Predictors for Initiation of Atypical Long-Acting Injectable Antipsychotic Agents in a Commercial Claims Cohort of Individuals With Early-Phase Schizophrenia

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ABSTRACT

Objective: Long-acting injectable antipsychotic agents (LAIs) have improved clinical effectiveness and adherence versus oral antipsychotic agents (OAs); however, a minority of individuals with schizophrenia are treated with LAIs compared with OAs. This cohort study aimed to evaluate predictors of initiation of atypical LAIs among patients with newly diagnosed schizophrenia in the United States.

Methods: Using claims data from IBM MarketScan Commercial and Medicare Supplemental databases between January 1, 2013, and March 31, 2020, adults with first diagnosis of schizophrenia, ≥ 1 OA claim following diagnosis, and continuous benefits were identified. To evaluate predictors of LAI initiation, a Cox proportional hazard regression model per independent predictors and main outcome (ie, LAI initiation) was performed.

Results: Of 3,639 patients with early-phase schizophrenia, 369 (10%) had ≥ 1 LAI claim(s) after ≥ 1 OA claim(s). Several factors present prior to LAI initiation were significantly ($P < .0001$) predictive of LAI initiation: greater monthly OA switches (hazard ratio [95% CI]: 11.39 [7.01–18.51]), unsuccessful OA implementation (3.09 [2.39–3.98]), greater monthly schizophrenia-related hospitalizations (20.83 [14.22–30.51]), and greater monthly schizophrenia-related emergency department visits (4.13 [2.07–8.22]).

Conclusions: In this analysis of pharmacy claims records for patients with early-phase schizophrenia, results suggest that LAIs are used less frequently in the early phase than reported in later stages. Their initiation is often reactive to relapse or disease exacerbation, rather than proactive as a relapse-prevention tool for early-phase schizophrenia. These data highlight the underuse of LAIs, particularly in the early phase when they could make the most difference.

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Schizophrenia is a serious, chronic psychiatric disease characterized by impaired perception, cognition, emotional expression, and social interactions, with symptoms including delusions, hallucinations, and impaired communication and function.[1,2] Schizophrenia affects approximately 1% of adults in the United States and is associated with a substantial burden of illness, being ranked among the top 20 illnesses that contribute to the total global burden of disease.[2,3]

Since the 1950s, oral antipsychotic agents (OAs) have been the mainstay therapy for patients with schizophrenia.[4,5] However, there has been a growing recognition of the challenges of adherence with OAs, along with the need for long-term maintenance treatments to prevent relapse in schizophrenia.[6,7] It is estimated that about half of individuals receiving treatment for schizophrenia may not be taking medicines as prescribed at any given time.[8] However, certainty of adherence is very difficult in routine care, with clinician assessment for nonadherence being only marginally superior to chance.[9] In this context, there has been growing evidence of the superiority of long-acting injectable antipsychotic agents (LAIs) for relapse prevention[10,11] and probable reduction in premature mortality.[12] This is particularly relevant for the early phase of the illness, before several relapses have occurred. There is a growing body of published evidence indicating not only that relapse may undo the progress made toward recovery and make returning to work or school more challenging in the short term,[13] but also that treatment response to antipsychotic medicines may be diminished after each relapse, as shown by lower response rates for the treatment of the second episode (ie, relapse) compared with the first episode.[14] In addition, the need for increased doses of antipsychotic drugs after each relapse suggests diminishing effectiveness of these medications for these patients.[15] This evidence has supported a paradigm shift for the utilization of LAI formulations, from use in only patients who have demonstrated nonadherence and experienced numerous relapses to expanding use to those who are earlier in the course of illness to prevent relapses while there is still better functioning and greater chance for recovery.[16–19]

Despite the growing consistency of the evidence in support of LAI formulations, the use of these agents has remained relatively low, with most of the data being

Clinical Points

- A dataset of mainly commercially insured patients with schizophrenia was analyzed to evaluate the initiation of long-acting injectable antipsychotic agents (LAIs) among young adults with first-episode schizophrenia.
- These data indicate that LAI utilization rates among individuals with first-episode schizophrenia were lower than those previously reported and in contrast with most treatment recommendations.
- Our data support previous findings that LAI use tends to follow reactive, rather than proactive, implementation in individuals with early-phase schizophrenia who may benefit the most from the relapse-prevention effects of LAIs.

derived from public insurance records, which generally reflect individuals in the chronic phase instead of those in the early phase of illness who tend to still be on private insurance. Currently, LAIs are used by only 13%–28% of adults receiving treatment for schizophrenia paid for by Medicaid in the United States,[20] with great geographic variability in their use.[21] Ethnographic research on the barriers to the use of LAIs has identified factors related to administrative obstacles, ineffective communication when presenting these options to patients and caregivers, and insufficient knowledge by the caregiving team about the advantages of these formulations.[22,23] Previous research on patient-related factors associated with low utilization rates of LAIs has focused on predictors of discharge from inpatient hospitalization on LAI formulations, including longer duration of illness, more previous hospitalizations, poorer insight, and demonstrated history of nonadherence,[24] as well as on premature discontinuation, with shorter time since diagnosis and lower educational status.[25–27]

Although there has been an increase in recognition of LAI benefits earlier in the course of illness, to our knowledge, there are no data on patient-level predictors of the initiation of LAIs in the early phase of psychosis in a large cohort from the United States. In this analysis, we leveraged the IBM Watson MarketScan Commercial and Medicare Supplemental databases, which reflect pharmacy claims from private insurance for individuals in the United States and provide additional information than that derived from public insurance records to study early-phase psychosis, assess the demographic and clinical characteristics of patients with a new schizophrenia diagnosis who used an LAI compared with those who did not, and examine predictors associated with initiation of an LAI.

METHODS

Study Design

In this cohort study, patients in the IBM Watson MarketScan Commercial and Medicare Supplemental databases aged 18–40 years with newly diagnosed schizophrenia (*International Classification of Diseases* [*ICD*] codes 295.0–3, 295.5–6, 295.8–9 [*ICD-9*] or F20.0–3, F20.5, F20.89, F20.9 [*ICD-10*]) between January 1, 2013, and March 31, 2020 (index date), no schizophrenia diagnosis or OA or LAI claims in previous 12 months (to confirm patients were newly diagnosed with schizophrenia), and at least 1 OA claim (first OA date) after the index date were identified. To confirm eligibility and be able to assess outcomes of interest, patients must have had either continuous medical and pharmacy benefits from 12 months before the index date (≤ 30-day gaps allowed) through the initiation of the first LAI (LAI group) or the last date of continuous enrollment after first OA date (non-LAI group). The IBM MarketScan Commercial Database contains medical and pharmacy claims data for individuals enrolled in fee-for-service, partially capitated, and fully capitated commercial health plans.[28] In addition, the IBM MarketScan Medicare Supplemental Database captures data for medical and pharmacy claims for individuals enrolled in Medicare Supplemental health plans.[28]

Patients were grouped according to their LAI use. The LAI group comprised patients who had at least 1 LAI claim after the index date, with the date of initiation of the first LAI on or after the first OA date. The non-LAI group comprised patients who had no LAI claim on or after index date. OAs included aripiprazole (Abilify, oral only), asenapine (Saphris), brexpiprazole (Rexulti), cariprazine (Vraylar), clozapine (Clozaril), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa), paliperidone (Invega, oral only), quetiapine (Seroquel), risperidone (Risperdal, oral only), and ziprasidone (Geodon). LAIs included aripiprazole (Abilify Maintena, Aristada), paliperidone (Invega Sustenna, Invega Trinza), risperidone (Risperdal Consta, Perseris), and olanzapine (Zyprexa).

Covariates and Outcomes

Demographic and clinical characteristics are described for patients overall and in the LAI and non-LAI groups. Demographic characteristics were recorded as of the index date and include patient age, age group, sex, insurance status, region, total follow-up days, Charlson Comorbidity Index (CCI),[29,30] number of monthly OA switches (between index date and first LAI [LAI group] or end of continuous enrollment [non-LAI group]), successful implementation of OA (treatment ≥ 90 consecutive days with ≤ 7-day gaps),[31,32] number of treatment discontinuations (no OA treatment for > 30 days), and monthly schizophrenia-related hospitalization and emergency department (ED) visits between index date and the first LAI (LAI group) or end of continuous enrollment (non-LAI group).

Statistical Analysis

All study variables were initially examined descriptively; continuous variables were summarized by mean, standard deviation (SD), median, and interquartile range (IQR) unless otherwise specified. Categorical variables were summarized by frequency (number [n]) and proportion (%) of patients observed in each category.

A full model and a multivariable model (determined through stepwise selection) were used as a sensitivity

Table 1. Selection of Study Population (Attrition Table)[a]

	Overall	
Patients in the IBM MarketScan databases between January 1, 2012, and March 31, 2020	98,416,202	
Patients with a schizophrenia diagnosis between January 1, 2013, and March 31, 2020	79,509	
Patients with no schizophrenia diagnosis *and* no LAI or OA claim during 12-month pre-index period	43,390	
Patients aged 18–40 years at index date	19,762	
Patients with ≥ 1 OA claim after index date	8,751	
	LAI	Non-LAI
Patients with ≥ 1 LAI claim after an OA claim *or* with no LAI claims after index date	769	7,771
Patients with continuous (< 30-day gap) enrollment with medical and pharmacy benefits 12 months before the index date to the date of initiation of first LAI ***or*** from 12 months before index date to the last date of enrollment after first OA	369	3,270

[a]Index date was the date of the first diagnosis of schizophrenia (*International Classification of Diseases* [*ICD*] codes 295.0–3, 295.5–6, 295.8–9 [*ICD-9*] or F20.0–3, F20.5, F20.89, F20.9 [*ICD-10*]) between January 1, 2013, and March 31, 2020.
Abbreviations: LAI = long-acting injectable antipsychotic agent, OA = oral antipsychotic agent.

analysis. Time-to-event survival analysis was performed for the entire cohort, where the event was the initiation of the LAI. Patients who did not use an LAI during the observation period were censored at the end of follow-up. In the full model, the independent predictors included age, sex, insurance type, region, CCI score, number of monthly OA switches, number of treatment discontinuations, successful implementation of OA(s), monthly schizophrenia-related hospitalizations, and monthly schizophrenia-related ED visits. In the selected model, the independent predictors included through stepwise regression were only a subset of those included in the full model: sex, region, number of monthly OA switches, successful implementation of OA(s), and monthly schizophrenia-related hospitalizations and ED visits. Both models were tested in order to cross-validate the results. Hazard ratios (HRs) and 95% confidence intervals were calculated.

RESULTS

Of 98,416,202 patients in the IBM MarketScan databases, 369 patients (10.1%) fit the criteria for the LAI group and 3,270 patients (89.9%) fit the criteria for the non-LAI group (Table 1). Of the 3,639 patients included in the analysis, 54.5% were aged 18–23 years, while only 8.7% of patients were aged 36–40 years. The mean age (SD) was 24.8 (5.71) years, which was similar between the LAI and non-LAI groups (23.7 [4.78] and 24.9 [5.79], respectively). Regionally, the largest number of patients resided in the South (35.5% LAI, 42.7% non-LAI), followed by the North central region for the LAI group (27.1%), and the West for the non-LAI group (19.6%) (Table 2).

Over half of total patients (54.1%) used a preferred provider organization (PPO) for insurance, which was reflected in both the LAI (55.8%) and non-LAI (53.9%) groups. The second most common insurance type was a consumer-directed health plan for the LAI group (11.9%) and a health maintenance organization (HMO) for the non-LAI group (13.2%; Table 2). As expected, more patients in the non-LAI group experienced successful implementation (treatment ≥ 90 consecutive days with ≤ 7-day gaps) of an OA as first atypical antipsychotic used after diagnosis (42.5%) compared with the LAI group (22.2%). Total follow-up days, Charlson Comorbidity Index score, number of monthly OA switches per patient, number of treatment gaps per patient, and monthly hospital and emergency care rates are presented in Table 2.

When the effects of baseline demographic and clinical characteristics were assessed by Cox proportional hazard regression with the full model, the predictors at baseline of LAI initiation that were the most statistically significant ($P < .0001$) were greater number of monthly OA switches (HR [95% CI]: 11.39 [7.0–18.5]; $P < .0001$); unsuccessful OA implementation (treatment < 90 consecutive days with ≤ 7-day gaps; 3.09 [2.39–3.98]; $P < .0001$); higher monthly schizophrenia-related hospitalization rate from index date to the first LAI (LAI group) or end of continuous enrollment (non-LAI group) (20.83 [14.22–30.51]; $P < .0001$); and higher monthly schizophrenia-related ED visit rate (4.13 [2.07–8.22]; $P < .0001$; Figure 1). Another significant predictor was being male (1.30 [1.01–1.68]; $P = .0405$; Figure 1).

After controlling for other variables (eg, age, sex, insurance types), being from the North Central region of the United States (1.49 [1.13–1.96]; $P = .0045$), being from the Northeast (1.50 [1.13–2.00]; $P = .005$), or being from location "unknown" (2.98 [1.20–7.36]; $P = .0182$) were significant in reference to the South. After controlling for other variables, HMO insurance was a predictor for lower likelihood of LAI initiation in reference to PPO insurance (0.65 [0.44–0.97]; $P = .0367$; Figure 1). The full and selected models produced similar results (Figure 1 and Supplementary Figure 1).

DISCUSSION

This cohort study was designed to identify predictors for initiation of LAI treatment in patients newly diagnosed with schizophrenia. The main findings included LAI utilization rates that were lower than those previously reported in patients with multiple-episode schizophrenia,[21] and their use being reactive to impending or current relapse, as opposed to a proactively implemented treatment that could delay relapse in schizophrenia.

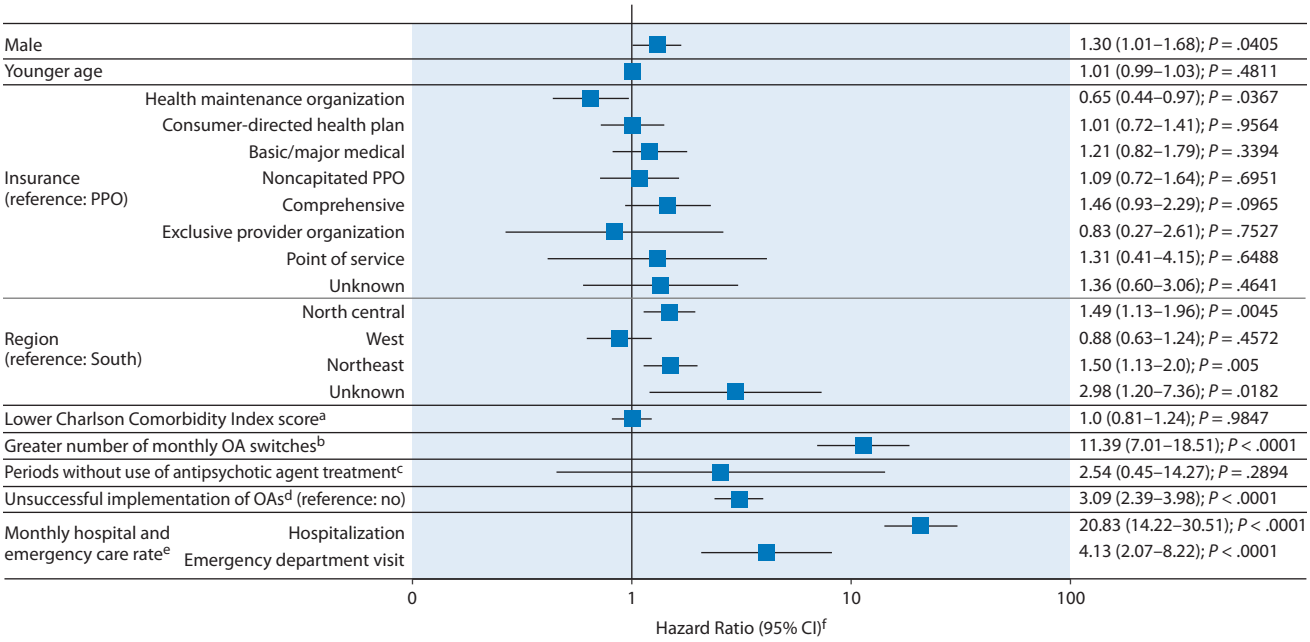
Table 2. Demographic and Clinical Characteristics for Overall Group

Characteristic	Overall (N = 3,639)	LAI group (n = 369)	Non-LAI group (n = 3,270)
Female, n (%)	1,122 (30.8)	83 (22.5)	1,039 (31.8)
Age, y			
Mean (SD)	24.8 (5.71)	23.7 (4.78)	24.9 (5.79)
Median (IQR)	23 (5)	22 (4)	23 (6)
Age group, n (%)			
18–23 y	1,983 (54.5)	225 (61.0)	1,758 (53.8)
24–29 y	948 (26.1)	96 (26.0)	852 (26.1)
30–35 y	392 (10.8)	36 (9.8)	356 (10.9)
36–40 y	316 (8.7)	12 (3.3)	304 (9.3)
Insurance type, n (%)			
PPO	1,970 (54.1)	206 (55.8)	1,764 (53.9)
Health maintenance organization	461 (12.7)	28 (7.6)	433 (13.2)
Consumer-directed health plan	446 (12.3)	44 (11.9)	402 (12.3)
Basic/major medical	282 (7.8)	30 (8.1)	252 (7.7)
Noncapitated PPO	236 (6.5)	26 (7.0)	210 (6.4)
Comprehensive	121 (3.3)	23 (6.2)	98 (3.0)
Exclusive provider organization	48 (1.3)	3 (0.8)	45 (1.4)
Point of service	25 (0.7)	3 (0.8)	22 (0.7)
Unknown	50 (1.4)	6 (1.6)	44 (1.3)
Region, n (%)			
South	1,528 (42.0)	131 (35.5)	1,397 (42.7)
North central	726 (20.0)	100 (27.1)	626 (19.1)
West	694 (19.1)	52 (14.1)	642 (19.6)
Northeast	663 (18.2)	81 (22.0)	582 (17.8)
Unknown	28 (0.8)	5 (1.4)	23 (0.7)
Total follow-up days[a]			
Mean (SD)	702.69 (566.42)	403.23 (417.45)	736.48 (571.11)
Median (IQR)	565.00 (762.00)	294.00 (516.00)	594.50 (767.00)
Charlson Comorbidity Index score[b,c]			
Mean (SD)	0.17 (0.597)	0.14 (0.547)	0.18 (0.602)
Median (IQR)	0 (0)	0 (0)	0 (0)
No. of monthly OA switches per patient[d]			
Mean (SD)	0.046 (0.128)	0.11 (0.285)	0.039 (0.0926)
Median (IQR)	0 (0.0506)	0.017 (0.111)	0 (0.0457)
No. of treatment gaps per patient[e]			
Mean (SD)	0.07 (0.07)	0.06 (0.08)	0.07 (0.07)
Median (IQR)	0.05 (0.09)	0.03 (0.10)	0.05 (0.08)
Successful implementation of OAs,[f] n (%)	1,473 (40.5)	82 (22.2)	1,391 (42.5)
Monthly hospital and emergency care rate[g]			
Hospitalization			
Mean (SD)	0.060 (0.2191)	0.214 (0.4421)	0.043 (0.1686)
Median (IQR)	0.00 (0.042)	0.052 (0.161)	0.00 (0.033)
Emergency department visit			
Mean (SD)	0.023 (0.5105)	0.115 (1.5874)	0.012 (0.0723)
Median (IQR)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)

[a]Follow up days = follow up end date—index date.
[b]For preindex period.
[c]For the Charlson Comorbidity Index, a score of 0 indicates that no comorbidities were found; a higher score indicates a higher risk of death within 1 year of hospitalization.
[d]Between the index date and the first LAI (for LAI group) or end of continuous enrollment (for non-LAI group).
[e]Interruption of OA treatments for > 30 days.
[f]Treatment with an OA for ≥ 90 consecutive days, allowing ≤ 7-day gap between each fill.
[g]Calculated from the index date to the date of initiation of first LAI (for LAI group) or the last date of continuous enrollment (for non-LAI group).
Abbreviations: IQR = interquartile range, LAI = long-acting injectable antipsychotic agent, OA = oral antipsychotic agent, PPO = preferred provider organization, SD = standard deviation.

These data are an important addition to the literature on the patterns of LAI use for schizophrenia in the United States. Unlike data from other countries with national registries, most of the representative data in the United States have been derived from public insurance claims, which cover only a subset of individuals, most often those who are chronically ill. Therefore, this work provides timely data on medication use patterns during the initial years of treatment. This early period is perhaps the most important decision point in the long-term course of the illness, because with each relapse, there may be decrements in treatment responsiveness.[14,15] Previous studies on individuals with multiple-episode schizophrenia reported variability in the use of LAIs by demographic factors; however, in all cases, the utilization rates were rarely > 20%,[21,33] which contrasts with the > 80% of individuals who develop several relapses over their course of illness.[34] In addition, the clinical factors that were most predictive of LAI use in these previous studies were similar to our results and also related to lower treatment effectiveness and history of previous relapses. These identified predictors

Figure 1. Effect of Demographic and Clinical Factors on Initiation of an LAI (Cox Proportional Hazard Regression—Full Model)



[a]For preindex period.
[b]Between the index date and the first LAI (for LAI group) or end of continuous enrollment (for non-LAI group).
[c]Interruption of any antipsychotic agent treatments for > 30 days.
[d]Treatment with an OA for ≥ 90 consecutive days, allowing ≤ 7-day gap between each fill.
[e]Calculated from index date to the date of initiation of first LAI (for LAI group) or the last date of continuous enrollment (for non-LAI group).
[f]The x-axis represents a logarithmic scale. The hazard ratio evaluates the predictors of an LAI initiation at any point in time in the LAI group compared with non-LAI group; hazard ratio greater than 1 means that independent variable was better to initiate LAI use in 1 of the groups; hazard ratio of 1 means that there is no difference in survival between the 2 groups.
Abbreviations: CI = confidence interval, LAI = long-acting injectable antipsychotic agent, OA = oral antipsychotic agent, PPO = preferred provider organization.

suggest that LAIs are used for a minority of individuals and generally as a reaction to having had multiple previous relapses, instead of as a prophylactic treatment before there have been several relapses. Therefore, it is not surprising that these data available for the treatment of the early phase of the illness reflect reduced use compared with later stages of illness, or that the predictors of LAI use are related to lack of treatment effectiveness. Overall, these results are in contrast to the current recommendation to consider LAI use for all patients (including those with first-episode psychosis and early-stage schizophrenia).[35]

This study benefited from a stringent age range (18–40 years) that increased the likelihood of capturing patients with newly diagnosed schizophrenia soon after a first episode of psychosis. Treatment choices in this patient population can have substantial effects on clinical outcomes as small gaps in treatment can significantly reduce the time to relapse.[36] Unlike other retrospective analyses that have used Medicare and/or Medicaid databases and, therefore, likely capture data for an older and/or unemployed population, the use of a commercially insured patient population in this study increased the likelihood of capturing younger patients (ie, patients with newly diagnosed schizophrenia), who were more likely to be employed and/or still on their parent's insurance plan.

There were several limitations in this study. As with all retrospective database analyses, some patients, characteristics, or services may not have been captured because of suboptimal coding and/or chart entry. The lack of coding for race and ethnicity in the MarketScan databases did not allow these analyses to evaluate well-established racial and ethnic disparities in populations of patients who are diagnosed with first-episode psychosis.[37] In addition, basing OA use on filled prescriptions may also have resulted in an overestimation of use as patients may have not taken all the provided medication before the next fill. Conversely, the strict eligibility criteria of this study (ie, patients aged 18–40 years with ≥ 1 OA claim) that aimed to identify comprehensive treatment histories of young patients with newly diagnosed schizophrenia may have excluded many patients who might have received additional treatment or health care that were not captured in insurance claim data provided by the MarketScan databases. Furthermore, the age criteria of this study may have excluded even more patients; a recent study suggests that a substantial proportion of patients receive their first diagnosis of schizophrenia outside the age range of 18–40 years.[38] During the patient selection process, many patients were identified to be diagnosed with newly diagnosed schizophrenia. However, most of these patients may have limited medical histories on the MarketScan databases because many were not identified to have ≥ 1 OA claim following a new diagnosis. In addition, the severity of schizophrenia was not able to be captured in these analyses and may have influenced the number of monthly OA

switches. Two key flaws with stepwise regression may have also been limitations in this study. First, stepwise regression underestimates certain combinations of variables; because the method adds or removes variables in a certain order, results could include combinations of predictors that could be determined by that order. These combinations of variables may not represent a real-world clinical setting. Second, the stepwise regression model is often selected out of the many possible models by statistical software and will often fit the data set that was analyzed much better than a new data set because of sample variance. However, stepwise regression methods can help to identify possible predictors.

These data suggest that despite increased awareness and discussion around the appropriate use of LAIs for first-episode psychosis and early-stage schizophrenia in therapeutic guidelines,[35] most patients are prescribed an LAI only after OA treatment failure and/or a substantial number of hospitalizations or ED visits, which follows older treatment approaches.[2] LAI implementation after first-episode psychosis should be considered for all patients because LAIs have been shown to increase patient quality of life and reduce the number of relapses and hospitalizations.[10,37] Further, several studies have shown that when informed about LAIs, many patients will accept and might prefer them.[22,39–41]

In conclusion, in this cohort study, we add to the findings about the patterns of LAI use for schizophrenia, showing that in contrast with most recommendations and previous literature, these formulations are markedly underused in individuals who may benefit the most from the relapse-prevention effects of LAIs, such as those with early-phase schizophrenia. Furthermore, LAI use tends to follow a reactive, rather than proactive, implementation. These data indicate that, in general, LAIs are underused in schizophrenia, particularly among patients experiencing the early phase of illness.

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Supplementary Material

Article Title: Predictors for Initiation of Atypical Long-Acting Injectable Antipsychotic Agents in a Commercial Claims Cohort of Individuals With Early-Phase Schizophrenia

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List of Supplementary Material for the article

1. Figure 1 — Effect of Demographic and Clinical Factors on Initiation of an LAI (Cox Proportional Hazard Regression—Select Model)

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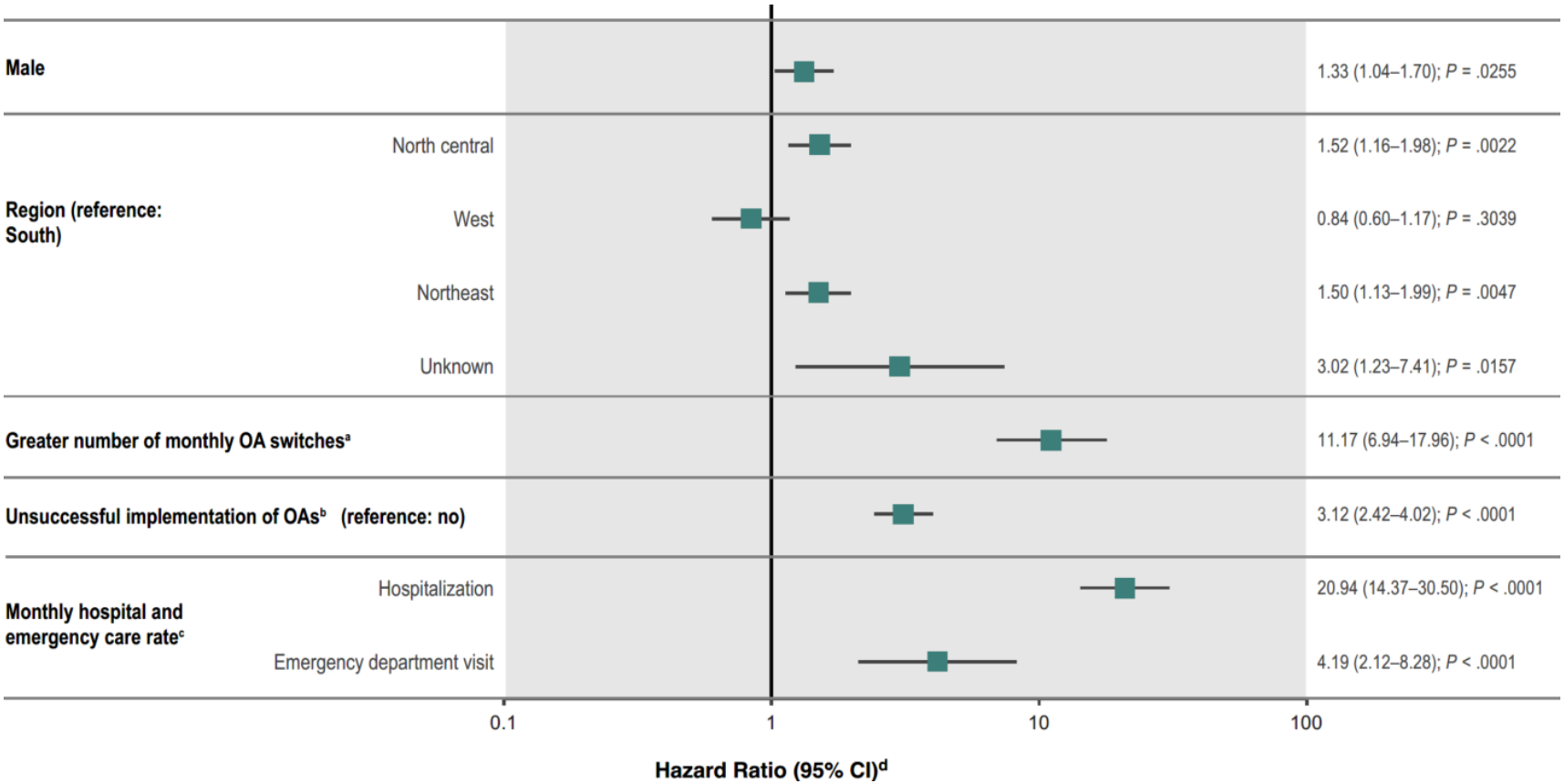
Predictors for Initiation of Atypical Long-Acting Injectable Antipsychotic Agents in a Commercial Claims Cohort of Individuals With Early-Phase Schizophrenia

Supplementary Figure 1: Effect of Demographic and Clinical Factors on Initiation of an LAI (Cox Proportional Hazard Regression—Select Model)



[a]Between the index date and the first LAI (for LAI group) or end of continuous enrollment (for non-LAI group). [b]Treatment with an OA for ≥ 90 consecutive days, allowing ≤ 7-day gap between each fill. [c]Calculated from index date to the date of initiation of first LAI (for LAI group) or the last date of continuous enrollment (for non-LAI group). [d]Hazard rate can only be inferred in a probabilistic sense from the occurrence of events in a population of at-risk individuals during a follow up time interval.
The x-axis represents a logarithmic scale.
Abbreviations: CI = confidence interval, LAI = long-acting injectable antipsychotic agent, OA = oral antipsychotic agent.