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Chapter 6

Impact of Switching to Long-Acting Injectable Antipsychotics on Health Services Use in the Treatment of Schizophrenia

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Objective: To better understand the treatment patterns, persistence and compliance, resource use, and associated costs, of long-acting injectable antipsychotics (LAI-AP), using the Régie de l'assurance maladie du Québec database.

Method: Patients with schizophrenia or schizoaffective disorder who were incident users of an LAI-AP prescribed between January 1, 2008, and March 31, 2012, were selected. Concomitant use of oral APs and treatment persistence and compliance with LAI-AP were analyzed. Patients were considered compliant if they had a medication possession ratio (MPR) of at least 0.80. Health care resource use (HCRU) and associated costs were analyzed during the year before and after LAI-AP initiation.

Results: A total of 1992 patients met the inclusion criteria. The average persistence with LAI-AP was 217.2 days (SD 144.2). The mean MPR with LAI-AP during the postinitiation year was 0.58 (SD 0.35), with 37.5% of patients being compliant. In the preinitiation year, 29.0% of patients were compliant with previous oral AP. In the pre- and postinitiation periods, 1484 and 958 patients had at least 1 hospitalization, and hospitalized days were reduced by one-half ($P < 0.001$). Cost of HCRU, including medication, was significantly decreased from $24 382 (SD $27 234) to $13 090 (SD $16 987), respectively, in the pre- and postinitiation years ($P < 0.001$).

Conclusions: The initiation of an LAI-AP improved treatment compliance, compared with previous oral APs, resulted in significantly lower HCRU and costs. The primary drivers were the reduction in the occurrence and days of hospitalizations.

L'effet de passer à des antipsychotiques injectables à action prolongée sur l'utilisation des services de santé dans le traitement de la schizophrénie

Objectif : Mieux comprendre les modèles de traitement, la persistance et l'observance, l'utilisation des ressources, et les coûts associés des antipsychotiques injectables à action prolongée (AP-IAP), à l'aide de la base de données de la Régie de l'assurance maladie du Québec.

Méthode : Les patients souffrant de schizophrénie ou d'un trouble schizo-affectif qui ont utilisé un AP-IAP prescrit entre le 1er janvier 2008 et le 31 mars 2012 ont été sélectionnés. L'utilisation concomitante d'AP oraux ainsi que la persistance et l'observance de l'AP-IAP ont été analysées. Les patients étaient estimés observants s'ils avaient un ratio de possession de médicaments (RPM) d'au moins 0,80. L'utilisation des ressources de santé (URS) et les coûts associés ont été analysés durant l'année avant et après l'initiation de l'AP-IAP.

Résultats : Un total de 1992 patients satisfaisait aux critères d'inclusion. La persistance moyenne pour l'AP-IAP était de 217,2 jours (ET 144,2). Le RPM moyen pour l'AP-IAP durant l'année post-initiation était de 0,58 (ET 0,35), et 37,5 % des patients étaient observants. Dans les périodes avant et après l'initiation, 1484 et 958 patients ont eu au moins

1 hospitalisation, et les journées hospitalisées ont été réduites de moitié (P < 0,001). Le coût de l'URS, incluant les médicaments, a diminué significativement de 24 382 $ (ET 27 234 $) à 13 090 $ (ET 16 987 $), respectivement dans les années avant et après l'initiation (P < 0,001).

Conclusions : L'initiation de l'AP-IAP a amélioré l'observance du traitement, comparativement aux AP oraux précédents, donnant lieu à une URS et des coûts significativement plus faibles. Les principaux pilotes étaient la réduction de l'occurrence et du nombre des jours d'hospitalisation.

There are many well-established AP treatments available for schizophrenia. APs have been shown in clinical trials to be effective in improving symptom control in schizophrenia and in preventing relapse.[1] However, in real life, poor medication compliance is very common, and represents a major concern for the treatment of patients with schizophrenia. The reasons for poor compliance are multiple and complex, and can include aspects of the disease itself (such as poor illness insight or cognitive dysfunction), or the adverse effects or perceived poor efficacy of the medication. Medication noncompliance is associated with symptom exacerbation, disease relapse, and increased hospitalization rates.[2] Without adequate continuity of treatment, most patients eventually relapse; the cumulative relapse rate in first-episode patients was estimated to range from 16% at 1 year to 82% at 5 years.[3] Relapse has been shown to be associated with cognitive impairment, neurotoxicity, and reduced response to future medication treatment,[4] and therefore prevention of relapse in schizophrenia is a very high-priority treatment goal.

LAI-APs requiring monthly or biweekly injections were developed to reduce problems with medication noncompliance. LAI-APs have significant advantages over oral APs, including a less burdensome dosing schedule, more consistent drug plasma levels, and the requirement of regular visits with a health care professional. Not surprisingly, LAI-APs have been shown to reduce relapse and hospitalization rates, compared with oral treatment.[5–7] Despite the known advantages of LAI-AP use, the use of these medications remains low in Canada; in 2011, Manchanda et al[8] reported that the Canadian use of LAI-APs was 2.4% of the overall use of oral and LAI, which is significantly lower than the rates of use in other countries.[9,10] Further research with more extensive Canadian data is needed to obtain a better understanding of the current use of LAI-APs in daily clinical practice and the clinical and economic benefits of these medications.

This retrospective analysis was undertaken to understand the treatment patterns of LAI-AP use in the Canadian province of Quebec, and to assess the persistence and compliance, HCRU, and associated costs in in- and outpatients followed for 12 months before and 12 months after the initiation of an LAI-AP, using information obtained from the RAMQ database.

Clinical Implications

- Patients who were initiated on LAI-AP treatment were more likely to be medication-compliant than when previously treated with oral APs.
- The cost of medication of newer second-generation LAI-APs is offset by lower cost of hospitalization.
- Increased use of LAI-APs may not only improve clinical outcomes but also provide a more cost-effective treatment strategy.

Limitations

- It was assumed that the reimbursed medications retrieved from the database were taken by the patient.
- In Quebec, physicians are not required to record an ICD-9 code, and only 1 code can be recorded.
- The direct costs reported in our study were estimations (from average daily costs reported by the Quebec Hospital Association).
- Results only allow comparison to previous oral AP treatment, as a poor response will lead to LAI initiation.

Abbreviations

AP	antipsychotic
DDD	defined daily dose
ED	emergency department
HCRU	health care resource use
ICD	International Classification of Diseases
LAI-AP	long-acting injectable antipsychotic
MEMS	Medication Event Monitoring System
MPR	medication possession ratio
RAMQ	Régie de l'assurance maladie du Québec

Methods

Our study design was a mirror-image cohort study based on administrative data. Data on patients' characteristics and on medical and pharmaceutical services were obtained from the RAMQ database; a province-wide database containing information on all publicly insured residents of Quebec. The RAMQ medical services database contains information from physicians' claims for services provided within and outside the hospital. The RAMQ pharmaceutical services database includes information from pharmacists' claims for dispensed medications reimbursed by the program, but not for medications received in a hospital. The RAMQ database also includes demographic information of the insured

person, and information on the prescribing physicians (including specialty).

Patient Population

In our analysis, patients receiving their first prescription of an LAI-AP between January 1, 2008, and March 31, 2012 (index date), and who were incident users of the index drug (no use in the 12 previous months) were selected. The index date was defined as the date of the first prescription for the index LAI-AP. Other eligibility criteria included a diagnosis of schizophrenia or schizoaffective disorder identified by ICD-9 codes 295.0 to 295.9, 20 years of age or older, and continuous enrollment in the drug reimbursement program throughout the 2-year study period. Age at the index date, sex, specialty of the prescriber of the index drug, and the index drug at the index date were included in the analysis.

Data Collection

Our study period consisted of 12 months of data history and 12 months of follow-up for each subject, corresponding to the year before the index date (12-month preinitiation period) added to the year after the index date (12-month postinitiation period).

Age at the index date, sex, specialty of the prescriber of the index drug, the index drug at the index date, and comorbidity indexes, such as Von Korff's chronic disease score[11] and the Charlson Comorbidity Index,[12] were analyzed. Von Korff's chronic disease score was assessed according to the participants' medication profile. Higher scores indicate higher levels of comorbidity and correlate with future HCRU. The Charlson Comorbidity Index was determined using ICD-9 codes of 19 different specific medical conditions. These conditions were then weighted according to their potential for influencing mortality to calculate the score. The period of 12 months preceding the index date was used for both the Von Korff and the Charlson scores.

Mental disorders and somatic conditions were identified using ICD-9 codes in the preinitiation period. Mental disorders included major depressive disorder, anxiety disorders, substance use disorders, and other psychotic disorders. Somatic conditions included cardiovascular diseases, hyperlipidemia, diabetes, gastrointestinal diseases, neurological disorders, obesity, and respiratory diseases.

Prescriptions of concomitant oral APs to LAI-AP index treatment were identified at the index date (SD 15 days) and at 6 months (SD 15 days) for patients still under the index LAI-AP treatment. The proportion of patients with no concomitant oral AP, or with 1, 2, or 3 and more oral APs was assessed.

Persistence and Compliance

Persistence was defined as the number of days of consecutive medication use during the first treatment episode, even if a patient experienced additional treatment episodes during the year after the initiation of the first LAI-AP. The first treatment episode was defined as the period from the index date to the date of drug discontinuation (date of dispensing that occurred before a gap greater than the duration of the last dispensation plus twice the standard injection treatment interval), plus the duration of the dispensation of the last script. The following standard injection treatment intervals were used for these index drugs of interest: flupentixol decanoate: 14 days; fluphenazine decanoate: 21 days; haloperidol decanoate: 28 days; zuclopenthixol LAI formulation: 14 days; risperidone LAI formulation: 14 days; and, paliperidone LAI formulation: 28 days. If a patient was hospitalized during the defined treatment episode, and the depot AP treatment was the same before and after the hospitalization period, it was assumed that treatment had been continued during the hospitalization period. If the treatment had changed after hospitalization, the treatment episode was considered terminated at the date of hospitalization. A switch to another depot AP was also considered to be a discontinuation of the index drug. Factors associated with nonpersistence were determined using Cox proportional hazards regression models. Several factors were tested in univariate and multivariate models, such as: sex, age, presence of mental disorders and somatic conditions, Charlson Comorbidity Index (medium, high, or very high score, compared with low score), the specialty of the prescriber of the index drug, previous use of depot APs other than the index drug during the preinitiation period, concomitant use of oral APs during the first treatment episode, hospitalization for any reason during the pre-initiation period, the number of hospitalization days, and the dose level of the LAI-AP received at the index date (below the DDD, or above the DDD, compared with about equal to the DDD). For each index drug, the prescribed dose received at the index date, or the maximum dose received at the index date when more than 1 daily dose of the index drug was prescribed, was compared with the DDD: flupentixol decanoate: 4.0 mg; fluphenazine decanoate: 1.0 mg; haloperidol decanoate: 3.3 mg; zuclopenthixol LAI formulation: 15.0 mg; risperidone LAI formulation: 2.7 mg; and paliperidone LAI formulation: 2.5 mg.[13] The class (first and second generation) of the index drug was also included in the model. Flupentixol decanoate, fluphenazine decanoate, haloperidol decanoate, and zuclopenthixol LAI formulation were classified as first-generation LAI-APs. Risperidone LAI formulation and paliperidone LAI formulation were classified as second-generation LAI-APs.

The average treatment duration estimated for the persistence was the cut-off point to determine factors of nonpersistence in the multivariate Cox proportional hazards regression models. A HR above one indicates an increased risk of being not persistent to treatment.

Some correlated variables were not included in the multivariate model (that is, presence of mental disorders and somatic conditions were chosen over the Charlson Comorbidity Index, and the occurrence of hospitalization during the preinitiation period was chosen over the number of hospitalization days during this period).

Table 1 Characteristics of patients at index date (*n* = 1992)

Age, years, mean (SD)	43.5 (14.3)
Male, *n* (%)	1319 (66.2)
Von Korff score, mean (SD)	2.5 (3.0)
Charlson Comorbidity Index, mean (SD)	0.4 (1.0)
Specialty of the prescriber of the index drug, *n* (%)	
Psychiatry	1601 (80.4)
General practice	379 (19.0)
Other	10 (1.0)
Not available	2 (0.1)
Index drug, *n* (%)	
Flupentixol decanoate	111 (5.6)
Fluphenazine decanoate	350 (17.6)
Haloperidol decanoate	200 (10.0)
Paliperidone long-acting injection	202 (10.1)
Risperidone long-acting injection	775 (38.9)
Zuclopenthixol long-acting injection	354 (17.8)

Table 2 Patients' medical history (*n* = 1992)

Medical history (12 months before the index date)	*n* (%)
Mental disorders	
Other psychotic disorder	750 (37.7)
Major depressive disorder	254 (12.8)
Anxiety disorder	819 (41.1)
Substance use disorder	395 (19.8)
Somatic conditions	
Cardiovascular disease (hypertensive disease)	126 (6.3)
Hyperlipidemia	35 (1.8)
Diabetes	150 (7.5)
Gastrointestinal disease	67 (3.4)
Neurological disorder	77 (3.9)
Obesity	27 (1.4)
Respiratory disease (chronic pulmonary disease)	97 (4.9)

Compliance was calculated for any oral medication taken during the preinitiation period and for LAI-AP during the postinitiation period using the MPR. Patients were considered to be compliant if their MPR was 0.80 or higher.

The MPR of the index LAI-AP during the postinitiation period was calculated using the formula:

$$\frac{\text{Number of prescriptions in the postinitiation period} \times \text{the standard injection treatment interval}}{\text{365 days} - \text{number of days of hospitalizations}}$$

The same methodology was used for the compliance with oral APs in the preinitiation period, but instead of taking the standard injection treatment interval, the average duration of each prescription for the different oral AP prescriptions was used for the calculations. The following formula was used:

$$\frac{\text{Number of prescriptions in the preinitiation period} \times \text{average duration of each prescription}}{\text{365 days} - \text{number of days of hospitalizations}}$$

The oral APs in this analysis included the following: aripripazole, chlorpromazine, clozapine, flupentixol, fluphenazine, haloperidol, loxapine, olanzapine, perphenazine, pimozide, quetiapine, risperidone, trifluoperazine, ziprasidone, and zuclopenthixol.

As quetiapine may be used in indications other than schizophrenia (such as a sleep aid), complementary analyses without quetiapine were also performed.

Health Care Resource Use

Resource use (specifically, hospitalizations, ED visits for psychiatric reasons, outpatient clinic visits for psychiatric reasons, office visits to psychiatrist, and other office visits) was estimated for the pre- and postinitiation periods. McNemar's tests were used to evaluate the occurrence of each type of resource use between the pre- and postinitiation episodes. For each patient, the number of visits and of hospitalization days were compared using paired *t* tests, and results were reported with confidence intervals, 2-sided, with an alpha risk of 0.05. Hospitalizations were subdivided into 3 groups: hospitalization for any reasons; hospitalization for psychiatric reasons; and hospitalization for schizophrenia. Costs (inpatient, outpatient, and medication) were estimated for the pre- and postinitiation periods. The costs of hospitalization, ED visits, and of outpatient clinic visits were estimated using the average daily cost reported by the Quebec Hospital Association. The costs associated with the office visits (psychiatrist or other) were derived from the fees paid to specialists and general practitioners for these activities. Medication costs included the costs of LAI-APs, oral APs, other psychotropics, and other general medications. Costs were reported in Canadian dollars (Can$1 = US$0.95 during the study period).

Analyses were performed using IBM SPSS Statistics, version 19 (IBM SPSS Inc, Armonk, NY). Quantitative variables were presented as mean and standard deviation.

Results

Data were collected for 1992 patients. The demographics of the patients included in the analysis and their comorbid somatic and psychiatric conditions are summarized in Table 1 and Table 2, respectively.

Oral APs were the most frequent concomitant medications prescribed, with atypical second-generation APs being prescribed more frequently than typical first-generation APs. A total of 1068 patients (53.6%) and 559 patients

Table 3 Concomitant use of oral APs

Detail of medication	At index date (SD 15 days) *n* = 1992		At 6 months (SD 15 days) *n* = 1137	
	With quetiapine *n* (%)	Without quetiapine *n* (%)	With quetiapine *n* (%)	Without quetiapine *n* (%)
Patients with				
0 oral APs	728 (36.5)	941 (47.2)	578 (50.8)	745 (65.5)
1 oral AP	924 (46.4)	875 (43.9)	453 (39.8)	354 (31.1)
2 oral APs	294 (14.8)	159 (8.0)	101 (8.9)	36 (3.2)
≥3 oral APs	46 (2.3)	17 (0.9)	5 (0.4)	2 (0.2)
At least 1 oral AP	1264 (63.5)	1051 (52.8)	559 (49.2)	392 (34.5)
Distribution of APs prescribed for patients with at least 1 oral AP				
Aripripazole	33 (2.6)	33 (3.1)	25 (4.5)	25 (6.4)
Chlorpromazine	26 (2.1)	26 (2.5)	11 (2.0)	11 (2.8)
Clozapine	86 (6.8)	86 (8.2)	48 (8.6)	48 (12.2)
Flupentixol	10 (0.8)	10 (1.0)	2 (0.4)	2 (0.5)
Fluphenazine	20 (1.6)	20 (1.9)	3 (0.5)	3 (0.8)
Haloperidol	92 (7.3)	92 (8.8)	31 (5.5)	31 (7.9)
Loxapine	86 (6.8)	86 (8.2)	32 (5.7)	32 (8.2)
Olanzapine	337 (26.7)	337 (32.1)	137 (24.5)	137 (34.9)
Perphenazine	9 (0.7)	9 (0.9)	3 (0.5)	3 (0.8)
Pimozide	2 (0.2)	2 (0.2)	2 (0.4)	2 (0.5)
Quetiapine	411 (32.5)	—	238 (42.6)	—
Risperidone	487 (38.5)	487 (46.3)	116 (20.8)	116 (29.6)
Trifluoperazine	12 (0.9)	12 (1.1)	2 (0.4)	2 (0.5)
Ziprasidone	16 (1.3)	16 (1.5)	14 (2.5)	14 (3.6)
Zuclopenthixol	29 (2.3)	29 (2.8)	6 (1.1)	6 (1.5)

— = no value

AP = antipsychotic

(49.2%) received an oral AP concomitantly with the index drug at the index date (SD 15 days), and at 6 months (SD 15 days), respectively (Table 3). A total of 1051 patients (52.8%) and 392 patients (34.5%) received an oral AP concomitantly with the index drug at the index date (SD 15 days), and at 6 months (SD 15 days), respectively, when analyses did not take quetiapine into account (Table 3).

A total of 37.5% of patients were medication-compliant in the postinitiation period (n = 1992), while during the preinitiation period the compliance with oral APs was 29.0% (n = 2600). The average MPR during the 1-year period following the initiation of LAI-AP was 0.58 (SD 0.35) for the overall cohort (compared with 0.44 [SD 0.30] in the preinitiation period). The mean persistence after the initiation of LAI-AP was 217.2 days (SD 144.2) (Table 4). Note, when quetiapine is removed (n = 2023) from the analysis, the proportion of patients being compliant in the preinitiation period was reduced from 29.0% to 27.2%.

Cox proportional hazards regression models were performed to assess factors associated with nonpersistence to treatment. When the covariates were adjusted in the multivariate model, treatments with typical first-generation LAI-APs (HR 1.84; 95% CI 1.60 to 2.11, $P < 0.001$), and previous use of LAI-APs other than the index drug during the preinitiation period (HR 2.05; 95% CI 1.30 to 3.24, P = 0.002) were associated with an increased risk of being nonpersistent. Concomitant use of oral APs during the first treatment episode decreased the risk of being nonpersistent (HR 0.87; 95% CI 0.76 to 0.99, P = 0.04). Again, following the removal of quetiapine, treatments with first-generation LAI-APs (HR 1.85, 95% CI 1.61 to 2.12, $P < 0.001$), and previous use of LAI-APs other than the index drug during the pre-initiation period (HR 2.03; 95% CI 1.29 to 3.21, P = 0.002) were associated with an increased risk of being nonpersistent. Note that concomitant use of oral APs during the first treatment episode was no longer statistically significant after the removal of quetiapine from the analyses.

The number of patients with at least 1 hospitalization was higher in the preinitiation period, compared with the postinitiation period (1484 patients, compared with 958 patients, $P < 0.001$). The total number of hospitalization days per patient was higher in the preinitiation period,

compared with the postinitiation period (30.2 days [SD 38.4], compared with 10.2 days [SD 23.3], $P < 0.001$), as well as the number of visits to the ED for psychiatric reasons. Outpatient clinic visits for psychiatric reasons and other office visits were lower in the preinitiation period, compared with the postinitiation period. The number of office visits to a psychiatrist was similar during both periods. These data are shown in Table 5.

The total cost of HCRU (including inpatient, outpatient, and medication costs) was reduced from $24 382 (SD $27 234) in the preinitiation period to $13 090 (SD 16 987) in the year following the initiation of the LAI-APs ($P < 0.001$).

Table 4 Persistence and compliance to index LAI-APs (*n* = 1992)

Persistence after initiation of LAI-APs	
Mean (SD)	217.2 (144.2)
Median	237.0
Compliance	
Mean MPR during 1 year (SD)	0.58 (0.35)
Patients with MPR < 0.80, *n* (%)	1245 (62.5)

LAI-AP = long-acting injectable antipsychotic; MPR = medication possession ratio

Discussion

Suboptimal medication persistence and compliance represent a major unmet need and thus a major challenge in the treatment of schizophrenia and related disorders. Results from our analysis showed that the initiation of an LAI-AP significantly improved treatment compliance, compared with previous oral APs, among patients with schizophrenia. It also showed that the initiation of LAI-AP treatment resulted in significantly lower HCRU, compared with previous oral AP use, with the primary drivers being a reduction in the occurrence of hospitalizations, the number of days spent in hospital (which were reduced by one-half), and the number of visits to the ED.

In general, differences between the populations studied and the methods used to quantify persistence and compliance may influence the estimates. In our study, the proportion of patients on medication that were medication-compliant in the postinitiation period increased by 8.5% (10.3% when quetiapine is removed from the analyses) in the postinitiation period is of potential clinical significance. This absolute increase in the compliance rate represents, in relative terms, a percentage improvement of almost 30% (that is, 8.5/29.0). A relative percentage improvement of almost 38% (that is, 10.3/27.2) is reached when quetiapine is removed from the analyses. Compliance with AP treatments is a real concern in the ongoing management of patients with schizophrenia. Factors commonly associated with noncompliance include higher total symptom scores and dosing complexity, that is, greater than once daily. LAI-APs are helpful in simplifying dosing, and are efficient in helping to control symptoms. The wide variation in reported adherence rates reflects the inconsistency between the definitions of full adherence, partial adherence, and nonadherence used in the different clinical trials. In addition, in clinical trials, a high compliance rate would be expected owing to the tight monitoring of patients. In Canada, a study specifically focused on AP compliance using MEMS data in schizophrenia patients, reported an overall mean level of compliance of 48%[14]; other studies using the Brief Adherence Rating Scale reported a compliance rate of 49.5%.[15] The RAMQ data set mirrors the actual compliance in a general population of patients with psychosis, better reflecting usual clinical practice with real-life patients. The ability of treating clinicians to predict compliance or noncompliance is limited[14]: for instance, 42% of subjects, rated as compliant by the prescribers were in fact noncompliant, while 44% rated as noncompliant were actually compliant according to MEMS data. LAI-APs can be a good solution to reduce discontinuation, and to improve adherence. Treatment guidelines (for example, the Canadian Psychiatric Association guideline,[16] the Quebec Expert consensus,[17] the American Psychiatric Association,[18] the Schizophrenia Patient Outcomes Research Team,[19] and the Texas Medication Algorithm Project[20]) strongly recommend using LAIs for patients who are nonadherent with oral agents, but psychiatrists seem still reluctant to modify their practice.[8]

These results are in line with previous findings from published mirror-image studies, which are designed to retrospectively compare a time period before and after patients are treated with a given medication. A systematic review of randomized controlled trials, prospective and retrospective observational studies, and mirror-image studies for first-generation LAI-APs, compared with oral APs in schizophrenia, demonstrated reduced inpatient days and hospital admissions following a switch from oral APs to first-generation LAI-APs.[21] Further, a recent meta-analysis of mirror-image studies for first- and second-generation LAI-APs, compared with oral APs, reported robust evidence that LAI-APs were superior to oral APs regarding the occurrence and the number of hospitalizations.[7] Kane et al[22] also showed recently that switching from oral APs to aripiprazole once-monthly, a second-generation LAI-AP, substantially reduced psychiatric hospitalization rates, compared with retrospective hospitalization rates, in patients with schizophrenia. The reduction in HCRU likely translates to cost savings.[22]

In addition to these findings with mirror-image studies, results from the cohort for the general study of schizophrenia, which followed a cohort of consecutively enrolled patients from French public and private study centres, found that the use of risperidone LAI significantly reduced the risk of hospitalization, compared with the other APs used (oral and long-acting) during a 1-year period.[23] A real-world, nationwide cohort of patients with schizophrenia in Finland hospitalized for the first time showed that treatment with LAI-APs lowered the risk of rehospitalization by 50% to 65%, compared with treatment with oral medications.[24]

Table 5 Resource use: comparison between pre-and postinitiation periods (*n* = 1992)			
Resource use	Preinitiation	Postinitiation	Comparison
Occurrence of hospitalization			
At least once, *n* (%)			
Any reason	1484 (74.5)	958 (48.1)	*P* < 0.001
All psychiatric reasons	1442 (72.4)	875 (43.9)	*P* < 0.001
Schizophrenia	1351 (67.8)	757 (38.0)	*P* < 0.001
Number of days of hospitalization			
All patients			
Any reason			
Mean (SD)	30.2 (38.4)	10.2 (23.3)	*P* < 0.001
Median	18.0	0.0	(18.18 to 21.76)
All psychiatric reasons			
Mean (SD)	28.9 (37.7)	9.2 (22.1)	*P* < 0.001
Median	17.0	0.0	(17.89 to 21.36)
Schizophrenia			
Mean (SD)	20.6 (31.9)	6.2 (16.1)	*P* < 0.001
Median	9.0	0.0	(12.99 to 15.88)
Emergency department visits			
Psychiatric reasons			
At least once, *n* (%)	1372 (68.9)	813 (40.8)	*P* < 0.001
Number of visits in all patients			
Mean (SD)	2.9 (4.1)	1.6 (3.3)	*P* < 0.001
Median	2.0	0.0	(1.08 to 1.46)
Outpatient clinic visits			
Psychiatric reasons			
At least once, *n* (%)	1572 (78.9)	1726 (86.6)	*P* < 0.001
Number of visits in all patients			
Mean (SD)	5.3 (7.1)	8.6 (10.0)	*P* < 0.001
Median	3.0	6.0	(2.92 to 3.73)
Office visits to psychiatrist			
At least once, *n* (%)	40 (2.0)	34 (1.7)	0.377
Number of visits in all patients			
Mean (SD)	0.1 (1.0)	0.1 (1.0)	0.634
Median	0.0	0.0	(–0.03 to 0.05)
Other office visits			
At least once, *n* (%)	1016 (51.0)	1079 (54.2)	*P* = 0.007
Number of visits in all patients			
Mean (SD)	3.5 (6.5)	3.7 (6.8)	*P* < 0.01
Median	1.0	1.0	(0.07 to 0.51)

Our finding that the concomitant use of oral APs with LAI-AP treatment during the first treatment episode was associated with a lower risk of being nonpersistent (HR 0.87; 95% CI 0.76 to 0.99, $P = 0.04$) was an interesting finding: 42.6% were on quetiapine, 24.5% were on olanzapine, 20.8% were on risperidone, and 8.6% were on clozapine at 6 months (SD 15 days). Quetiapine was likely prescribed as an add-on medication to help patients sleep,[25] which could explain the high concomitant use of this agent with LAI-APs observed in our study. We could speculate that the concomitant use of oral APs, including quetiapine, may improve the persistence of schizophrenic patients with their LAI-APs, owing to improved sleep (for quetiapine), and (or) improved plasma drug levels (with other add-on oral APs). To help mitigate misleading conclusions about the high concomitance of quetiapine with LAI-APs, which may be related to the use of quetiapine in indications other than schizophrenia, analyses without quetiapine were also performed.

Our study has some inherent limitations, as in other studies based on administrative databases. It is assumed that the reimbursed medications retrieved from the database were taken by the patient, although this may not always be the case. Also, the database does not include medications received in a hospital. Another limitation of our study is related to the use

of ICD-9 codes to identify patients. In Quebec, physicians are not required to record an ICD-9 code, although most of them do (but a large proportion of psychiatrists use the code for unspecified mental disorders). Therefore, the number of patients with schizophrenia included in the RAMQ database is likely underestimated. In addition, because only a single ICD-9 code can be recorded on the form for each claim submitted to the RAMQ for reimbursement of a medical service, the prevalence of any specific diagnosis, such as medical history, can be underestimated when patients present more than one medical condition. Some costs were estimated using the average daily cost reported by the Quebec Hospital Association, and may therefore be underestimated or overestimated. Finally, the results obtained in this mirror-image study can only be compared with previous oral AP treatment, but cannot necessarily be compared with AP treatment in general. Improved outcomes may be explained by an LAI formulation that is likely to be initiated following a poor response to oral APs. Some information is not provided in the database, such as adverse events, limiting accurate, and comprehensive conclusions.[7]

Conclusions

In patients with schizophrenia or schizoaffective disorder, the initiation of an LAI-AP significantly improved treatment compliance and resulted in significantly lower HCRU and lower overall costs, compared with previous oral APs, in the province of Quebec.

The results of our study support the recommendations of the Canadian Psychiatric Association and the Association des Médecins Psychiatres du Québec regarding the use of LAI-APs.[16,17]

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