1 years)	Time until readmission (in months)		50.0%, P = 0.004) but no difference in time to readmission (6.14months vs 5.85 months, P = 0.425)
46. Valevski *et al.* (2012), Israel	Retrospective cohort Geha Mental Health Center affiliated Between 1991 and 2005	Long-Acting First-Generation Antipsychotic (FGA-LAI), (N = 293) Clozapine (N = 74)	Readmission Rate	12 months	Patients treated with clozapine had significant lower readmission rate compared with Long-acting FGA medications (HR = 1.646, 95% CI = 1.039 2.610, P = 0.034)
47. Varner *et al.* (2001), United States	Retrospective cohort Harris County Psychiatric Hospital, Houston	N = 153 Depot haloperidol (n = 95) Oral haloperidol (n = 58)	Rehospitalization	96 months	No difference between groups in subsequent rehospitalization (oral = 3.0 ± 2.7 vs depot=4.3 ± 4.6)
48. Xiao *et al.* (2015), United States	Retrospective study Medicaid beneficiaries (New Jersey, Iowa, Missouri, and Kansas) between 2009 and 2012	Paliperidone Palmitate (PP), (n = 952), male (63.1%), White (46.7%), mean age (40.3 years) Oral Atypical Antipsychotics (OAAs), (n = 12 174), male (57.6%), White (58.3%), mean age (45.3 years)	Inpatient visits	36 months	Patients treated with PP had fewer inpatient visits (RR: 0.91, 95% CI = 0.90 to 0.92, P < 0.0001) compared with those treated with OAAs
49. Xiao *et al.* (2016), United States	Retrospective cohort Medicaid data from 6 states (Florida, Iowa, Kansas, Missouri, Montana, New Jersey) 2009-2013	Paliperidone Palmitate (PP), (n = 876), male (54.7%), White (53.2%), mean age (40.8 years) Oral Atypical Antipsychotics (OAAs), (n = 10 778), male (45.2%), White (57.6%), mean age (43.2 years)	Hospitalizations Hospitalization days	12 months	PP compared with OAA had significantly lower risk for hospitalization (IRR=0.96, 95% CI = 0.94 to 0.99, P = 0.004) and hospitalization days (IRR=0.85, 95% CI = 0.84 to 0.86, P < 0.001)
50. Young-Xu *et al.* (2016), United States	Retrospective Cohort VHA Corporate Data Warehouse Between January 2010 and October 2014	Paliperidone Palmitate (PP), (n = 2285) Oral Atypical Antipsychotics (OAAs), (n = 8005)	Number of patients with inpatient stays (%) Time to first hospital admission (days) Number of stays per patient Number of days in inpatient setting Number of mental health stays per patient Number of days in mental health setting	18 months	PP compared with OAA had significantly lower proportion of patients with inpatient stays (83.3% vs 89.1%, P < 0.001), greater time to first hospital admission (116.2 ± 149.0 vs 90.6 ± 78.9, P < 0.001), lower stays per patient (2.3 ± 5.4 vs 2.6 ± 3.0, P < 0.001) and days in inpatient setting (43.7 ± 104.0 vs 53.4 ± 65.2, P < 0.001), lower number of mental health stays per patient (1.8 ± 4.2 vs 2.0 ± 2.1, P < 0.001) and days in mental health setting (35.9 ± 90.3 vs 40.6 ± 51.9, P < 0.001)

TABLE 4 *Characteristics of studies assessing outpatient and/or emergency department visits*

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
1. Baser *et al.* (2015), United States	Retrospective cohort VA Medical records July 2007 to May 2012	Paliperidone Palmitate Long-Acting Injection (PP), (n = 381), male (92.0%), mean age (50.2 years) Oral Atypical Antipsychotics (OAT), (n = 3537), male (92.0%), mean age (52.2 years)	Outpatient visits Number of outpatient visits per patient Any ED visits	12 months	Compared with OAT, PP had significantly lower outpatient visits (335 vs 327, P = 0.004) but not outpatient visits per patient (46.68 vs 42.71, P = 0.189) No significantly different in number of ER visits (7% vs 10%, P = 0.163)
2. Chan *et al.* (2015), Taiwan	Retrospective cohort Regional hospital with outpatient department or psychiatric wards	All oral antipsychotic (N = 336), male (53%), mean age (39.4 years) Long-Acting Injection Risperidone (RLAI) (N = 43), male (53.5%), mean age (33.8 years) Oral Risperidone (N = 103), male (46.6%), mean age (39.0 years)	ED visits	12 months	RLAI compared with all-oral antipsychotic and oral risperidone had a significantly higher rate of ED visits (23.3% vs 12.8% vs 8.7%, P < 0.029)
3. Fan *et al.* (2018), Taiwan	Retrospective-matched cohort National Health Research Institute Database-Psychiatric Inpatient Medical Claim Dataset	Long-Acting Injectable (LAI) Risperidone (n = 691), male (45.88%), age; 16–30 (36.9%) and 31–45 (37.05%) Oral Risperidone (n = 1382), male (45.88%), age; 16–30 (37.12%), and 31–45 (37.05%)	Outpatient visits ED visits	12 months	LAI compared with oral group had no differences in mean number of outpatient visits (68.4 ± 36.7 vs 66.1 ± 38.4, P = 0.13) LAI compared with oral had significantly higher mean number of ED visits (0.18 ± 0.34 vs 0.16 ± 0.25, P < 0.01)
4. Joshi *et al.* (2018), United States	Retrospective cohort Medicaid databases from 6 US states (Iowa, Kansas, Mississippi, Missouri, New Jersey, Wisconsin) July 2009 to March 2015	Paliperidone Palmitate Once Monthly (PP1M), (n = 351), male (71.2%), mean age (38.4 years) Oral Atypical Antipsychotics (OAA), (n = 4869), male (58.8%), mean age (41.9 years)	Outpatient visits	12 months	PP1M compared with OAA had significantly lower rates of outpatient visits (IRR=0.90, P = 0.036)
5. Joshi *et al.* (2018), United States	Prospective cohort study 46 CBHOs outpatient services	Long-Acting Injection Antipsychotics Therapy (LAI-APT), (n = 599 for schizophrenia), male (72.5%), White (50.6%), mean age (41.1 years) Oral Antipsychotics APT (n = 281), male (65.8%), White (49.1%), mean age (42.1 years)	Nurse practitioner visits Therapist visits Nurse visits Group sessions ED visits	12 months	LAI APT compared with oral APT had significantly higher mean rates of nurse practitioner visits (0.8 ± 1.74 vs 0.4 ± 1.29), therapist visits (5.8 ± 15.2 vs 2.7 ± 7.87), nurse visits (6.7 ± 7.29 vs 1.6 ± 3.11), and group sessions attended (7.2 ± 22.3 vs 1.9 ± 8.47), P = n/a LAI APT compared with oral had no significant difference in ER visits (13.6% vs 13.6%), P = n/a
	Retrospective cohort	Long-Acting Injectable Paliperidone Palmitate (PP),	ED visits	12 months	No significant difference between PP and OAA groups

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TABLE 4 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
6. Joshi *et al.* (2018), United States	Medicare Advantage Claims Data	(n = 295), male (50.8%), White (65.8%), mean age (48.7 years) Oral atypical antipsychotics (OAA), (n = 2296), male (45.5%), White (72.3%), mean age (55.9 years)	Outpatient visits		in mean number of outpatients' visits (18.0 ± 30.8 vs 19.2 ± 12.2, P = 0.228) and ED visits (2.3 ± 9.7 vs 2.5 ± 4, P = 0.432) No significant difference between groups in likelihood of ED visits (OR = 1.12, 95% CI=0.95-1.33)
7. Lafeuille *et al.* (2015), United States	Retrospective cohort Premier Perspective Comparative Hospital Database	Paliperidone Palmitate Cohort (n = 374), male (67.9%), White (47.6%), mean age (41.1 years) Oral Antipsychotic Cohort (n = 45 251), male (61.5%), White (45.1%), mean age (45.6 years)	ED visits ED hospital stay	12 months	Paliperidone palmitate cohort compared with oral antipsychotic significantly less likely to visit ER (HR = 0.53, P < 0.0001) Mean proportion of hospital stay spent in ER was 0.08 ± 0.10 in Paliperidone Palmitate group and 0.13 ± 0.19 in oral Antipsychotics and it was significant (P < 0.001)
8. Lafeuille *et al.* (2013), United States	Retrospective cohort Premier Hospital Database 2006 to 2010	Atypical LAT (N = 1032), male (56.4%), White (46.8%), mean age (42.1 years) Oral Antipsychotic, (N = 2796), male (55.4%), White (46.6%), mean age (42.4 years)	Number of ED visits	30 months	Atypical LAT patients compared with oral AP patients had significantly lower all-cause ER visits (2.33 vs 2.67, P < 0.0158)
9. Lafeuille *et al.* (2018), United States	Retrospective cohort Medicaid databases from 6 states (Iowa, Kansas, Mississippi, Missouri, New Jersey, Wisconsin) July 2009 to 2015	Paliperidone Palmitate Once Monthly (PPIM), (n = 371), mean age (45.0 years) Oral Atypical Antipsychotics (n = 8296), mean age (47.5 years)	Schizophrenia-related outpatient visits ED visits	12 months	PP1M compared with OAA had no significant differences in all-cause of outpatient visits (IRR=0.98, 95%CI=0.86 to 1.11), but there was significantly higher schizophrenia-related outpatient visits (IRR=1.44, 95%CI=1.23 to 1.67) No significant differences in ER visits of all cause among PP1M compared with OAA (IRR=0.80, 95%CI=0.56 to 1.10) nor the schizophrenia-related ER visits among PP1M compared with OAA (IRR=0.73, 95%CI=0.46 to 1.02).
10. Lefebvre *et al.* (2017), Vermont	Retrospective cohort The VHA's Corporate Data Warehouse January 2010 to June 2015	Paliperidone Palmitate (PP), (n = 1684), male (93.3%), mean age (49.0 years) Oral Antipsychotic OAA (n = 5188), male (93.5%), mean age (52.4 years)	Outpatient services Mental Health intensive case management	18 months	PP compared with OAA had significantly fewer number of days in long-term care setting (4.3 ± 38.6 vs 5.2 ± 27.2, P < 0.001), but greater proportion with outpatient

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TABLE 4 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
			Other outpatient visits Number of ED visits		service visits (100.0% vs 99.9%, $P = 0.040$) and mean number of outpatient service visits (68.5 ± 62.8 vs 68.0 ± 41.5, $P = 0.011$) PP compared with OAA had significantly greater mean number of mental health intensive case management visits (13.3 ± 38.9 vs 8.8 ± 19.4, $P < 0.001$) but significantly fewer mean number of other outpatient visits (52.6 ± 55.9 vs 56.5 ± 37.2, $P < 0.001$) PP compared with OAA had significantly fewer ED visits (2.6 ± 6.4 vs 2.7 ± 3.9, $P = 0.020$)
11. Lu *et al.* (2020), United States	Retrospective cohort Community-based outpatient psychiatric hospital	Long-Acting Injectable (LAI), ($n = 23$), male (60.9%), Caucasian (47.8%), mean age (49.6 years) Oral ($n = 24$), male (62.5%), African American (62.5%), mean age (56.0 years)	Number of ED visits	12 months	Number of ED visits significantly decreased in the LAI group after LAI treatment was initiated ($t = 3.70$, $P = 0.002$)
12. Manjelievskaia *et al.* (2018), United States	Retrospective cohort IBM Watson Health MarketScan Medicaid Multi-State Database January 2010 to December 2014	Paliperidone Palmitate Once Monthly (PP1M), (n.7672), male (48.8%), Black (52.4%), mean age (40.3 years) Oral Atypical Antipsychotics (OAA), (n.7926), male (48.9%), Black (52.4%), mean age (40.0 years)	Outpatient office visit	12 months	PP1M compared with OAA had significantly lower outpatient visits (83.1% vs 84.5%, $P = 0.019$)
13. Pesa *et al.* (2017), United States	Retrospective cohort California Medicaid Patients Database 2009 to 2013	Paliperidone Palmitate Once Monthly (PP1M), ($n = 722$) Oral Antipsychotic Therapy (OAT), ($n = 722$)	Any outpatient visits Number of ED visits	12 months	PP1M compared with OAT had significantly lower outpatient visit (49.0% vs 56.0%, $P = 0.008$) and ER visits (2.1 vs 2.9, $P = 0.016$).
14. Pesa *et al.* (2015), United States	Retrospective cohort MarketScan Medicaid Multi-State Database (Truven Health Analytics, Ann Arbor, MI, USA) 2009 to 2011	Paliperidone Palmitate (PP), ($n = 984$), male (58.2%), Black (51.9%), mean age (38.8 years) Oral Antipsychotic Therapy (OAT), ($n = 4199$), male (48.8%), Black (47.3%), mean age (41.6 years)	ED visits	12 months	PP compared with OAT had significantly lower risks for any ED visits (by 18%, 95%CI=21 to 15, $P = 0.013$).
15. Pilon *et al.* (2017), United States	Retrospective cohort Medicaid data from 5 states 09/2008 to 03/2015	Once Monthly Paliperidone Palmitate (PP1M), ($n = 227$), male (75.3%), White (43.2%), mean age (22.3 years)	Outpatient visits	12 months	PP1M compared with OAAs had non-significant lower outpatient visits (0.91, 95% CI=0.83 to 1.01, $P = 0.072$).

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TABLE 4 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
		Oral Atypical Antipsychotics (OAAs), (n = 2168), male (58.9%), White (52.9%), mean age (21.6 years)			
16. Pilon *et al.* (2017), United States	Retrospective cohort Medicaid data from 6 states 2010 to 2015	Second-Generation Long-Acting Injectable Therapies (SGA-LAIs), (n = 3307), male (59.5%), mean age (41.8 years) Oral Atypical Antipsychotics (OAAs), (n = 21 355), male (50.0%), mean age (44.2 years)	Outpatient visits ED visits	12 months	SGA-LAI compared with OAA non-significantly lower outpatient visits (IRR=0.97, 95% CI=0.92 to 1.02, P = 0.204). However, likelihood of PP-LAI vs OAA was significantly lower (IRR=0.92, 95%CI=0.87 to 0.97, P = 0.004), but not A-LAI vs OAA, P = 0.056 SGA-LAI compared with OAA had no significant difference in ED visits (Adjusted IRR=0.94, 95% CI=0.82 to 1.08, P = 0.389)
17. Remington and Khramov, (2001), Canada	Retrospective cohort Schizophrenia and Continuing Care Program Between 1993 and 1995,	Clozapine (N = 15) Risperidone (N = 15) Depot Conventional (N = 18) Oral Conventional (N = 18)	ED visits Outpatient visits with physicians and non-physician caretakers	18 months	There was no significant difference between depot conventional and oral conventional, clozapine, or risperidone groups in the mean number of ED visits (2.1 vs 1.6 vs 1.5 vs 1.4, P = n/a) However, there were significant differences between depot conventional and oral conventional, clozapine, or risperidone groups in the number of physician (23.7 vs 15.4 vs 58.9 vs 40.9, P = 0.0001) and non-physician visits (27.3 vs 8.4 vs 32.2 vs 17.1, P = 0.004)
18. Varner *et al.* (2001), United States	Retrospective cohort Harris County Psychiatric Hospital, Houston	N = 153 Oral Haloperidol (n = 58) Depot Haloperidol (n = 95)	Outpatient visits	48 months	No significant difference between the two groups on the outpatient visit (x^2 = 0.00, P = n/a)
19. Xiao *et al.* (2015), United States	Retrospective cohort Medicaid beneficiaries (New Jersey, Iowa, Missouri, and Kansas) Between 2009 and 2012	Paliperidone Palmitate (PP), (n = 952), male (63.1%), White (46.7%), mean age (40.3 years) Oral Atypical Antipsychotics (OAAs), (n = 12 174), male (57.6%), White (58.3%), mean age (45.3 years)	Outpatient visits ED visits	36 months	Patients treated with PP had less frequent visits for ED visits (RR = 0.58, 95% CI = 0.57–0.60, P < 0.0001) and more outpatient visits (RR = 1.15, 95% CI = 1.15–1.16, P < 0.0001) compared with those treated with OAAs
20. Xiao *et al.* (2016), United States	Retrospective cohort Medicaid databases for Florida, Iowa, Kansas, Mississippi, Missouri, and New Jersey	Once Monthly Paliperidone Palmitate (PP), (n = 876), male (54.7%), White (53.2%), mean age (40.8 years)	Outpatient visits ED visits	12 months	Patients treated with PP had less frequent visits for ED (RR = 0.71, 95% CI = 0.70, 0.73, P < 0.001) compared with those treated with OAAs

(*Continued*)

TABLE 4 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
		Oral Atypical Antipsychotics (OAAs), (n = 10 778), male (45.2%), White (57.6%), mean age (43.2 years)			No difference was found on outpatient visits between two groups on outpatient visits (IRR = 1.00, 95% CI = 0.99, 1.02, P = 0.832)
21. Young-Xu *et al*. (2016), United States	Retrospective cohort VHA Corporate Data Warehouse Between January 2010 and October 2014	Paliperidone Palmitate (PP) (n = 2285), male (89.9%), White (36.0%), mean age (50.2 years) Oral Atypical Antipsychotics (OAAs), (n = 8005), male (90.7%), White (39.9%), mean age (53.7 years)	Outpatient services within 7 days of discharge Outpatient services within 30 days of discharge Number of ED visits	18 months	PP compared with OAA had significantly lower outpatient visits per patients (69.1 ± 68.4 vs 67.4 ± 41.1, P < 0.001) No significant difference between the two groups on the number of ED visits per patients (2.3 ± 6.1 vs 2.4 ± 3.5, P = 0.062)

ED, Emergency Department or Emergency Room.

Joshi *et al*. 2018c; Pilon *et al*. 2017b; Varner *et al*. 2001; Xiao *et al*. 2016) and ED visits (Baser *et al*. 2015; Joshi *et al*. 2018b, 2018c; Lafeuille *et al*. 2018; Pilon *et al*. 2017c; Remington & Khramov 2001; Young-Xu *et al*. 2016) between LAI and oral users. Pooled together, eight studies (Baser *et al*. 2015; Fan *et al*. 2018; Joshi *et al*. 2018c; Lefebvre *et al*. 2017; Manjelievskaia *et al*. 2018; Pesa *et al*. 2017; Remington & Khramov 2001; Young-Xu *et al*. 2016) found no differences between LAI or oral users in mean number of outpatient visits per patient (n = 39574, 95% CI = −0.047 to 0.080, P < 0.611; τ^2 = 0.006, I^2 = 84.18%, Q = 44.262, df = 7, P < 0.001). However, pooled together, nine studies (Baser *et al*. 2015; Fan *et al*. 2018; Joshi *et al*. 2018c; Lafeuille *et al*. 2013; Lefebvre *et al*. 2017; Manjelievskaia *et al*. 2018; Pesa *et al*. 2017; Remington & Khramov 2001; Young-Xu *et al*. 2016) showed that LAI users were less likely than oral users to visit ED (n = 43402, 95%CI = −0.087 to −0.002, P = 0.038; τ^2 = 0.002, I^2 = 68.26%, Q = 25.206, df = 8, P < 0.001) (Figure 4).

Healthcare costs

Changes in healthcare costs were reported in 15 studies (Baser *et al*. 2015; Fan *et al*. 2018; Joshi *et al*. 2018a, 2018c; Lafeuille *et al*. 2015, 2018; Lefebvre *et al*. 2017; Manjelievskaia *et al*. 2018; Moore *et al*. 1998; Pesa *et al*. 2015; Pilon *et al*. 2017b, 2017c; Xiao *et al*. 2015, 2016; Young-Xu *et al*. 2016) (Table 5). Among these studies, 11 (Joshi *et al*. 2018a, 2018c; Lafeuille *et al*. 2018; Lefebvre *et al*. 2017; Moore *et al*. 1998; Pesa *et al*. 2015; Pilon *et al*. 2017b, 2017c; Xiao *et al*. 2015, 2016; Young-Xu *et al*. 2016) found lower and one (Fan *et al*. 2018) found higher medical costs among LAI compared with oral users. In addition, among ten studies examining pharmacy costs, all (Baser *et al*. 2015; Joshi *et al*. 2018a, 2018c; Lafeuille *et al*. 2018; Manjelievskaia *et al*. 2018; Pesa *et al*. 2015; Pilon *et al*. 2017b; Xiao *et al*. 2015, 2016; Young-Xu *et al*. 2016) found higher costs among LAI compared with oral users. Of four studies (Fan *et al*. 2018; Joshi *et al*. 2018c; Lefebvre *et al*. 2017; Young-Xu *et al*. 2016) reporting the annual mean medical costs, pooled analysis showed no signifcant differences between LAI and oral users on medical costs (n = 21826, 95% CI = −0.178 to 0.154, P = 0.887; τ^2 = 0.027, I^2 = 96.47%, Q = 85.099, df = 3, P < 0.001). Our meta-analysis of three studies (Baser *et al*. 2015; Lefebvre *et al*. 2017; Young-Xu *et al*. 2016) assessing annual mean pharmacy costs found that LAI users had statistically significantly higher pharmacy costs as compared with oral users (n = 17832, 95%CI = 0.215 to 0.382, P < 0.001; τ^2 = 0.002, I^2 = 70.56%, Q = 6.794, df = 3, P = 0.033) (see Figure 5).

Social functioning

Nine studies (Barnett *et al*. 2012; Barrio *et al*. 2013; Bozzatello *et al*. 2019; Joshi *et al*. 2018b; Keks *et al*.

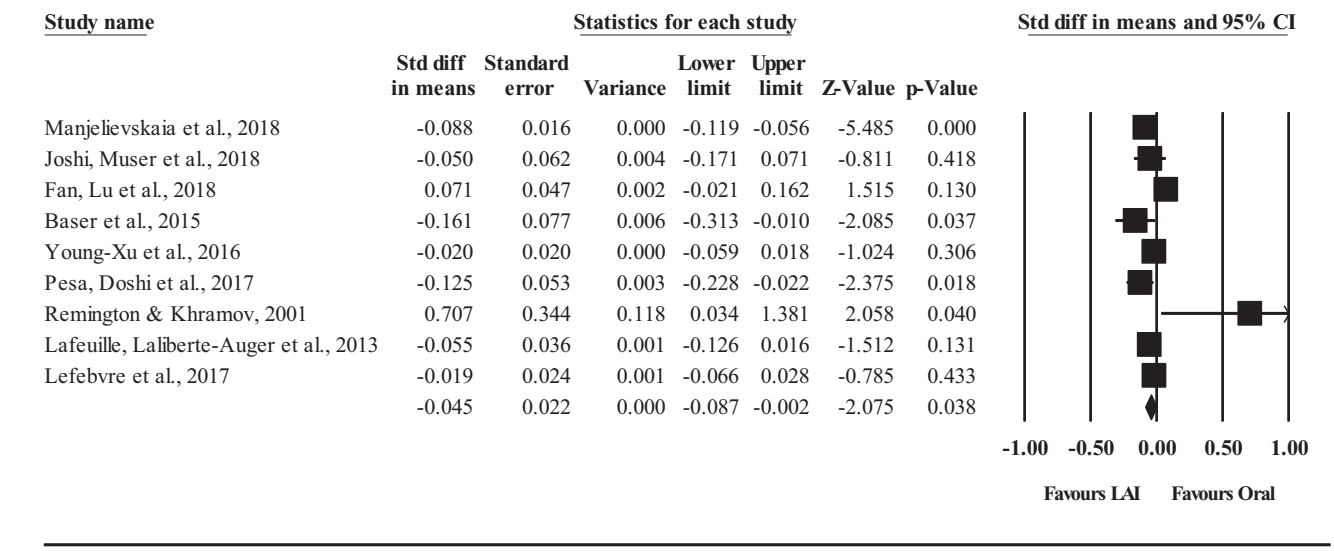

FIG. 4 Forest plot of studies assessing the differences between long-acting injectable (LAI) and oral antipsychotics using the mean number of emergency room visits per patient.

2007; Leatherman *et al*. 2014; Levitan *et al*. 2016; Petrić *et al*. 2019; Rosenheck *et al*. 2011) reported changes in the PSP, WQLI, and HCQL scale scores among LAI compared with oral users (Table 6). Of these, five studies (Barrio *et al*. 2013; Joshi *et al*. 2018b; Leatherman *et al*. 2014; Levitan *et al*. 2016; Petrić *et al*. 2019) reported improvements in PSP scores among LAI as compared with oral users. However, four studies (Bozzatello *et al*. 2019; Joshi *et al*. 2018b; Leatherman *et al*. 2014; Rosenheck *et al*. 2011) reported no differences in LAI and oral users as observed on the PSP scale. In pooled analysis of four studies (Barrio *et al*. 2013; Bozzatello *et al*. 2019; Petrić *et al*. 2019; Rosenheck *et al*. 2011), LAIs were no different than orals in improving PSP mean scores (n = 529, 95%CI = −0.162 to 1.335, P = 0.125; τ^2 = 0.513, I^2 = 90.9%, Q = 33.136, df = 3, P < 0.001).

Publication bias

The funnel plots for three outcomes (PDC, PANSS, and rehospitalization) were asymmetrical. We used the Trim-and-Fill method to adjust for potential publication biases. We found that the point estimate and 95% CIs was 1.81893 (1.56458, 2.11462) for the PDC studies, −0.32593 (−0.43202, −0.21984) for the PANSS studies, and −0.07453 (−0.09487, −0.05419) for the rehospitalization studies. In other words, the lack of effect size changes as a result of the publication bias analysis suggest no indications of publication bias.

DISCUSSION

The overarching hypothesis as the impetus for our review and meta-analysis was that LAIs would be comparable to orals in our examined health outcomes. However, our systematic review findings showed that in most included studies, patients treated with LAIs were more adherent to medications, had improvements in symptom remission and social functioning, and had lower likelihood of rehospitalizations, ED visits, and medical care costs compared with those taking orals. Yet, our meta-analytic results provide support that LAIs only reduce ED visits and increase pharmacy costs as compared with orals. The low availability of studies with similar outcomes for the meta-analysis likely affects the differences between systematic review and meta-analysis findings. Nevertheless, these findings have important clinical and policy implications regarding antipsychotic treatment for people with schizophrenia.

Medication adherence

Our systematic review showed that LAI users were more adherent to medications than oral users. These results are consistent with a previous systematic review,

TABLE 5 *Characteristics of studies assessing healthcare costs*

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
1. Baser *et al.* (2015), United States	Retrospective cohort VA Medical records July 2007 to May 2012	Paliperidone Palmitate Long-Acting Injection (PP), (n = 381), male (92.0%), mean age (50.2 years) Oral Atypical Antipsychotics (OAT), (n = 3537), male (92.0%), mean age (52.2 years)	Inpatient costs Pharmacy costs ER costs Outpatient office costs Other costs Total costs	12 months	PP compared with OAT had significantly lower mean inpatient ($18 560 vs $31505, P = 0.002) and ER cost ($20 vs $64, P = 0.015). But had significantly higher pharmacy ($10 063 vs $4167, P < 0.001) costs No significant difference in outpatient office ($16 723 vs $16 556, P = 0.908), other outpatient ($163 vs $276, P = 0.099) or total costs ($45 529 vs $52 569, P = 0.128).
2. Fan *et al.* (2018), Taiwan	Retrospective matched cohort National Health Research Institute Database- Psychiatric Inpatient Medical Claim Dataset	Long-Acting Injectable (LAI) Risperidone ((n = 691), male (45.88%), age range 16–30 (36.9%) and 31–45 (37.05%) Oral Risperidone (n = 1382), male (45.88%), age range 16 –30 (37.12%) and 31–45 (37.05%)	Medical costs (outpatient, emergency room, total psychiatric services)	12 months	LAI compared with Oral group had significantly higher costs in outpatient services ($287.74 ± 194.862 vs $208.25 ± 180 643, P < 0.01), emergency room services ($0.35 ± 1.070 vs $0.25 ± 0.620, P < 0.01), and total psychiatric services ($591.65 ± 224.727 vs $511.78 ± 232.887, P < 0.01).
3. Joshi, *et al.* (2018) United States	Retrospective cohort Medicaid databases from 6 US states (Iowa, Kansas, Mississippi, Missouri, New Jersey, Wisconsin) July 2009 to March 2015	Paliperidone Palmitate Once Monthly (PP1M), (n = 351), male (71.2%), mean age (38.4 years) Oral Atypical Antipsychotics (OAA), (n = 4869), male (58.8%), mean age (41.9 years)	All-cause medical costs Pharmacy costs	12 months	PP1M compared with OAA had lower medical, MMCD= $191, P < 0.020 and similar total costs MMDC=$59, P = 0.517, but higher pharmacy costs ($250, P < 0.0001)
4. Joshi, *et al.* (2018), United States	Retrospective cohort Medicare Advantage Claims Data	Long-Acting Injectable Paliperidone Palmitate (PP), (n = 295), male (50.8%), White (65.8%), mean age (48.7 years) Oral Atypical Antipsychotics (OAA), (n = 2296), male (45.5%), White (72.3%), mean age (55.9 years)	Medical costs Pharmacy costs	6 months	PP compared with OAA had significantly lower medical costs ($11 095, 95%CI= $10374 to 11867 vs $15 551, 95%CI= $14584 to 16583), but higher pharmacy costs ($14 787, 95%CI=$14117 to 15488 vs $5781, 95%CI= $5530 to 6043)
5. Lafeuille *et al.* (2015), United States	Retrospective cohort Premier Perspective Comparative Hospital Database	Paliperidone Palmitate Cohort (n = 374), male (67.9%), White (47.6%), mean age (41.1 years) Oral Antipsychotic Cohort (n = 45 251),	All-cause costs (including costs of rehospitalization, ER visits, and outpatient hospital visits)	12 months	Paliperidone Palmitate cohort compared with Oral Antipsychotic cohort had non-significant lower costs (-$212, P = 0.2164)

(*Continued*)

TABLE 5 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
		male (61.5%), White (45.1), mean age (45.6 years)			
6. Lafeuille *et al.* (2018), United States	Retrospective cohort Medicaid databases from 6 states (Iowa, Kansas, Mississippi, Missouri, New Jersey, Wisconsin) July 2009 to 2015	Paliperidone Palmitate Once Monthly (PP1M), (n = 371), mean age (45.0 years) Oral Atypical Antipsychotics (OAA), (n = 8296), mean age (47.5 years)	Monthly medical costs	12 months	PP1M compared with OAA had significantly lower all-cause medical costs (-$369, P = 0.004), but higher all-cause pharmacy costs ($279, P < 0.0001)
7. Lefebvre *et al.* (2017), Vermont	Retrospective cohort The VHA's Corporate Data Warehouse January 2010 to June 2015	Paliperidone Palmitate (PP), (n = 1684), male (93.3%), mean age (49.0 years) Oral Antipsychotic (n = 5188), male (93.5%), mean age (52.4 years)	Annual Medical costs Schizophrenia-related medical costs	18 months	PP compared with OAA had significantly lower mean annual all-cause (-$10 473, 95%CI=-$17 to 827 to -$3491, P < 0.001) and schizophrenia related (-$8457, 95%CI=-$12 to 710 to -$3638, P < 0.001) medical costs.
8. Manjelievskaia *et al.* (2018), United States	Retrospective cohort IBM Watson Health MarketScan Medicaid Multi-State Database January 2010 to December 2014	Once monthly paliperidone palmitate (PP1M), (n = 7672), male (48.8%), Black (52.4%), mean age (40.3 years) Oral atypical antipsychotics (OAA), (n = 7926), male (48.9%), Black (52.4%), mean age (40.0 years)	All-cause costs Outpatient pharmacy costs	12 months	PP1M compared with OAA had no difference in all cause monthly costs ($225, 95% CI=-$31 to $573, P = n/a), but outpatient pharmacy costs were significantly higher in PP1M patients ($634, 95% CI=-$554 to $728, P = n/a)
9. Moore *et al.* (1998), United States	Prospective study Spring Grove Hospital Center Between March 1994, and December 1995	Haloperidol Decanoate (n = 14) Fluphenazine Decanoate (n = 29) Risperidone (n = 75)	Annual costs (both the outpatient medication and hospitalization costs)	12 months	The annual costs was lower in Risperidone compared with fluphenazine and haloperidol ($12 137 vs $13 693 vs $23 649, P = n/a)
10. Pesa *et al.* (2015), United States	Retrospective cohort MarketScan Medicaid Multi-State Database (Truven Health Analytics, Ann Arbor, MI, USA) 2009 to 2011	Paliperidone Palmitate (PP), (n = 984), male (58.2%), Black (51.9%), mean age (38.8 years) Oral Antipsychotic Therapy (OAT), (n = 4199), male (48.8%), Black (47.3%), mean age (41.6 years)	All-cause monthly cost differentials (inpatient, emergency, outpatient, pharmacy, total) Monthly mental health-related costs (inpatient, emergency, outpatient, pharmacy, total)	12 months	In terms of all-cause costs, PP compared with OAT had significantly lower inpatient costs (−234.19, 95%CI= −361.70 to −106.67, P = 0.0003) and outpatient costs (−335.89, 95%CI= −382.11 to −289.67, P < 0.0001); but higher pharmacy costs (1003.65, 95%CI=986.21 to 1021.09, P < 0.00001) and total costs (433.58, 95%CI=297.88 to 569.27, P < 0.0001) In terms of mental health related costs, PP compared with OAT had significantly

(*Continued*)

TABLE 5 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
					lower inpatient costs (−270.56, 95%CI=−354.67 to −186.45, $P = 0.0003$) and outpatient costs (−285.94, 95%CI=−317.70 to −254.17, $P < 0.0001$); but higher pharmacy costs (1019.30, 95% CI=1004.50 to 1034.10, $P < 0.0001$) and total costs (462.80, 95%CI=373.95 to 551.65, $P < 0.0001$)
11. Pilon, *et al.* (2017), United States	Retrospective cohort Medicaid data from 5 states 09/2008 to 03/2015	Paliperidone Palmitate (PP1M), ($n = 227$), male (75.3%), White (43.2%), mean age (22.3 years) Oral Atypical Antipsychotics (OAAs), ($n = 2168$), male (58.9%), White (52.9%), mean age (21.6 years)	Medical costs Pharmacy costs Total health care costs	12 months	PP1M compared with OAAs had significantly lower medical costs (-$286, 95%CI= −412 to −150, $P < 0.0001$) but higher pharmacy costs (323, 95%CI=250 to 392, $P < 0.0001$) but non-significant total health care costs ($37, 95%CI= −117 to 212, $P = 0.709$)
12. Pilon, *et al.* (2017), United States	Retrospective cohort Medicaid data from 6 states 2010 to 2015	Second-Generation Long-Acting Injectable Therapies (SGA-LAIs), ($n = 3307$), male (59.5%), mean age (41.8 years) Oral Atypical Antipsychotics (OAAs), ($n = 21\,355$), male (50.0%), mean age (44.2 years)	Medical costs 1-day mental health institute visit costs	12 months	SGA-LAI compared with OAA had significantly lower medical costs (-$168, 95%CI= −238 to −94, $P < 0.001$), lower inpatient costs (-$107, 95%CI= −145 to −64, $P < 0.001$), and lower home care costs (-$100, 95%CI= −139 to −60, $P < 0.001$) SGA-LAI compared with OAA had higher 1-day mental institute visit costs ($33, 95%CI = 25 to 41, $P < 0.001$).
13. Xiao *et al.* (2015), United States	Retrospective cohort Medicaid beneficiaries (New Jersey, Iowa, Missouri, and Kansas) Between 2009 and 2012	Paliperidone Palmitate (PP), ($n = 952$), male (63.1%), White (46.7%), mean age (40.3 years) Oral Atypical Antipsychotics (OAAs), ($n = 12\,174$), male (57.6%), White (58.3%), mean age (45.3 years)	Medical Costs Pharmacy Costs	36 months	Compared with OAAs, PP group had lower medical costs (MMCD=-$136.15; $P = 0.0001$) and higher pharmacy costs (MMCD= $232.88; $P < 0.001$)
14. Xiao *et al.* (2016), United States	Retrospective cohort Medicaid databases for Florida, Iowa, Kansas, Mississippi, Missouri, and New Jersey	Once Monthly Paliperidone Palmitate (PP), ($n = 876$), male (54.7%), White (53.2%), mean age (40.8 years) Oral Atypical Antipsychotics (OAAs), ($n = 10\,778$), male	Medical Costs Pharmacy Costs	12 months	Compared with OAAs, PP was associated with significantly lower medical costs (MMCD= -$383, $P < 0.001$) and higher pharmacy costs (MMCD= $270, $P < 0.001$)

(*Continued*)

TABLE 5 (Continued)

Author (Year) and Country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related main outcomes
		(45.2%), White (57.6%), mean age (43.2 years)			
15. Young-Xu *et al.* (2016), United States	Retrospective cohort VHA Corporate Data Warehouse Between January 2010 and October 2014	Paliperidone Palmitate (PP) mean age (50.2 years) Oral Atypical Antipsychotics (OAAs) mean age (53.7 years)	Outpatients visit costs Pharmacy costs Inpatient costs	18 months	PP compared with OAA had significantly lower total outpatient costs ($8511.36, $P = 0.012$). PP treatment had greater outpatient visit ($2527.44, $P < 0.0001$) and pharmacy ($3416.96, $P < 0.0001$), but lower inpatient stay costs (-$14 455.76, $P < 0.0001$)

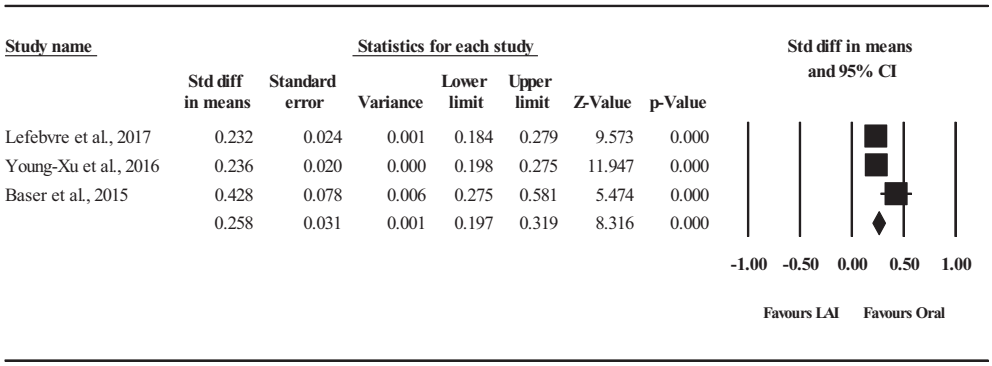

FIG. 5 Forest plot of studies assessing the differences between long-acting injectable (LAI) and oral antipsychotics using the mean number of pharmacy costs.

which found that LAIs improved medication adherence compared with oral use among patients with schizophrenia (Kaplan *et al*. 2013). In our study, the pooled effect size showed no statistically significant difference between LAIs and orals regarding the number of patients who had 80% PDC. This lack of differences observed in the effect size across the included studies may be related to the fact that the pooled studies included individuals in the early episodes of schizophrenia (Weiden *et al*. 2012), or who were compliant and regularly attended outpatient services (Stanković & Ille 2013), or had frequently switched between LAIs and orals (Schreiner *et al*. 2014).

Symptom remission/relapse

It is important to study the risks and benefits of long-term antipsychotic modality on symptoms remission because of potiential long-term treatment effects on brain shrinkage, metabolic effects, and cardiac side effects (Correll *et al*. 2018). In addition, antipsychotic treatment may present complications related to rebound psychosis when not properly managed (Keks *et al*. 2019). Our systematic review results showed that in just over half the studies ($n = 18$), LAI users had greater symptom remission than orals. However, the pooled effect size showed no superiority of LAIs over orals in decreasing PANSS or CGI scores. These results are similar to an earlier meta-analysis of randomized controlled trials (Kishimoto *et al*. 2014), which found that LAIs were not superior to orals in preventing relapse except for first-generation antipsychotic medications. However, a large review of randomized controlled trials comparing orals with LAIs found statistically significant differences in relapse rates (Leucht *et al*. 2011). Some of the reasons for

TABLE 6 *Characteristics of studies assessing social function and quality of life*

Author (Year) and country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
1. Barnett *et al.* (2012), United States	Comparative Effectiveness RCT Between 2006 and 2009	Long-Acting Injectable (LAI Risperidone), (n = 187), male (92.0%), White (46.5%), mean age (50.7 years) Standard care (oral antipsychotic), (n = 182), male (92.2%), Black (47.8%), mean age (51.3 years)	Health related quality life: Self-Administered Quality of Well – Being (QWB)	18 months	No significant differences between the LAI Risperidone (0.66 ± 0.02) and oral antipsychotic (0.67 ± 0.02) on QWB, P = 0.63
2. Barrio *et al.* (2013), Spain	Case–control study Patients with schizophrenia from a psychiatry unit 2004 to 2008	Risperidone Long-Acting Injectable (RLAI), (n = 26), male (61.5%), White (84.6%), mean age (26.9 years) Oral Antipsychotics, (n = 26), male (57.7%), White (92.3%), mean age (27.4 years)	Personal and Social Performance Scale (PSP)	24 months	RLAI group had significantly higher PSP scores compared to oral group (RLAI = 72.4 ± 14.8 vs oral = 59.7 ± 13.5, P < 0.001) suggesting better psychosocial functioning
3. Bozzatello *et al.* (2019), Italy	Open label RCT	Long Acting Paliperidone Palmitate (PP1M), (n = 36) Oral Paliperidone Extended Release (ER), (n = 36)	Personal and Social Performance (PSP)	6 months	There was no significant difference between the two groups on the PSP (PP1M = 65.41 ± 9.91 vs Paliperidone ER = 62.39 ± 13.33, P = 0.112)
4. Joshi *et al.* (2018), United States	Prospective cohort 46 CBHOs outpatient services	Long-Acting Injectable (LAI-APT), (n = 599), male (72.5%), White (50.6%) or black (32.8%), mean age (41.1years) Oral APT (n = 281), male (65.8%), white (49.1%), mean age (42.1 years)	Lehman's Quality of Life Interview Personal and Social Performance (PSP)	12 months	Mean general life satisfaction scores were 5.0 ± 1.30 for total LAI APT and 4.8 ± 1.31 for oral APT cohorts, P = n/a Among patients treated with LAI APT, the mean total PSP scores were 65.2 ± 16.43 compared to patients treated with oral APT 61.2 ± 13.08, P = n/a
5. Keks *et al.* (2007), Australia, Belgium, France, Germany, Greece, Luxembourg, Poland, Russia, Spain, Netherlands and UK	Prospective cohort 48 centers (Australia, Belgium, France, Germany, Greece, Luxembourg, Poland, Russia, Spain, Netherlands and UK)	Long-Acting Injectable Risperidone (n = 247), Male (56.0%), White (96.0%), mean age (35.1 years) Oral Olanzapine, (n = 300), Male (58.0%), White (97.0%), mean age (35.2 years)	Wisconsin Quality of Life Index	12 months	Among both groups, there was similarity in improvements in patients' quality of life from baseline to endpoint on all subscale ratings, but no comparisons between groups
6. Leatherman *et al.* (2014), United States	RCT	Long-Acting Injectable (LAI) Risperidone, (n = 187), male (92.0%), White (46.5%), age ≥ 53 (53.5%) Oral (n = 182), male (90.7%), White (43.4%), age ≥ 53 (54.9%)	Quality of life: Heinrichs-Carpenter Quality of Life scale (HCT)	24 months	There was a significant difference between groups on the mean of HCQT who were hospitalized at randomization (2.72 vs 2.58, P = 0.05

(*Continued*)

TABLE 6 (Continued)

Author (Year) and country	Study design	Sample description (by gender, age, and race)	Measures	Time points of study measures	Key findings related to main outcomes
7. Levitan *et al.* (2016), United States	Post-hoc assessment of two RCT Multicenter from various settings	Paliperidone Palmitate Once Month (PP1M) (N = 193), mean age (26.3 years) Placebo (N = 192) Paliperidone ER (N = 104), mean age (27.1 years) Placebo (N = 101)	Personal and Social Performance (PSP)	40 weeks	There were fewer PSP worsening events (PP1M = 64 vs Paliperidone ER = 204, risk difference = −165, 95% CI = −93, −237) per 1000 patients treated with PP1M, $P < 0.05$
8. Petrić *et al.* (2019), Croatia	Retrospective cohort Between 2014 and 2017	Long Acting Paliperidone Palmitate antipsychotic (n = 18), male (55.6%), mean age (16.6 years) Oral Antipsychotic Risperidone (n = 18), male (50.0%), mean age (16.2 years)	Personal and Social Performance Scale (PSP)	12 months	Patients treated with paliperidone palmitate had significantly greater improvement in PSP 36.83 ± 6.09) compared with those in the risperidone group (29 ± 4.31), P = 0.001
9. Rosenheck *et al.* (2011), United States	Randomized Clinical Trial	Oral Antipsychotic (n = 182) Injectable Risperidone (n = 187)	Heinrichs–Carpenter Quality of Life Scale Personal and Social Perfor mance scale (PSP)	24 months	There was no significant difference in the quality of life scores (2.86 ± 0.06 vs 2.78 ± 0.06, P = 0.28) and the PSP between two groups (0.66 ± 0.02 vs 0.67 ± 0.02, P = 0.63)

non-statistically significant differences between LAI and oral users on psychiatric symptom measures may be because of small sample sizes (22 and 28 participants) (Kim *et al*. 2008), using different types of oral medications (Barnett *et al*. 2012) or having higher dropout rates in the LAI group (Malla *et al*. 2016). However, a recent study lends support that individulas stablized on LAIs have lower relapse at compared with those stablized on orals in the short term (Schoretsanitis *et al*. 2021).

Rehospitalizations

Individuals treated with LAIs had a lower mean number of rehospitalizations and fewer days hospitalized compared with those treated with orals. These results are consistent with a prior study (n = 75 274 patients), which found that LAIs reduced readmission rates by 59% compared with orals among patients with repeated admissions (Kim *et al*. 2020). Another study of nearly 30 000 patients found that LAIs decreased rates of hospitalization by 20% to 30% compared with orals (Tiihonen *et al*. 2017).

The pooled effect size of the mean number of rehospitalization per patients indicated that treatment with LAIs did not differ from orals in the number of rehospitalizations. However, this effect varied across the included studies and was inconsistent. This variation is likely driven by study designs, small sample sizes, or baseline differences between groups. Also, the effect size variations that we found across our included studies may be related to the focus of different studies on specific types of orals or LAIs. These differences in findings are also consistent with a study that reported variations in effectiveness when comparing results from randomized controlled trials and observational studies (Kirson *et al*. 2013). Therefore, more research is needed.

Outpatient/emergency department visits

Most reviewed studies reported higher outpatient visits among LAI users compared with oral users. But the

pooled effect size showed no statistically significant difference between LAI and oral users in outpatient visits. Consistent with a previous study, the number of outpatient visits increases after starting LAIs (Latorre *et al*. 2020). Furthermore, under the assumption that patients receiving LAIs are generally more adherent with medications and have frequent outpatient visits, we would anticipate an increase in the number of outpatient visits. Since patients on LAIs receive injections on a biweekly, monthly, or three-month basis, it is reasonable to have an increase in outpatient visits. In contrast, both the reviewed studies and meta-analyses showed that the number of ED visits among patients treated with LAIs were lower compared with orals. These results are also consistent with a previous study of 2302 patients with schizophrenia showing that patients on LAIs had fewer ED visits and hospitalizations compared with orals (Shah *et al*. 2018).

Healthcare costs

The reviewed results of medical costs showed that LAI users had overall lower medical costs compared with oral users. These results are consistent with a prior study (Shah *et al*. 2018) showing that the total healthcare costs among patients using LAIs decreased relative to orals. However, the pooled effect showed no signifcant difference between LAIs and orals on decreasing medical costs; and the effect varied across the included studies. An explantion for the non-difference in the meta-analysis is that one of the included studies measured the overall psychiatric service costs as medical costs, which were increased by expenses encountered from greater use of outpatient services and LAI risperidone medication costs (Fan *et al*. 2018).

On the other hand, our meta-analysis suggests that LAI use incurs higher pharmacy costs compared with orals. The higher LAI-incured pharmacy costs may be because of higher prescription costs and outpatient visits. These findings are consistent with a previous study (Higashi *et al*. 2013), which showed that LAIs were associated with better adherence, lower ED visits, and rehospitalizations, and reduced the need for clinician intervention, all of which led to decreased healthcare system costs. Thus, higher pharmacy costs incurred by LAIs may be offset by lower medical costs.

Social functioning

The review and meta-analysis showed no greater benefit of LAIs as compared with orals in the improvements of PSP and quality of Life measures. In fact, recent studies question whether long-term antipsychotic mediactions use is better than short term use in functional recovery for people who have experinced first episode psychosis (Begemann *et al*. 2020). Hence, future studies should examine the impact of long-term antipsychotic medication use and discontinuation on functional outcomes.

Limitations

This review has some limitations. First, socioeconomic status, psychiatrist's personal preferences, and patients' social support were not included as confounding factors in our review. Therefore, we cannot completely rule out the possibility that these factors may have influenced our outcomes. Second, heterogeneity may be related to inclusion of patients with different clincal features, different settings, or different study designs. Moreover, in assessing for publication bias (see supplementary materials) most of the studies had homogeneous sample sizes. For better interpertation of the data and more robust findings, studies should be heterogeneous to limit publication bias. Hence, future studies with hetergeneous samples are needed to draw firmer conclusions. Last, our target population was patients with schizophrenia and these findings cannot be generalized to those with other psychiatric disorders.

CONCLUSION

In summary, LAIs can be considered first-line treatment in regards to potentially improving individuals' medication adherence, supporting symptom remission, and decreasing the number of rehospitalizations and ED visits. However, future studies should clarify wether LAIs may be advantageous over orals in reducing the side effects associated with antipsychotic medications. In addition, given our observed variations of effect sizes in outcomes across included studies, more research is required to examine LAIs and orals across specific populations and different types of antipsychotic medications.

RELEVANCE TO CLINICAL PRACTICE

These results provide support for healthcare provider to consider LAIs (Owen *et al*. 2003) as first-line treatment in regards to improving patient medication adherence and supporting other healthcare outcomes. Overall pharmacy costs incurred by using LAIs as compared with orals may be offset by the benefits gained by reducing other factors associated with increased

medical expenditure. Clinicians can be confident in teaching patients about the risks and benefits of each antipsychotic modality when using an evidence-based approach to treat schizophrenia.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1 PRISMA flow chart illustrating the selection strategies of articles for the systematic review.

Figure S2 Forest plot of studies assessing the differences between Long-Acting Injectable (LAI) and oral antipsychotics in the proportion of patients that had 80% or more Proportion of Days Covered (PDC).

Figure S3 Forest plot of studies assessing the differences between Long-Acting Injectable (LAI) and oral antipsychotics using the Drug Attitude Inventory (DAI) scale.

Figure S4 Forest plot of studies assessing the differences between Long-Acting Injectable (LAI) and oral antipsychotics using the Positive and Negative Syndrome Scale (PANSS).

Figure S5 Forest plot of studies assessing the differences between Long-Acting Injectable (LAI) and oral antipsychotics using the Clinical Global Impressions (CGI) scale.

Figure S6 Forest plot of studies assessing the differences between Long-Acting Injectable (LAI) and oral antipsychotics using the mean number of rehospitalizations per patient.

Figure S7 Forest plot of studies assessing the differences between Long-Acting Injectable (LAI) and oral antipsychotics using the mean number of outpatient visits per patient.

Figure S8 Forest plot of studies assessing the differences between Long-Acting Injectable (LAI) and oral antipsychotics using the mean number of emergency room visits per patient.

Figure S9 Forest plot of studies assessing the differences between Long-Acting Injectable (LAI) and oral antipsychotics using the mean number of medical healthcare costs.

Figure S10 Forest plot of studies assessing the differences between Long-Acting Injectable (LAI) and oral antipsychotics using the mean number of pharmacy costs.

Figure S11 Forest plot of studies assessing the differences between Long-Acting Injectable (LAI) and oral antipsychotics using mean Personal and Social Performance (PSP) scores.

Figure S12 Prediction interval for the dispersion effect size for the PDC outcomes.

Figure S13 Prediction interval for the dispersion effect size for the PANSS outcomes

Figure S14 Prediction interval for the dispersion of true effect size for the rehospitalization outcomes.

Figure S15 Observed and imputed studies by Trim and Fill for the PDC outcomes.

Figure S16 Observed and imputed studies by Trim and Fill for the PANSS outcomes.

Figure S17 Observed and imputed studies by Trim and Fill for the rehospitalization outcomes.

Appendix S1 Search strategy with MeSh terms and keywords.

Appendix S2 Quality appraisal scores for included studies.