Real-World Comparative Effectiveness of Long-Acting Injectable and Oral Antipsychotics Among US Medicare Beneficiaries With Schizophrenia

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Introduction

- Schizophrenia is a chronic mental illness characterized by delusions, hallucinations, and other disabling psychiatric symptoms
- Continuous treatment with antipsychotic medications is crucial in the management of schizophrenia to reduce the risk of acute psychotic episodes and prevent relapse and psychiatric hospitalization[1]
- Oral antipsychotics (OAPs) have been the mainstay of schizophrenia treatment, though their effectiveness has been hindered by poor adherence[1]
- Long-acting injectable antipsychotics (LAIs) that require less frequent administration (e.g., every 1 month, every 3 months) were developed to improve medication adherence relative to daily OAPs[2]
- Little real-world evidence exists comparing the benefits of LAIs relative to daily OAPs in the Medicare population, which includes about half of US patients with schizophrenia[3]

Objective

- To compare effectiveness of LAIs and daily OAPs across different agents and dosing intervals in a national sample of Medicare beneficiaries with schizophrenia

Methods

Data source

- Data were taken from the 2006-2019 national Chronic Conditions Warehouse 100% Medicare Part A, B, and D claims and beneficiary summary files available from the Centers for Medicare and Medicaid Services

Study sample

- The sample included all fee-for-service Medicare beneficiaries with standalone Part D prescription drug coverage with schizophrenia and ≥1 antipsychotic fill between 01/01/2006 and 12/31/2019
  - Index date = first antipsychotic prescription date
- Patients were required to meet the following criteria:
  - Age ≥18 years on index date
  - Continuous fee-for-service Medicare Parts A, B, and D coverage 6 months before and after the index date

Follow-up period and treatment sub-periods

- The follow-up period for each patient was from the index date until death, transition to Medicare Advantage Prescription Drug (MAPD) plan, or December 31, 2019, whichever occurred earlier
- Each patient's follow-up period was divided into treatment periods, with a new treatment period starting on the date of change in the treatment exposure
  - The treatment periods continued until there was evidence of a ≥60-day continuous gap of the specific treatment exposure
  - Periods with a 60-day or longer continuous gap in any antipsychotic use were categorized as no antipsychotic use treatment periods
  - The treatment periods were then further divided into sub-periods, with a new sub-period starting on the day after the date of occurrence of an outcome event (see Outcomes section below)

Outcomes

- Treatment failure, the primary study outcome, was a composite measure of psychiatric hospitalization, antipsychotic discontinuation, suicide attempts, or death
  - Antipsychotic discontinuation was defined as a continuous gap of ≥60 days after the days' supply of the most recent antipsychotic prescription was exhausted
  - Psychiatric hospitalization was defined as the presence of a medical claim for an inpatient admission with a diagnosis code of a psychiatric disorder in the first or second position
- Relapse was defined as the occurrence of an inpatient admission or Emergency Room visit with a diagnosis of schizophrenia in the first or second position

Analysis

- The primary analytic approach was within-individual Cox regressions, in which each individual served as his or her own control to remove selection bias
- In the first set of analyses, we compared outcomes across all LAIs (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, and risperidone) and OAPs (first-generation antipsychotics [FGA]: fluphenazine, haloperidol, and other FGA; second-generation anti-psychotics [SGA]: aripiprazole, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone, and other SGA)
- In the second set of analyses (i.e., main analyses), we further separated the LAI agents with sufficient sample size by dosing interval: paliperidone (every month and every 3 months), aripiprazole (every month and every 1.5-2 months), and fluphenazine (every month and every 1.5 months)
- LAI haloperidol was used as the reference group in both sets of analyses
- All outcomes (**except death**) were recurrent and were treated as such in the regression models
  - Follow-up time was reset to zero after each outcome event to allow comparison of treatment sub-periods within each individual
  - The unit of analysis was the sub-period
- Given the within-individual analyses, control variables for time-invariant covariates were not required; however, we controlled for the following time-varying covariates: years from the first ever schizophrenia diagnosis date in Medicare claims until the starting date of each sub-period, number of relapses within 3 months before the starting date of a sub-period, and order of exposure (number of treatments used before this sub-period)

Results

- The final sample included 152,835 beneficiaries (mean age 53.5 years [SD: 16.7], 54.0% male, 61.5% White, **Table 1**)

TABLE 1. Baseline characteristics

Characteristics	N	%
Number of patients	152,835	100%
Age, mean (SD)	53.5 (16.7)	
≤24 years	3,557	2.3%
25 to 34 years	18,814	12.3%
35 to 44 years	25,268	16.5%
45 to 54 years	35,706	23.4%
55 to 64 years	27,096	17.7%
≥65 years	42,394	27.7%
Sex		
Female	70,271	46.0%
Male	82,564	54.0%
Race		
White	94,050	61.5%
Black	45,936	30.1%
Hispanic	6,486	4.2%
Other	6,363	4.2%
Part D low-income subsidy status		
Full LIS	130,604	85.5%
Partial LIS	1,884	1.2%
Non-LIS	20,347	13.3%
Original reason for Medicare eligibility		
Age	26,153	17.1%
Disability	126,210	82.6%
ESRD	1210	0.8%
Census region		
Midwest	35,609	23.3%
Northeast	27,656	18.1%
South	61,672	40.4%
West	27,455	18.0%
Metropolitan status		
Urban	127,216	83.2%
Rural	25,619	16.8%
Number of Elixhauser comorbidities		
0	7,348	4.8%
1 to 2	45,478	29.8%
3 to 4	39,509	25.9%
5+	60,500	39.6%

ESRD, end-stage renal disease; LIS, low-income subsidy; SD, standard deviation.

Treatment failure

- In the first set of agent-level analyses, oral clozapine (HR 0.79; 95% CI 0.76-0.82) was the only OAP associated with significantly lower hazard of treatment failure than LAI haloperidol (**data not shown**)
  - With the exception of LAI fluphenazine (HR 1.09; 95% CI 1.04-1.13) and LAI olanzapine (HR 1.56; 95% CI 1.41-1.73), all LAIs were associated with lower hazard of treatment failure (HRs 0.78-0.88) than LAI haloperidol
- In the second set of analyses further breaking out LAIs by dosing intervals, all OAPs were associated with a significantly higher hazard (HRs 1.03-1.56) of treatment failure than LAI haloperidol, with the exception of clozapine, olanzapine, paliperidone, and fluphenazine and all LAIs except aripiprazole every month (HR 0.88; 95% CI 0.83-0.93), risperidone (HR 0.81; 95% CI 0.79-0.84), and paliperidone every month (HR 0.78; 95% CI 0.75-0.80) (**Figure 1**)
  - LAI paliperidone every 3 months (HR 0.55; 95% CI 0.49-0.62) had the lowest hazard of failure compared with LAI haloperidol

Antipsychotic discontinuation

- Compared with LAI haloperidol, nearly all OAPs were associated with lower hazard of antipsychotic discontinuation (HRs 0.67-0.94), the only exceptions being oral haloperidol (HR 0.96; 95% CI 0.92-1.01), oral lurasidone (HR 0.96; 95% CI 0.90-1.04), and other oral SGA (HR 1.05; 95% CI 0.96-1.14) (**Figure 2**)
- LAI fluphenazine every month (HR 1.58; 95% CI 1.47-1.71) was the only LAI associated with a significantly higher odds of antipsychotic discontinuation than LAI haloperidol
  - LAI paliperidone every 3 months (HR 0.17; 95% CI 0.13-0.21) had the lowest hazard of antipsychotic discontinuation compared with LAI haloperidol

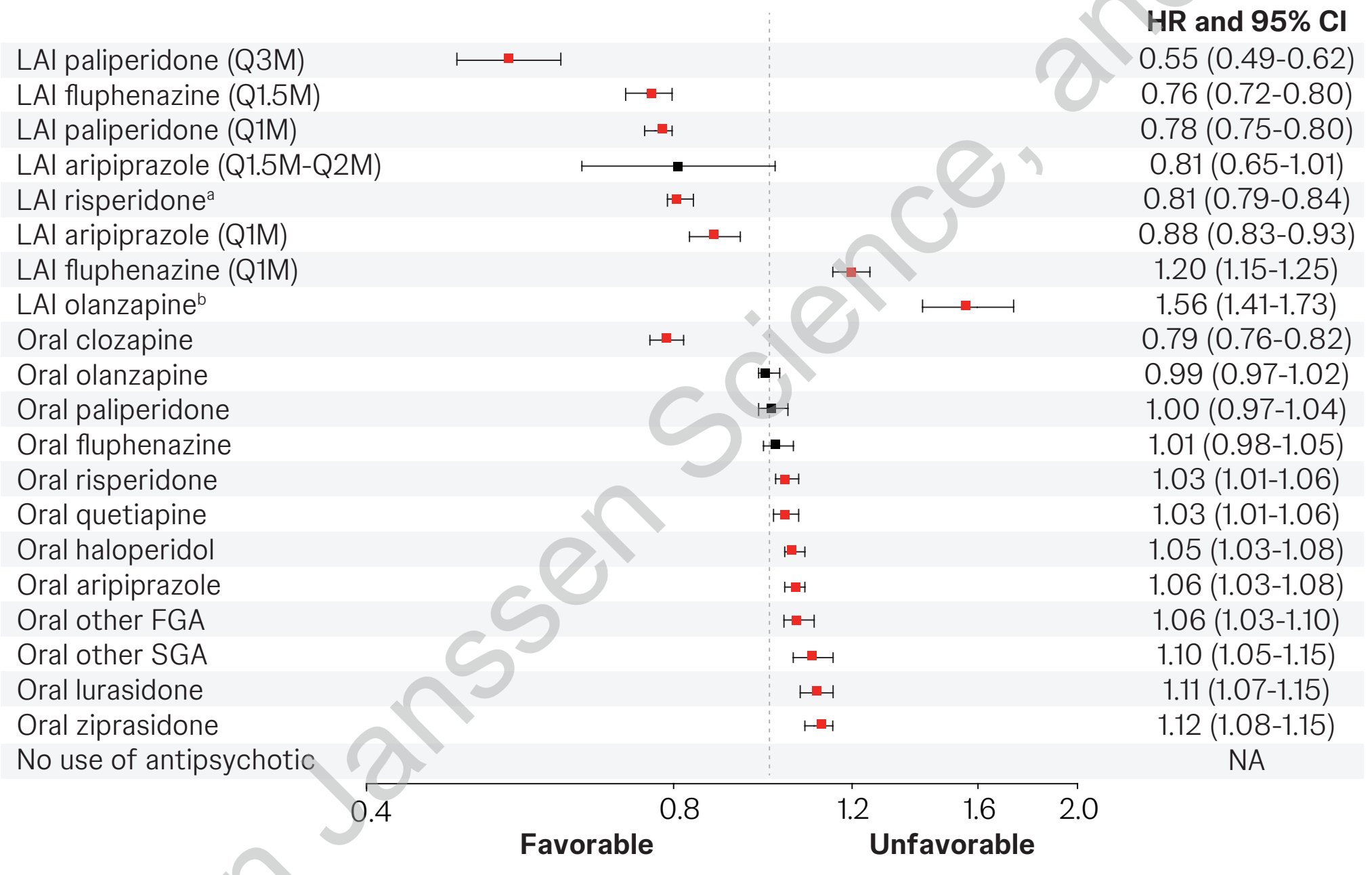
Psychiatric hospitalization

- Compared with LAI haloperidol, all OAPs except oral clozapine (HR 0.92; 95% CI 0.88-0.96) were associated with a significantly higher hazard of psychiatric hospitalization (**Figure 3**)
- Compared with LAI haloperidol, LAI olanzapine (HR 2.13; 95% CI 1.91-2.37) and LAI aripiprazole every month (HR 1.08; 95% CI 1.01-1.16) were associated with a significantly higher risk of psychiatric hospitalization
- LAI paliperidone every month (HR 0.93; 95% CI 0.89-0.97) was the only LAI associated with a significantly lower hazard of psychiatric hospitalization relative to LAI haloperidol

Relapse

- Compared with LAI haloperidol, all OAPs except oral clozapine (HR 0.96; 95% CI 0.93-0.99) were associated with a significantly higher hazard of relapse (**Figure 4**)
- LAI paliperidone every month (HR 0.94; 95% CI 0.91-0.97) and LAI paliperidone every 3 months (HR 0.84; 95% CI 0.76-0.94) were the only LAIs with a significantly lower hazard of relapse than LAI haloperidol

FIGURE 1. Within individual Cox regressions using LAI haloperidol as reference [end point: treatment failure]



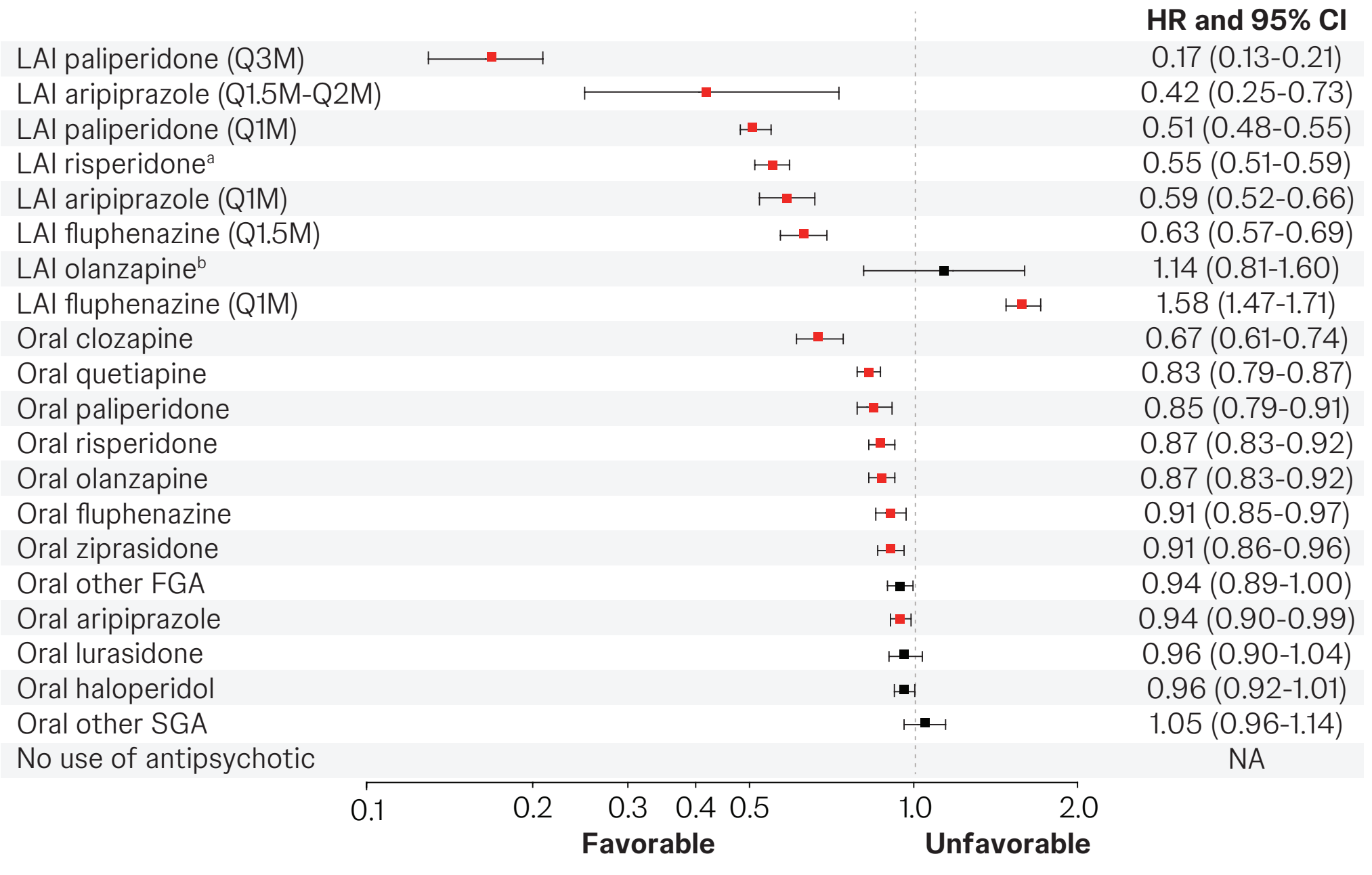
FGA, first-generation antipsychotic; HR, hazard ratio; LAI, long-acting injectable; NA, not available; QXM, every X months; SGA, second-generation antipsychotic.

[a]Although use of biweekly and monthly LAI risperidone formulations were observed in our study, the vast majority (>99%) of LAI risperidone use was for the biweekly formulation (i.e., every 2 weeks).

[b]Although use of biweekly and monthly LAI olanzapine formulations were observed in our study, the vast majority (>83%) of LAI olanzapine use was for the monthly formulation (i.e., Q1M).

Red squares highlight statistically significant HRs, while black squares are HRs that did not reach statistical significance.

FIGURE 2. Within individual Cox regressions using LAI haloperidol as reference [end point: antipsychotic discontinuation]



FGA, first-generation antipsychotic; HR, hazard ratio; LAI, long-acting injectable; NA, not available; QXM, every X months; SGA, second-generation antipsychotic.

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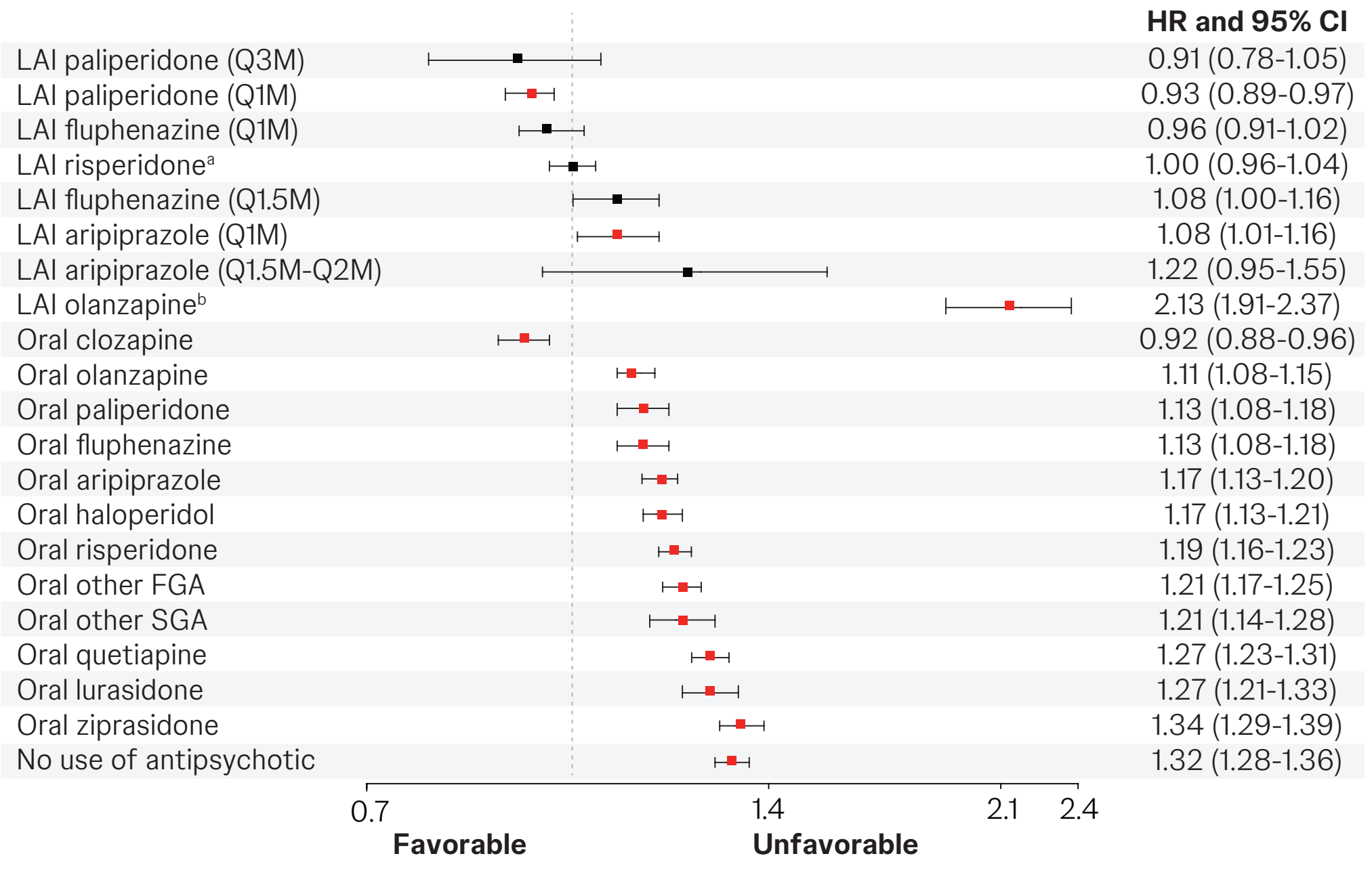
FIGURE 3. Within individual Cox regressions using LAI haloperidol as reference [end point: psychiatric hospitalization]



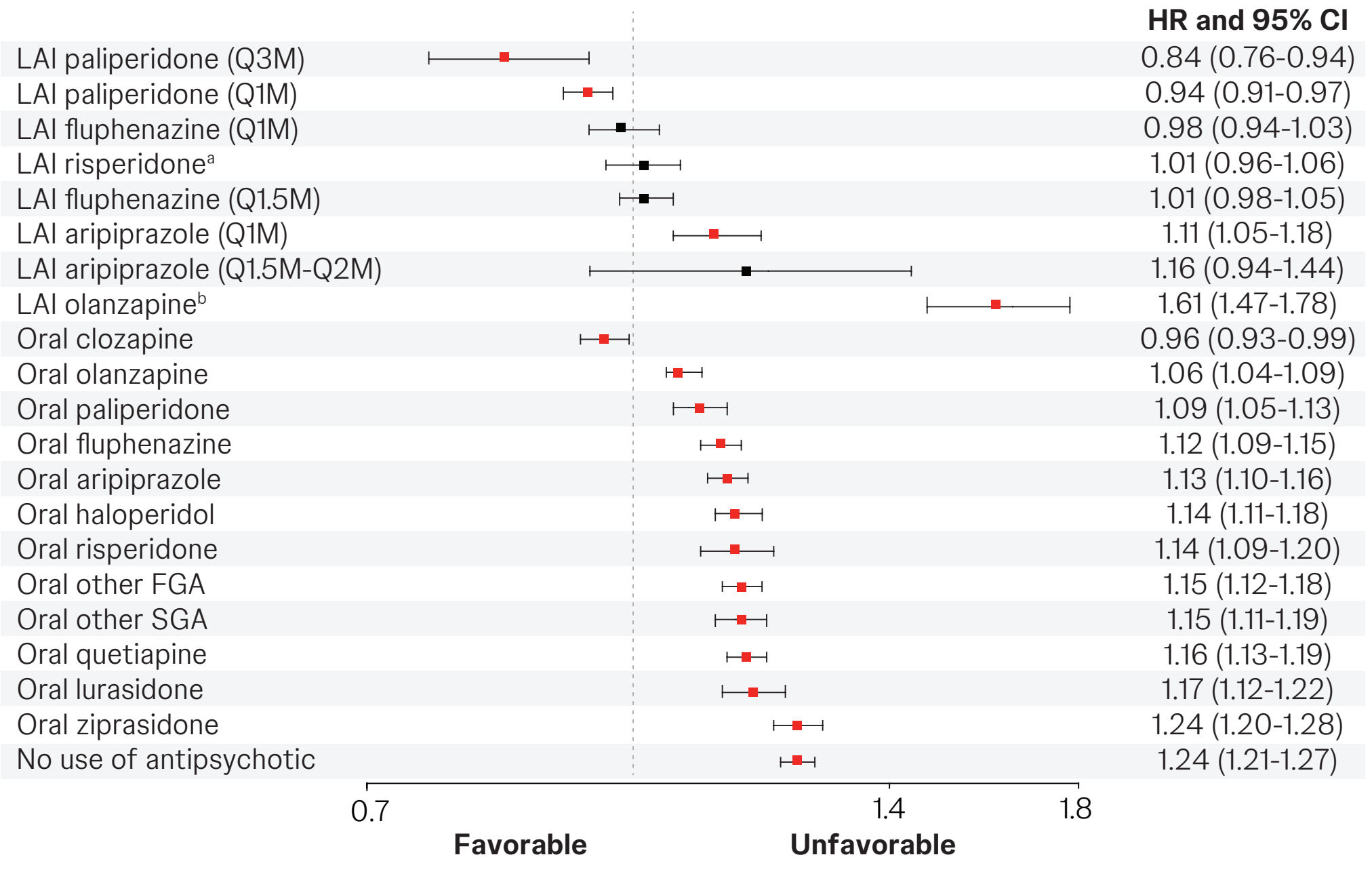
FGA, first-generation antipsychotic; HR, hazard ratio; LAI, long-acting injectable; NA, not available; QXM, every X months; SGA, second-generation antipsychotic.

[a]Although use of biweekly and monthly LAI risperidone formulations were observed in our study, the vast majority (>99%) of LAI risperidone use was for the biweekly formulation (i.e., every 2 weeks).

[b]Although use of biweekly and monthly LAI olanzapine formulations were observed in our study, the vast majority (>83%) of LAI olanzapine use was for the monthly formulation (i.e., Q1M).

Red squares highlight statistically significant HRs, while black squares are HRs that did not reach statistical significance.

FIGURE 4. Within individual Cox regressions using LAI haloperidol as reference [end point: relapse]



FGA, first-generation antipsychotic; HR, hazard ratio; LAI, long-acting injectable; NA, not available; QXM, every X months; SGA, second-generation antipsychotic.

[a]Although use of biweekly and monthly LAI risperidone formulations were observed in our study, the vast majority (>99%) of LAI risperidone use was for the biweekly formulation (i.e., every 2 weeks).

[b]Although use of biweekly and monthly LAI olanzapine formulations were observed in our study, the vast majority (>83%) of LAI olanzapine use was for the monthly formulation (i.e., Q1M).

Red squares highlight statistically significant HRs, while black squares are HRs that did not reach statistical significance.

Limitations

Our study is only generalizable to the fee-for-service Medicare population with standalone Part D coverage and not other insurance types (Medicaid, commercial, etc.)

Our within-individual Cox regressions controlled for observed and unobserved time-invariant confounders as well as observed time-varying confounders, but we cannot rule out the possibility of unobserved time-varying confounders that could bias our results

Conclusions

✓ This real-world comparative effectiveness study found that most OAPs were associated with a significantly higher risk of treatment failure, psychiatric hospitalization, and relapse than LAI haloperidol
  - Additionally, virtually all OAPs had a lower risk of antipsychotic discontinuation relative to LAI haloperidol

✓ Several LAIs showed a greater benefit relative to LAI haloperidol for all outcome measures studied

✓ LAI paliperidone every 3 months, the LAI with the longest dosing interval, had the lowest risk of treatment failure, antipsychotic discontinuation, and psychiatric hospitalization

Disclosures

Dr Li received personal fees from Cobbs Creek Healthcare and SKB Consulting Inc. unrelated to the work. Ms Benson and Ms Patel are employees of Janssen Scientific Affairs, LLC , a Johnson & Johnson company, and stockholders of Johnson and Johnson. Dr Doshi received grants from Janssen Scientific Affairs, LLC, a Johnson & Johnson company, during the conduct of the study; personal fees from AbbVie, Acadia, Janssen, Merck, Otsuka, and Takeda; and grants from Merck and Spark Therapeutics unrelated to the work. No other authors reported disclosures.

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