Noninterventional, Naturalistic, Retrospective Study to Describe Prescription Patterns of Long-Acting Injectable Antipsychotics and the Impact of Introducing a New Atypical Antipsychotic in the Spanish Province of Tarragona Catchment Area

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ABSTRACT

Background: We studied the patterns and predictors of long-acting injectable (LAI) antipsychotic (AP) use in the treatment of schizophrenia and the effect of introducing a new LAI (paliperidone palmitate [paliperidone-LAI]) in the Spanish province of Tarragona.

Methods: This noninterventional, naturalistic, retrospective study included electronic medical record data from a large population-based database of 1,646 patients who were diagnosed with schizophrenia according to *ICD-10* criteria and treated between January 2011 and December 2013.

Results: During the study period, 42.0% of patients were treated with an LAI AP. The most frequently prescribed initial LAI was risperidone (52.0% of patients). A total of 23% of patients initially treated with an oral AP were switched to an LAI AP, a change that was associated with younger age ($P = .001$), undifferentiated schizophrenia ($P = .015$), substance abuse ($P < .001$), and neuropsychiatric comedication with the following agents: anticonvulsants ($P = .004$), anticholinergics ($P < .001$), and hypnotics/sedatives ($P = .03$). The change from an oral AP to paliperidone-LAI was predicted by younger age ($P < .001$). Overall, 27.5% of patients switched to another LAI AP, and paliperidone-LAI was the preferred option in 64.7% of cases. The most frequent change involved patients taking risperidone-LAI, many of whom transitioned to paliperidone-LAI (85.0% of cases), particularly patients with a disease duration > 5 years ($P = .019$).

Conclusions: There was a progressive increase in the use of LAI formulations in our catchment area. These agents were preferentially prescribed to patients with chronic disease and a history of substance abuse, as well as patients receiving neuropsychiatric comedication. One-month LAI formulations were commonly used in young patients.

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Schizophrenia is characterized by a chronic course that in most cases requires continued, long-term treatment.[1] Core pharmacologic treatment involves the use of antipsychotics (APs),[2] although medication responsiveness varies widely among affected patients. Approximately half of these patients require a change in their AP medication due to limited effectiveness, intolerance of side effects, lack of adherence, or psychiatric comorbidities.[3–5]

Typical long-acting injectable (LAI) APs, which are administered every 2 to 4 weeks, were developed in the 1960s to improve partial or covert nonadherence rates and to simplify complex medication schedules in the long-term maintenance treatment of psychiatric diseases.[6] More recently, with the introduction of atypical APs, which are characterized by improved efficacy and tolerability profiles,[7] several LAI formulations have also become available and increased the number of pharmacotherapeutic options for schizophrenia.[8]

Most clinical guidelines[1,9,10] recommend using LAI APs for maintenance treatment in patients who prefer them to oral APs and in patients with a history of multiple relapses and nonadherence. In addition, it has been increasingly recognized that LAI APs can be effective in all phases of schizophrenia,[11] particularly during the early stages of the illness.[12] However, their use in routine clinical practice is still restricted and in most cases is limited to chronic patients with severe symptoms, patients with a history of multiple psychotic episodes, and patients who are likely to have a poor outcome.[13,14] Moreover, there are no formal recommendations regarding the use of specific LAIs when initiating treatment because, as shown in a recent review,[15] there are only a few available head-to-head studies and even fewer studies assessing which medications are more effective when transitioning from an oral AP or another LAI formulation. Prescription of LAIs compared to oral APs for outpatient maintenance varies considerably across countries from 10% to 80%.[16,17]

At the time of this study, 2 main typical LAI APs were prescribed in our catchment area, namely, fluphenazine decanoate (fluphenazine-LAI) and zuclopenthixol decanoate (zuclopenthixol-LAI), which are both administered as an intramuscular (IM) injection every 2 weeks. In addition, 2 atypical LAI APs were prescribed, risperidone microspheres (risperidone-LAI), which are also administered as an IM injection every 2 weeks, and paliperidone palmitate (paliperidone-LAI), which is the primary active metabolite of risperidone,[18] is administered as a monthly IM injection, and was authorized in Spain for maintenance treatment of schizophrenia in March 2011.

A systematic review[19] on the prescription patterns of oral and LAI APs in real-life settings in nonrandomized studies has shown that data are lacking regarding the patterns and predictors of use of different

Clinical Points

- Real-world data confirm that use of long-acting injectable (LAI) formulation antipsychotics is increasing in our catchment area.
- LAI antipsychotic formulations are mainly prescribed to chronic complex patients.
- Prescription of 1-month LAI antipsychotic formulation in young patients is increasing.

LAI formulations, and the effect of introducing new LAI drugs has drawn even less attention.[20] The aim of this study was to analyze LAI AP prescription patterns during a 3-year follow-up period in the Spanish province of Tarragona and to identify predictors of medication changes, specifically when a new LAI is introduced.

METHODS

Design

This noninterventional, naturalistic, retrospective study included all patients who were diagnosed with schizophrenia and treated at any community mental health care center in the province of Tarragona in southern Catalonia, Spain.

Data Extraction

Data pertaining to patients older than 18 years with a diagnosis of schizophrenia (*ICD-10* F20.xx) who visited at least 1 mental health center between January 1, 2011, and December 31, 2013, were extracted from electronic medical records as previously described.[21] The variables analyzed included age, sex, marital status, schizophrenia subtype, duration of disease, psychiatric comorbidities (affective disorders, personality disorders, intellectual disabilities, and substance abuse disorders), and substance use (alcohol, tobacco, cannabis, and cocaine). Principal APs, which were defined as the drugs that were prescribed continuously for the longest amount of time, and additional psychiatric drugs were categorized according to their anatomic therapeutic chemical classifications as antiepileptics, anticholinergics, anxiolytics, hypnotics and sedatives, or antidepressants. Moreover, monotherapy was defined as treatment with a single AP (oral or LAI) throughout the entire study period, and polytherapy was defined as simultaneous treatment with 2 or more APs for more than 3 consecutive months. The routes and doses of APs marketed in Spain during the study period were grouped as oral formulations and LAIs, namely, fluphenazine-LAI, zuclopenthixol-LAI, risperidone-LAI, and paliperidone-LAI.

The study received ethical approval from the Clinical Research Ethics Committee of the Hospital Universitari de Sant Joan and the Clinical Research Committee of the Hospital Universitari Institut Pere Mata, Reus, Spain.

Statistical Analysis

All statistical analyses were performed using R Statistical Software (version 3.2.3, R Foundation for Statistical Computing, Vienna, Austria). Descriptive analysis results are expressed as means and standard deviations for continuous variables and as percentages for categorical variables. The Kruskal-Wallis test was used to compare quantitative variables, and a χ^2 test was used to compare proportions. Multivariate linear regression analyses and binary multiple logistic regression models were used to analyze predictive factors pertaining to the continuous and categorical variables, respectively. Moreover, time series analysis was used to identify trends in incident LAI AP use during the study period. Finally, we used Kaplan-Meier survival curves and a log rank test to determine the cumulative probability of switching to another LAI and Cox proportional hazards regression (stratified by LAI treatment) to simultaneously adjust for potential confounders, namely, sex, age, marital status, and psychiatric comorbidities. The level of significance was set at $\alpha < .05$, and Bonferroni correction was used when necessary.

RESULTS

Demographic and Clinical Characteristics Associated With Long-Acting Injectable Prescription

This study included a total of 1,646 patients who were diagnosed with schizophrenia and prescribed at least 1 AP, which during the follow-up period was an oral medication in 954 patients (57.9%) and an LAI medication in 692 patients (42.0%) (Table 1). At the end of the follow-up period, 509 (74%) patients continued receiving an LAI. Overall, the majority of patients were male (68.4% and 69.5% in the oral and LAI AP groups, respectively), and the mean age was similar between the groups (44.1 ± 13.6 years in the oral AP group and 43.5 ± 13.6 years in the LAI AP group). Patients treated with an LAI AP were more likely to have been diagnosed with paranoid, hebephrenic, catatonic, or residual schizophrenia than patients treated with an oral AP ($P = .008$). Furthermore, patients treated with an LAI AP exhibited more psychiatric comorbidities ($P < .001$), were more likely to be treated with neuropsychiatric comedication ($P = .014$), were more likely to be substance users ($P < .001$), and were more likely to have lived with their disease for longer than 5 years ($P = .036$) (Table 1) compared to the oral AP group. Only 12% of patients who were treated with an LAI as their principal AP received monotherapy; 43.6% of patients in the oral AP group received monotherapy ($P < .001$). The mean doses (mg/injection) of fluphenazine-LAI, zuclopenthixol-LAI, risperidone-LAI, and paliperidone-LAI were 16.5 ± 9.6, 167.3 ± 82.0, 45.9 ± 17.4, and 122.2 ± 34.1, respectively.

Multiple binary logistic regression analysis showed that the variables associated with prescription of an LAI AP versus an oral AP were undifferentiated schizophrenia ($\beta = -0.74$, $P = .004$), substance abuse ($\beta = 0.53$, $P < .001$), and neuropsychiatric comedication with the following agents: anticonvulsants ($\beta = 0.31$, $P < .001$), anticholinergics ($\beta = 0.84$, $P < .001$), hypnotics/sedatives ($\beta = 0.26$, $P = .02$), and antidepressants ($\beta = -0.27$, $P = .04$) (Table 2).

Table 1. Demographic and Clinical Characteristics of the Study Sample According to the Mode of Administration of the Principal AP (Oral or LAI) at the End of the Study Follow-Up

Variable	Oral AP (n = 954)	LAI AP (n = 692)	Test Statistic, *P* Value[a]
Sex, n (%)			
Male	653 (68.4)	481 (69.5)	
Female	301 (31.6)	211 (30.5)	
Age, mean ± SD, y	44.1 ± 13.6	43.5 ± 13.6	
Marital status, n (%)			
Single	634 (66.5)	499 (72.1)	
Married/domestic partner	136 (14.3)	85 (12.3)	
Separated/divorced	54 (5.7)	34 (4.9)	
Widowed	11 (1.2)	10 (1.5)	
Unknown/not reported	119 (12.5)	64 (9.3)	
Schizophrenia subtype, n (%)			$\chi^2 = 20.4$, $P = .008$
Paranoid	678 (71.1)	523 (75.6)	
Hebephrenic	21 (2.2)	20 (2.9)	
Catatonic	2 (0.2)	2 (0.3)	
Undifferentiated	69 (7.2)	23 (3.3)	
Postschizophrenic depression	1 (0.1)	0 (0.0)	
Residual	91 (9.5)	79 (11.4)	
Simple	38 (4.0)	22 (3.2)	
Other	9 (0.9)	4 (0.6)	
Unspecified	45 (4.7)	19 (2.8)	
Neuropsychiatric comedication, n (%)[b]	763 (80.0)	587 (84.8)	$\chi^2 = 6.06$, $P = .014$
Type of neuropsychiatric comedication, n (%)			
Anticonvulsants	266 (27.9)	266 (38.4)	
Anticholinergics	226 (23.7)	293 (42.3)	
Anxiolytics	467 (49.0)	345 (49.9)	
Hypnotics/sedatives	280 (29.4)	256 (37.0)	
Antidepressants	372 (39.0)	247 (35.7)	
Antipsychotic prescription pattern, n (%)			
Monotherapy	416 (43.6)	81 (11.7)	$\chi^2 = 192.13$, $P < .001$
Polytherapy	538 (56.4)	611 (88.3)	
Psychiatric comorbidity, n (%)[b]	341 (35.7)	303 (43.8)	$\chi^2 = 10.6$, $P < .001$
Type of psychiatric comorbidity, n (%)			
Affective disorders	26 (2.7)	11 (1.6)	
Personality disorders	21 (2.2)	17 (2.5)	$\chi^2 = 31.4$, $P < .001$
Intellectual disabilities	15 (1.5)	14 (2.0)	
Substance abuse disorders	227 (23.8)	248 (35.8)	
Substance use, n (%)[b]	252 (26.4)	261 (37.7)	$\chi^2 = 19.13$, $P < .001$
Type of substance use, n (%			
Tobacco	206 (21.6)	217 (33.6)	
Alcohol	50 (5.2)	72 (10.6)	
Cannabis	33 (3.4)	56 (8.8)	
Cocaine	9 (0.9)	22 (3.1)	
Duration of disease, n (%)			$\chi^2 = 4.4$, $P = .036$
≥ 5 y	746 (78.2)	571 (82.5)	
< 5 y	208 (21.8)	121 (17.5)	

[a]Test statistic and P value are shown only if $P < .05$.
[b]The n (%) represents "presence of."
Abbreviations: AP = antipsychotic, LAI = long-acting injectable.

Patterns of Long-Acting Injectable Prescription According to Duration of Treatment

The most frequently prescribed initial LAI formulation during the study period was risperidone-LAI (in 52.0% of patients), followed by zuclopenthixol-LAI (in 20.1%), paliperidone-LAI (in 14.3%), and fluphenazine-LAI (in 12.9%). Multivariate linear regression analysis showed that older age ($\beta = 0.24$, $P < .001$) and widowhood ($\beta = -13.2$, $P < .001$) were associated with the duration of treatment with any LAI during the study period (Table 2).

Patterns of Long-Acting Injectable Prescription in Patients Who Switched Antipsychotic Medications

Overall, 391 (23%) patients who were initially treated with an oral AP were switched to an LAI AP during the study period. Ninety-two (23.5%) were switched to a typical LAI AP (16.4% to zuclopenthixol-LAI and 7.2% to fluphenazine-LAI), 200 (51.2%) were switched to risperidone-LAI, and 99 (25.3%) were switched to the newly available paliperidone-LAI. Bivariate logistic regression showed that the switch from an oral AP to an LAI AP among LAI-naive patients was associated with younger age ($\beta = -0.19$, $P = .001$), undifferentiated schizophrenia ($\beta = -0.78$, $P = .015$), substance abuse disorders ($\beta = 0.87$, $P < .001$), and comedication with anticonvulsants ($\beta = 0.39$, $P = .004$), anticholinergics ($\beta = 0.87$, $P < .001$), or hypnotics/sedatives ($\beta = 0.30$, $P = .03$) (Table 2). Moreover, the only demographic or clinical characteristic that predicted the change from an oral AP to paliperidone-LAI was younger age ($\beta = -0.053$, $P < .001$) (Table 2).

A total of 190 (27.5%) of 692 patients who were treated with an LAI AP switched from their initial LAI formulation to an oral AP or another LAI AP for any reason during the study period, and 138 patients (19.9%) discontinued LAI treatment, which was slightly more frequent among patients who were treated with paliperidone-LAI (Table 3). A multiple linear regression model showed that the variables associated with the duration of treatment with the initial prescribed LAI were age ($\beta = 0.24$, $P < .001$), widowhood ($\beta = -13.7$, $P = .001$), hebephrenic schizophrenia ($\beta = 6.7$, $P = .023$), and comedication with hypnotics/sedatives ($\beta = -2.31$, $P = .03$) (Table 2). Paliperidone-LAI was the preferred second option in 64.7% of patients (n = 123) who switched between LAI formulations (Table 3), and the only demographic and clinical predictors of this particular change were unspecified schizophrenia ($\beta = -1.98$, $P = .05$) and comedication with anticonvulsants ($\beta = 0.70$, $P = .001$), anticholinergics ($\beta = 0.50$, $P < .01$), and hypnotics/sedatives ($\beta = 0.54$, $P = .006$) (Table 2). Among all patients treated with LAI APs, the most frequent switch involved patients who were treated with risperidone-LAI, as 127 (35.3%) transitioned to another LAI formulation, mainly paliperidone-LAI (n = 108, 85.0%) (Table 3). The only difference between patients who stayed on risperidone-LAI (n = 165) and those who switched to paliperidone-LAI (n = 108) was that patients in the latter group were more likely to have lived with their disease > 5 years ($\chi^2 = 5.4$, $P = .019$).

Patterns of Long-Acting Injectable Prescription According to the Time and Impact of Paliperidone Palmitate Availability

There was a substantial increase in the total number of patients treated with 1 of the available LAI formulations during the months preceding

Table 2. Regression Analyses Assessing the Predictors of Oral Versus LAI AP Treatment, Duration of LAI Treatment (Any Formulation During the Study Period), Duration of Initial Treatment With an LAI AP Before Switching to Another AP (Oral or LAI), and Switching Between Formulations

Independent Variable	Oral vs LAI AP Treatment[a] *P* Value	Duration of LAI AP Treatment[b] *P* Value	Duration of Initial LAI AP Treatment[c] *P* Value	Switch to LAI or Stay on Oral AP[d] *P* Value	Switch From Any Oral AP To Paliperidone LAI[e] *P* Value	Switch From Any LAI AP to Paliperidone-LAI[f] *P* Value
Sex (male)	.51	.60	.99	.32	.52	.20
Age	.40	<.001* (β=0.24, SE=0.04)	<.001* (β=0.24, SE=0.04)	.001* (β=–0.19, SE=0.006)	<.001* (β=–0.053, SE=0.01)	.15
Marital status						
Single	Reference	Reference	Reference	Reference	Reference	Reference
Married/domestic partner	.58	.36	.18	.88	.78	.87
Separated/divorced	.51	.46	.91	.75	.97	.72
Widowed	.75	<.001* (β=–13.2, SE=3.91)	.001* (β=–13.7, SE=4.3)	.19	.99	.48
Unknown/not reported	.02 (β=–0.39, SE=0.17)	.13	.45	.23	.64	.29
Schizophrenia subtype						
Paranoid	Reference	Reference	Reference	Reference	Reference	Reference
Hebephrenic	.63	.45	.023 (β=6.7, SE=2.95)	.80	.96	.66
Catatonic	.66	.19	.46	.97	1.00	.27
Undifferentiated	.004 (β=–0.74, SE=0.25)	.96	.42	.015 (β=–0.78, SE=0.32)	.17	.06
Postschizophrenic depression	.97	…	…	0.98	1.00	.99
Residual	.12	.82	.32	.77	.10	.20
Simple	.48	.53	.63	.22	.98	.30
Other	.45	.29	.91	.98	.85	.98
Unspecified	.06	.64	.99	.28	.80	.05 (β=–1.98, SE=1.03)
Psychiatric comorbidity						
Affective disorders	.17	.28	.10	.09	.99	.21
Personality disorders	.55	.87	.89	.32	.63	.48
Intellectual disabilities	.36	.39	.85	.11	.99	.63
Substance abuse disorders	<.001* (β=0.53, SE=0.12)	.42	.29	<.001* (β=0.87, SE=0.14)	.09	.37
Neuropsychiatric comedication						
Anticonvulsants	<.001 (β=0.31, SE=0.12)	.91	.06	.004 (β=0.39, SE=0.14)	.21	<.001* (β=0.7, SE=0.20)
Anticholinergics	<.001* (β=0.84, SE=0.11)	.61	.86	<.001* (β=0.87, SE=0.14)	.53	.01 (β=0.50, SE=0.20)
Anxiolytics	.55	.99	.70	.54	.70	.56
Hypnotics/sedatives	.02 (β=0.26, SE=0.12)	.41	.03 (β=–2.31, SE=1.06)	.03 (β=0.30, SE=0.14)	.21	.006 (β=0.54, SE=0.20)
Antidepressants	.04 (β=–0.27, SE=0.12)	.10	.17	.31	.31	.71

[a]Binary linear multiple regression model: estimated intercept = –0.50, $P = .04$, $R^2 = 0.62$.
[b]Multivariate linear regression model: estimated intercept = 19.6, $P = 1.4e\text{-}06$, $R^2 = 0.065$.
[c]Multivariate linear regression model: estimated intercept = 15.3, $P = 3.3e\text{-}10$, $R^2 = 0.096$.
[d]Multivariate linear regression model: estimated intercept = –0.64, $P = .035$, $R^2 = 0.96$.
[e]Binary linear regression model: estimated intercept = –0.87, $P = .09$, $R^2 = 0.13$.
[f]Binary linear regression model: estimated intercept = –2.34, $P = 4.9e\text{-}07$, $R^2 = 0.11$.
*Significant after Bonferroni correction (q < 0.002).
Abbreviations: AP = antipsychotic, LAI = long-acting injectable, SE = standard error.
Symbol: . . . = no data.

Table 3. Number and Frequency of Switches From an Initial Assigned LAI AP to Another LAI AP During the Study Period

Initial Assigned Treatment	Switch to a Second LAI, n				Switched to Another LAI AP, n (%)	Stayed on the Same LAI AP, n (%)	Quit LAI Treatment, n (%)
	Fluphenazine-LAI	Zuclopenthixol-LAI	Risperidone-LAI	Paliperidone-LAI			
Fluphenazine-LAI	…	3	2	4	9 (10.1)	62 (69.7)	18 (20.2)
Zuclopenthixol-LAI	3	…	12	11	26 (18.1)	90 (62.5)	28 (19.4)
Risperidone-LAI	5	14	…	108	127 (35.3)	165 (45.8)	68 (18.9)
Paliperidone-LAI	5	11	12	…	28 (28.3)	47 (47.5)	24 (24.2)
Total	13	28	26	123	190 (27.5)[a]	364 (52.6)	138 (19.9)

[a]Forty-five patients discontinued their LAI after the switch, and these were not included in the Quit LAI treatment column.
Abbreviations: AP = antipsychotic, LAI = long-acting injectable .

paliperidone-LAI use, launched on March 31, 2011, in Spain and November 30, 2011, in our catchment area, a trend that was most marked for risperidone-LAI but least noticeable for typical LAI APs (fluphenazine-LAI and zuclopenthixol-LAI) (Figure 1A). After the introduction of paliperidone-LAI, there was a substantial decrease in the number of patients treated with risperidone-LAI, which coincided with a sharp increase in the number of patients treated with paliperidone-LAI, although the prescription rate of both formulations continued to increase until the end of the study follow-up. Conversely, paliperidone-LAI availability did not seem to significantly impact the number of patients who were treated with typical LAI APs. Finally, Kaplan-Meier estimates of the time to switch medications showed that patients taking fluphenazine-LAI and zuclopenthixol-LAI were more likely to stay on their assigned medication for a longer period than patients taking risperidone-LAI ($\chi^2 = 51.2$, $P < .001$) or paliperidone-LAI ($\chi^2 = 51.9$, $P < .001$) (Figure 1B). Of note, the time to switch in patients treated with risperidone-LAI decreased abruptly, coinciding with the time point at which the introduction of paliperidone-LAI took place in our area (Figure 1B).

Patterns of Long-Acting Injectable Prescription According to Duration of Disease

Overall, patients with a disease duration longer than 5 years were more likely to be older (mean ± SD age of 45.5 ± 13.8 vs 36.9 ± 10.3 years, $P < .001$) and have a diagnosis of hebephrenic or residual schizophrenia ($P < .001$) and were less likely to be treated with atypical APs ($P = .0017$) (Supplementary Table 1) than patients in the early phase of their disease (illness duration < 5 years). Regarding differences in the initial LAI AP prescribed, we observed that risperidone-LAI was the most frequently used formulation regardless of the duration of disease (55.3% when < 5 years and 51.3% when ≥ 5 years), but patients with a disease duration < 5 years took paliperidone-LAI more frequently than patients with a disease duration ≥ 5 years ($\chi^2 = 12.9$, $P = .05$, Supplementary Figure 1).

DISCUSSION

Patterns of Long-Acting Injectable Prescription

In the present study, we assessed LAI AP prescription practices during a 3-year follow-up period that began shortly before the marketing authorization and use of a new LAI formulation in the Tarragona area of Spain in late 2011. We observed that the prescription of all LAI formulations increased gradually with time and that at the end of the study, around one-third of patients were receiving an LAI. This finding falls within the mean of the wide range of LAI AP prescription rates reported, ranging from 10% to 80%.[16,17]

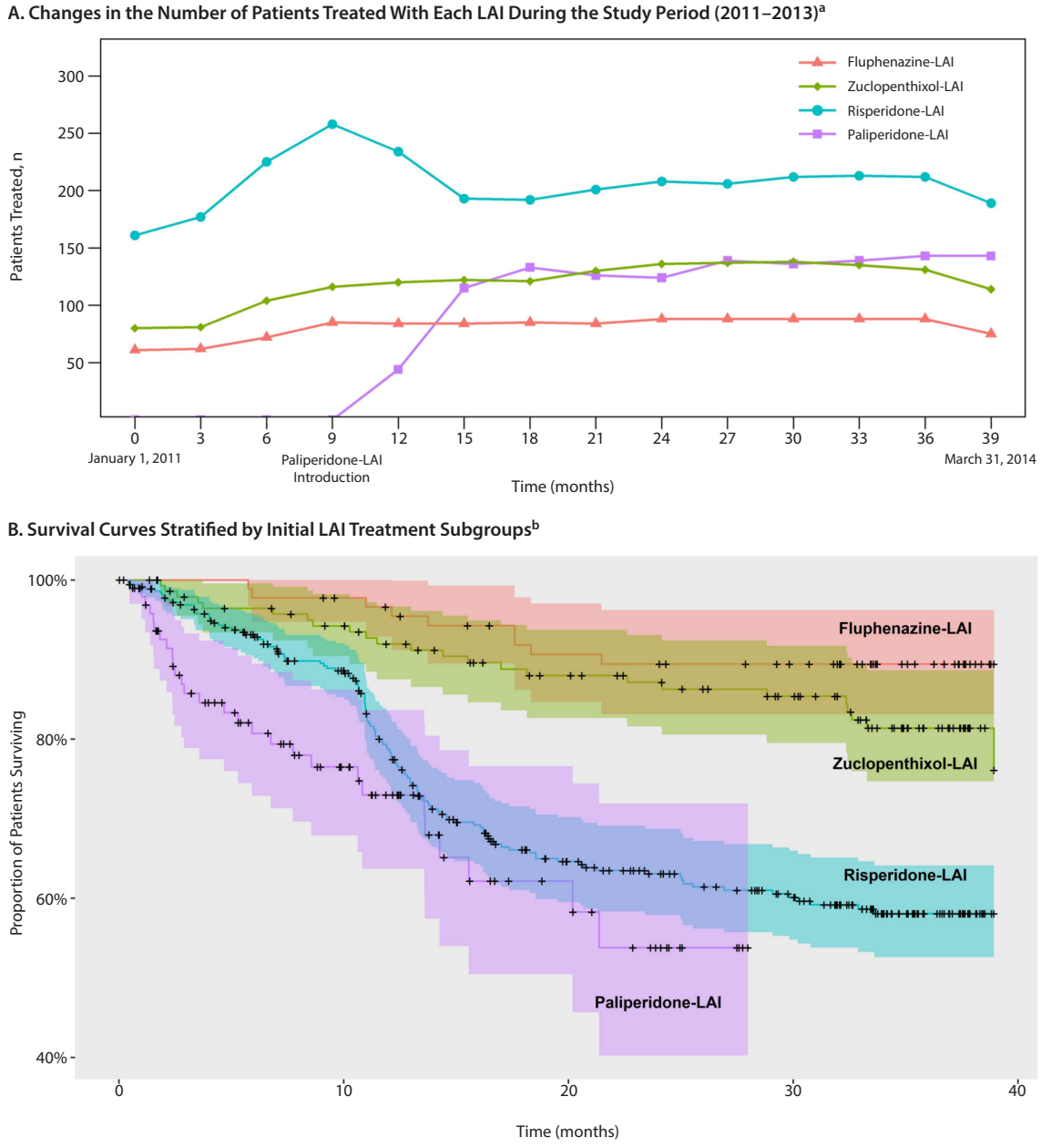
We observed that patients treated with an LAI AP had longer disease durations and were more likely to suffer from other psychiatric comorbidities including substance abuse than patients treated with an oral AP; however, only undifferentiated schizophrenia, substance abuse disorder, and neuropsychiatric comedication predicted the use of an LAI over an oral AP. These findings confirm previous observations that LAI formulations are preferred in challenging chronic disease patients[13,14] and are also in agreement with the finding that LAI formulations are generally recommended to improve nonadherence in patients with comorbid substance abuse disorders.[22,23] Moreover, our results confirm previous observations that a high proportion of patients taking LAIs use adjunctive psychotropic medications in real-world settings.[24]

Our data also show that hebephrenic schizophrenia and the need of hypnotic/sedative prescription predicted the treatment duration with the initially assigned LAI AP. Hebephrenic schizophrenia is linked to AP nonresponsiveness, use of comedications, and poor long-term prognoses.[25]

When we assessed the profiles of LAI-naive patients who switched from their initial assigned oral AP medication to an LAI formulation, we observed that younger age, substance abuse disorders, and concomitant use of anticholinergics strongly predicted a switch. Although we did not assess specific reasons for switching, our findings are consistent with previous studies reporting that LAI formulations are appropriate in younger patients because these patients are at higher risk for noncompliance.[22,26] In addition, the higher frequency of anticholinergic treatment among subjects who changed from oral to LAI formulations can be considered an indirect indicator of the presence of extrapyramidal effects, which are one of the main reasons why AP treatments need to be changed.[1]

The transition from any LAI formulation to paliperidone-LAI (which in 65% of cases was the preferred second LAI option) was strongly predicted by a higher probability of

Figure 1. Changes in the Number of Patients Treated With Each Long-Acting Injectable(LAI) During the Study Period



[a]The total number of individuals on a specific LAI treatment (Y axis) was obtained at several time points every 3 months (X axis) until March 31, 2011.
[b]The term *survival* indicates that an individual survived if he or she continued the same LAI that was initially prescribed without switching to another treatment. The crosses represent censored observations, and the shaded areas represent 95% CIs.

neuropsychiatric comedication. This finding is in agreement with a previous report[27] showing a high rate of concomitant prescription of mood stabilizers in patients treated with paliperidone-LAI compared with risperidone-LAI and zuclopenthixol-LAI, respectively. Because comorbid psychiatric disorders were not predictors of this particular switch, it is possible that this subgroup of patients required intensive treatment, leading to more adverse effects and a chronic disease course, which suggests that paliperidone-LAI is being prescribed for more severely affected patients (channeling effect).[20]

Impact of Paliperidone Palmitate Availability

Risperidone-LAI was the most frequently prescribed LAI AP regardless of the duration of illness. Switching from risperidone-LAI to paliperidone-LAI was the most frequent transition between LAI formulations, particularly in patients with illness duration > 5 years. However, as an initial LAI prescription, paliperidone-LAI was more frequently used among patients in the early phase of their disease (duration < 5 years). This pattern seems to explain the rapid acceptance and widespread use of paliperidone-LAI in our health care area, as we observed that while its

introduction did not significantly impact the frequency of typical LAI AP prescription, the use of risperidone-LAI decreased in parallel with an initial sharp increase in its use. Similarly, the time to switch to another LAI formulation was longer among patients treated with a typical LAI but was much shorter among patients treated with risperidone-LAI immediately after the market authorization of paliperidone-LAI. This pattern is consistent with the findings of previous reports[20] showing that the introduction of a new AP to the market is followed by very quick adoption by physicians and patients because of the convenience of its monthly administration. The increase in the number of overall LAI prescriptions throughout the study period may indicate a change in psychiatrist prescribing practices because of the availability of new second-generation LAI APs, which have increased the number of therapeutic options for patients with schizophrenia[8] and also attenuated the negative attitudes of patients and psychiatrists, especially in the early phases of the illness, toward LAI APs compared with oral APs.[13,28]

Strengths and Limitations

The present study was based on a large sample of the overall population of schizophrenic patients in Tarragona who were taking APs, which is representative of southern Europe in terms of sociodemographic characteristics. Most importantly, the study was conducted in a real-life clinical setting, thus allowing the inclusion of patients who were otherwise excluded from randomized clinical trials. One of the limitations of this study was its retrospective design, which by nature means that some of the variables were recorded poorly and may have biased our results. Moreover, medication regimens were extracted from patient medical records, and we did not have access to information regarding patients' reasons for medication discontinuation and nonadherence, which prevented us from analyzing a potential association between efficacy and tolerability and the switch from an oral or another LAI AP to paliperidone-LAI.

CONCLUSIONS

Our results provide further evidence that LAI formulations are generally prescribed to patients with longer disease durations, a greater number of associated psychiatric comorbidities, and more frequent substance use as well as to patients receiving concomitant neuropsychiatric medication compared with patients taking oral APs. The number of patients treated with at least 1 LAI formulation increased from 18.0% to 30.9% during the study period, and although risperidone-LAI was the most frequently prescribed LAI, we observed a decrease in the use of risperidone-LAI in parallel with an initial sharp increase in the use of paliperidone-LAI, particularly in young patients. Additional extensive long-term observational studies are needed to address whether the selective prescription of new LAI formulations is a channeling effect or the result of its favorable efficacy and tolerability profile and its advantageous mode of delivery.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

THE PRIMARY CARE COMPANION FOR CNS DISORDERS

Supplementary Material

Article Title: Noninterventional, Naturalistic, Retrospective Study to Describe Prescription Patterns of Long-Acting Injectable Antipsychotics and the Impact of Introducing a New Atypical Antipsychotic in the Tarragona Catchment Area

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List of Supplementary Material for the article

1. Table 1
2. Figure 1

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Table 1. Demographic and clinical characteristics of patients with long (≥5 years) and short (<5 years) disease evolution

Variable	≥5 years	<5 years	Statistic p-value
N	1317	329	
Gender			X^2=9.25, p=0.00236
Male	884 (67.1%)	250 (76%)	
Female	433 (32.9%)	79 (24%)	
Age (years, mean ± SD)	45.5±13.8	36.9±10.3	D=0.27, p<0.001
Marital status			X^2=15.73, p=0.0034
Single	918 (69.7%)	215 (65.3%)	
Married / Domestic Partner	175 (13.3%)	46 (14%)	
Separated / Divorced	75 (5.7%)	13 (4%)	
Widowed	20 (1.5%)	1 (0.3%)	
Unknown/Not reported	129 (9.8%)	54 (16.4%)	
Schizophrenia subtype			X^2=26.48, p<0.001
Paranoid	941 (71.5%)	260 (79%)	
Hebephrenic	38 (2.9%)	3 (0.9%)	
Catatonic	2 (0.2%)	2 (0.6%)	
Undifferentiated	75 (5.7%)	17 (5.2%)	
Post-schizophrenic depression	-	1 (0.3%)	
Residual	155 (11.8%)	15 (4.6%)	
Simple	47 (3.6%)	13 (4%)	
Other	10 (0.8%)	3 (0.9%)	
Unspecified	49 (3.7%)	15 (4.6%)	
Principal Antipsychotic			X^2=9.802, p=0.0017
Typical	237 (18%)	35 (10.6%)	
Atypical	1080 (82%)	294 (89.4%)	
Antipsychotics Pattern			X^2=9.30, p=1
Monotherapy	398 (30.2%)	99 (30.1%)	
Polypharmacy	919 (69.8%)	230 (69.9%)	
Neuropsychiatric co-medication	1080 (82%)	270 (82%)	X^2=0, p=1
Anticonvulsants	419 (31.8%)	113 (34.3%)	
Anticholinergics	428 (32.5%)	91 (27.7%)	
Anxiolytics	664 (50.4%)	148 (45%)	
Hypnotics / sedatives	426 (32.3%)	110 (33.4%)	
Antidepressants	481 (36.5%)	138 (42%)	
Presence of psychiatric co-morbidity	501 (38%)	143 (43.5%)	X^2=3.03, p=0.082
Affective disease	26 (2%)	11 (3.3%)	
Personality disease	29 (2.2%)	9 (2.7%)	
Intellectual disability	20 (1.5%)	9 (2.7%)	
Substance abuse consumption disease	387 (29.4%)	88 (26.7%)	
Presence of consumption of substances	**414 (31.43%)**	**99 (30%)**	X^2=3.6, p=0.058
Tobacco	343 (26%)	80 (24.3%)	
Alcohol	106 (8%)	16 (4.8%)	
Cannabis	70 (5.3%)	19 (5.8%)	
Cocaine	23 (1.7%)	8 (2.4%)	

Figure 1. **Frequency of patients treated with LAI**