Adherence to Atypical Antipsychotic Treatment Among Newly Treated Patients: A Population-Based Study in Schizophrenia

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Background: Lack of adherence to drug treatment is a major obstacle to disease control. Although many studies have examined adherence to antipsychotic treatment, they have generally suffered from lack of differentiation between persistence and compliance as 2 separate components of adherence.

Objectives: In an outpatient population, to (1) measure the proportion of atypical antipsychotic users who were still on antipsychotic treatment after 12 months, (2) measure the proportion of compliant users among them, and (3) identify the determinants of persistence and of compliance.

Method: We carried out a population-based cohort study using the Quebec Health Insurance Board database. Patients previously diagnosed with schizophrenia (ICD-9 criteria) and initiated on clozapine, olanzapine, quetiapine, or risperidone treatment between January 1, 1997, and August 31, 1999, were included. Patients still undergoing treatment with any atypical antipsychotic drug 1 year after their first prescription were considered persistent. Of these patients, those with a supply of drugs for at least 80% of the days were deemed compliant. To identify the characteristics associated with both outcomes, we built a multivariate logistic regression model using a stepwise procedure and calculated odds ratios and their 95% confidence interval.

Results: Of 6662 individuals initiated on treatment with atypical antipsychotics, 4495 (67.5%) were still on the treatment after 1 year, and 3534 (78.6% of those who persisted) were compliant. Patients more likely to be both persistent and compliant were those initiated on clozapine, those who received a treatment of medium or high intensity, those who had used atypical antipsychotics, those without a history of substance-use disorder, and those on welfare. On the other hand, patients who were prescribed their first atypical antipsychotic by a psychiatrist were more likely to be persistent, whereas those with a high comorbidity index and those aged 35 years or more were more likely to be compliant.

Conclusions: One year after treatment initiation, almost a third of patients were no longer treated with atypical antipsychotics. Of those still being treated, more than 20% were noncompliant. Further studies should focus on means of improving such erratic treatment behaviors.

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Atypical antipsychotics are first-line medications in the treatment of schizophrenia, and most clinical guidelines suggest an antipsychotic treatment duration of at least 1 year after a first episode.[1] Lack of adherence to these drugs in this indication is a major impediment to disease control.[2] Adherence is a broad concept that can be divided into 2 separate components.[3] The first is persistence, defined as continuously refilling prescriptions in accordance with the suggested duration of therapy. Even if schizophrenic patients persist with their treatment, they may not take their drug in accordance with the prescribed dosage and schedule. This pertains to compliance with treatment, the second major component of adherence.

Adherence to atypical antipsychotic treatment has been assessed in many studies. Some of these have examined treatment persistence specifically,[4–14] while most either had a follow-up duration of less than 1 year[6,7] or limited their focus to persistence with the initial[5–9,11–15] or second-line[13,14] atypical antipsychotic medication. On the other hand, some studies[4,8,10,16–20] have tentatively examined compliance with atypical antipsychotic treatment; however, they have failed to measure compliance among persistent users only. To the best of our knowledge, persistence and compliance have not been studied at the same time and in the same population.

Lastly, the determinants of persistence and of compliance are not well established. The few studies on this topic share the above-mentioned limitations: they either

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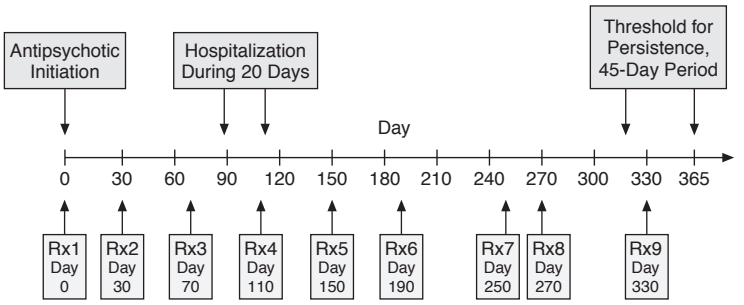
Figure 1. Persistence Definition and Compliance Measurement[a]



[a]Days supply: 9 × 30-day supply claim = 270 days. Number of days in which claims overlapped hospitalization periods = 10 (day 90 to day 99). Number of days in which claims overlapped each other: 10 (day 270 to day 279). Proportion of days in which an atypical drug was available (continuous multiple-interval measure of medication availability): (270 – 10 – 10)/345 = 72.5%.
Abbreviation: Rx = prescription.

focused on the initial medication[7,9,11,16,17] or did not differentiate between persistence and compliance.[7,9,11,16–18,20]

Employing an outpatient population of new users of atypical antipsychotics, this study had the following objectives: (1) to measure the proportion of users persistent with treatment after 12 months; (2) among those patients still on treatment after 12 months, to measure the proportion of compliant users; and (3) to identify the determinants of persistence and of compliance.

METHOD

We undertook a population-based cohort study using the Quebec Health Insurance Board (RAMQ) database and the Quebec registry of hospitalizations. The RAMQ health insurance plan covers all permanent residents of the province of Quebec, Canada. Its public drug plan covers all residents aged 65 years or over (receiving the guaranteed income supplement [GIS] or not), welfare recipients, and those who are not eligible for a private drug insurance group plan. The drug plan database is known to be accurate for prescription claims.[21]

In short, the RAMQ beneficiary demographic database provided data on patients' age, gender, region (rural or urban, as defined by Canada Post according to the national postal code), beneficiary type, and drug plan eligibility. The physician claims database furnished data on physician services (date and diagnosis). The prescription claims database provided data on dispensed drugs (drug identification, dispensing date, number of days' supply, and prescriber specialty). The hospitalizations registry yielded data on length of stay and on diagnoses (dates, primary diagnosis, and up to 16 secondary diagnoses).

We asked RAMQ to identify all those drug plan beneficiaries who had received at least 1 prescription of an atypical antipsychotic between January 1, 1997, and August 31, 1999. The date of first claim for any atypical antipsychotic during this period was defined as the index date. For each atypical antipsychotic user, RAMQ furnished us with data on all drugs claimed for the entire period between July 1, 1996, and August 31, 2000, as well as data on eligibility periods, beneficiary type, age, sex, and medical services. Using information from both the RAMQ databases and the registry for hospitalizations, we excluded those patients who were not beneficiaries of the drug plan for the entire 180-day period prior to the index date, those who had received any atypical antipsychotic during this same time period, those who had received 2 atypical antipsychotics at the index date, those with only claims with a 0-day supply, and those patients for whom we did not find a diagnosis of schizophrenia (*International Classification of Diseases*, Ninth Revision [ICD-9], codes 295.0 to 295.9) in the 180-day period prior to the index date. Finally, to ensure that we had complete data on every patient, we excluded all those patients who had moved out of province, become ineligible for the drug plan, or died during our 365-day period of follow-up.

To guarantee anonymity, RAMQ assigned each patient a unique encrypted number. This research was approved by the Commission d'accès à l'information du Québec.

Variables

We used data registered in the prescription claims database to assess each of our dependent variables: persistence and compliance. Patients were considered persistent with their treatment if they had filled at least 1 prescription of an atypical antipsychotic in the 45 days before the first anniversary of treatment initiation. In the province of Quebec, schizophrenic patients generally receive a 30-day supply. Consequently, this period of 45 days allows patients sufficient time to refill their prescription at the end of the 1-year follow-up and still be considered persistent.

Next, we measured compliance among those who persisted with their treatment using a continuous multiple-interval measure of medication availability (CMA).[22] The CMA equals the number of days in which an atypical antipsychotic is available, divided by the number of outpatient treatment days. As drugs taken in the hospital are not registered in the RAMQ database, we retrieved from the CMA measurement the number of days spent in the hospital (Figure 1). Day supplies overlapping 2 consecutive refills were not double-counted. People with a CMA of 80% or more were deemed compliant. This 80% threshold has been used in the past to assess adherence to antipsychotic treatment.[17,18,23,24]

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Using the beneficiary demographic database, we classed individuals into 2 groups: (1) patients on welfare or receiving GIS and (2) others. We grouped together welfare recipients and those receiving GIS since they both share similar copayment terms, which are lower than for other beneficiaries. We used the prescription claims database to assess potential determinants of persistence and of compliance: the atypical antipsychotic initially dispensed, specialty of the initial prescriber, previous use of typical antipsychotics, the intensity of the antipsychotic treatment, and the comorbidity index.[25] To define the intensity of the antipsychotic treatment, we determined groups according to tertiles of the distribution, using the dose taken at day 30 of the follow-up: low intensity (dose lower than or equal to 9.7 mg for olanzapine, 1.9 mg for risperidone, 300.0 mg for clozapine, and 100.0 mg for quetiapine), medium intensity (dose higher than 9.7 mg and lower than or equal to 10.0 mg for olanzapine, higher than 1.9 mg and lower than or equal to 4.0 mg for risperidone, higher than 300.0 mg and lower than or equal to 425.0 mg for clozapine, higher than 100.0 mg and lower than or equal to 300.0 mg for quetiapine), and high intensity (dose higher than 10.0 mg for olanzapine, 4.0 mg for risperidone, 425.0 mg for clozapine, and 300.0 mg for quetiapine). We computed the comorbidity index using empirically derived weights based on age and sex and the prescription claims registered in the database for the 180-day period prior to the index date. Scores ranged from 252.3 to 55,168.0. We classed individuals into 2 equal categories according to their score: low comorbidity (scores less than 4146) and high comorbidity (4146 and over).

We also looked at data recorded during the 180-day period prior to the index date in both the hospitalization registry and the medical services database. We searched the hospitalization registry for hospitalizations for mental disorder (first diagnosis: ICD-9 codes 290 to 319) or for substance-use disorder (ICD-9 codes 291, 292, 303 to 305). In the medical services database, we looked for medical visits for substance-use disorder and for the number of medical services claims with a diagnosis of mental disorder (ICD-9 codes 290 to 319). To assess the subtypes of schizophrenia, we used the last schizophrenia-related ICD-9 code registered in either database before the index date.

Statistical Analysis

We calculated the proportion of patients who persisted with therapy throughout the first year following treatment initiation. Among those who persisted, we calculated the mean, with its standard deviation (SD), and the median CMA, as well as the proportion of compliant patients. To identify those characteristics associated with persistence, we calculated adjusted odds ratios (ORs) with their 95% confidence interval (95% CI) using a multivariate logistic regression model that we built using a stepwise procedure with significance values of .10 as entry level and .15 as exit level. A similar method was used to identify those characteristics associated with compliance. Two-tailed p values of less than .05 were considered statistically significant. To test the sensitivity of the 80% CMA cut-off point for compliance, we repeated the analysis using different thresholds (70% and 90%). All analyses were conducted using SAS, version 8.[26]

RESULTS

Of the 6662 patients included in the study, 4495 (67.5%) were persistent with the atypical antipsychotic treatment. Of these, 3619 (80.5%) received only the initial atypical antipsychotic throughout the follow-up period, while 815 (18.1%) received a second, 59 (1.3%) received a third, and 2 patients (0.04%) received the 4 atypical antipsychotics. When compared to patients initiated on olanzapine, patients initiated on clozapine were more likely to be persistent, whereas those initiated on risperidone were less likely. Patients who received a treatment of medium or high intensity as opposed to those who received lower doses were also more likely to be persistent, as were those who had used typical antipsychotics in the 180-day period before the index date, those without a history of substance-use disorder, those who were prescribed their first atypical antipsychotic by a psychiatrist rather than a general practitioner or other physician, and patients on welfare or receiving GIS as opposed to others (Table 1).

Among those patients who persisted, the mean CMA was 86.4% (SD = 18.5; median = 94.2%), and 3534 (78.6%) of them were deemed compliant. Patients more likely to be compliant were those initiated on clozapine treatment as opposed to those initiated on olanzapine treatment, those who received a medium or high intensity treatment compared with those on a low intensity treatment, and those who had used typical antipsychotics in the 180-day period before the index date; those with a high comorbidity index; those without a history of substance-use disorder; those aged 35 or more compared with those aged 34 or less; and those on welfare or receiving GIS as opposed to others (Table 2).

There was little variation in the variables retained in the compliance model when thresholds for compliance were varied. Of the 7 variables statistically associated with compliance using the 80% CMA cut-off point, 6 were also statistically associated with compliance when a CMA of 70% or of 90% was used as the cut-off point (data not shown).

DISCUSSION

Our results suggest that there is a major hiatus in the use of atypical antipsychotics in schizophrenia by newly

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Table 1. Characteristics of Patients Who Were Persistent (N = 4495; 67.5%) and Nonpersistent (N = 2167; 32.5%) With Atypical Antipsychotic Treatment 365 Days After Treatment Initiation[a]

Characteristic	Persistent	Nonpersistent	Crude Odds Ratio	95% CI	Adjusted[b] Odds Ratio	95% CI
Age						
34 y or less	1210 (26.9)	648 (29.9)	1.00			
35 to 64 y	2859 (63.6)	1289 (59.5)	1.19	1.06 to 1.33		
65 y or over	426 (9.5)	230 (10.6)	0.99	0.82 to 1.20		
Gender						
Female	1882 (41.9)	955 (44.1)	1.00			
Male	2613 (58.1)	1212 (55.9)	1.09	0.99 to 1.21		
Welfare recipient or receiving guaranteed income supplement						
No	661 (14.7)	407 (18.8)	1.00		1.00	
Yes	3834 (85.3)	1760 (81.2)	1.34	1.17 to 1.54	1.18	1.02 to 1.36
Region						
Rural	617 (13.7)	308 (14.2)	1.00			
Urban	3877 (86.3)	1858 (85.7)	1.04	0.90 to 1.21		
Missing	1 (0.02)	1 (0.05)				
Prescriber specialty						
Psychiatrist	3309 (73.6)	1486 (68.6)	1.00		1.00	
General practitioner or other	986 (21.9)	575 (26.5)	0.77	0.68 to 0.87	0.80	0.71 to 0.91
Missing	200 (4.5)	106 (4.9)				
Previous[c] hospitalization for a mental disorder						
No	2964 (65.9)	1394 (64.3)	1.00			
Yes	1531 (34.1)	773 (35.7)	0.93	0.84 to 1.04		
Previous[c] no. of physician claims						
Fewer than 8	2234 (49.7)	1067 (49.2)	1.00			
8 or more	2261 (50.3)	1100 (50.8)	0.98	0.89 to 1.09		
First atypical antipsychotic prescribed						
Olanzapine	2537 (56.4)	1103 (50.9)	1.00		1.00	
Risperidone	1711 (38.1)	983 (45.4)	0.76	0.68 to 0.84	0.82	0.74 to 0.92
Clozapine	137 (3.1)	27 (1.3)	2.21	1.45 to 3.35	2.77	1.80 to 4.25
Quetiapine	110 (2.5)	54 (2.5)	0.89	0.64 to 1.24	1.00	0.71 to 1.41
Intensity of antipsychotic treatment at day 30[d]						
Low	1108 (24.6)	552 (25.5)	1.00		1.00	
Medium	1661 (37.0)	733 (33.8)	1.13	0.99 to 1.29	1.18	1.03 to 1.36
High	1326 (29.5)	433 (20.0)	1.53	1.31 to 1.77	1.59	1.36 to 1.85
No treatment at day 30	400 (8.9)	449 (20.7)				
Previous[c] use of typical antipsychotic						
No	1138 (25.3)	785 (36.2)	1.00		1.00	
Yes	3357 (74.7)	1382 (63.8)	1.68	1.50 to 1.87	1.68	1.50 to 1.89
Comorbidity index[e]						
Low (less than 4146)	2115 (47.1)	1210 (55.8)	1.00			
High (4146 or over)	2380 (53.0)	957 (44.2)	1.42	1.28 to 1.58		
Type of schizophrenic disorder						
Paranoid	1769 (39.4)	894 (41.3)	1.00		1.00	
Acute	78 (1.7)	45 (2.1)	0.88	0.60 to 1.28	1.01	0.68 to 1.48
Residual	225 (5.0)	100 (4.6)	1.14	0.89 to 1.46	1.05	0.81 to 1.35
Schizoaffective	662 (14.7)	312 (14.4)	1.07	0.92 to 1.25	1.05	0.90 to 1.24
Other[f]	1761 (39.2)	816 (37.7)	1.09	0.97 to 1.22	1.12	0.99 to 1.26
Substance-use disorder[c]						
No	4204 (93.5)	1972 (91.0)	1.00		1.00	
Yes	291 (6.5)	195 (9.0)	0.70	0.58 to 0.85	0.76	0.62 to 0.92

[a]Data shown as N (%).
[b]Model adjusted for variables retained in a stepwise procedure including all characteristics with a statistical entrance level of 0.10 and an exit level of 0.15.
[c]Number of physician claims, hospitalizations diagnosed with a mental disorder (ICD-9 codes 290 to 319), previous use of typical antipsychotics, and substance-use disorder (ICD-9 codes 291, 292, 303, 304, 305) were computed in the 180-day period prior to the index date.
[d]Daily doses according to tertiles of the distribution: Low intensity: lower than or equal to 9.7 mg for olanzapine, 1.9 mg for risperidone, 300.0 mg for clozapine, and 100.0 mg for quetiapine. Medium intensity: higher than 9.7 mg and lower than or equal to 10.0 mg for olanzapine, higher than 1.9 mg and lower than or equal to 4.0 mg for risperidone, higher than 300.0 mg and lower than or equal to 425.0 mg for clozapine, higher than 100.0 mg and lower than or equal to 300.0 mg for quetiapine. High intensity: higher than 10.0 mg for olanzapine, 4.0 mg for risperidone, 425.0 mg for clozapine, and 300.0 mg for quetiapine.
[e]Comorbidity score computed in the 180-day period prior to the index date, using empirically derived weights.[25]
[f]Other types of schizophrenic disorder include simple, disorganized, catatonic, latent, undifferentiated, and other specified types of schizophrenia.

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Table 2. Characteristics of Patients Who Were Compliant (N = 3534; 78.6%) and Noncompliant (N = 961; 21.4%) With Atypical Antipsychotic Treatment Among Patients Who Persisted 365 Days After Treatment Initiation[a]

Characteristic	Compliant[b]	Noncompliant	Crude Odds Ratio	95% CI	Adjusted[c] Odds Ratio	95% CI
Age						
34 y or less	853 (24.1)	357 (37.2)	1.00		1.00	
35 to 64 y	2341 (66.2)	518 (53.9)	1.89	1.62 to 2.21	1.61	1.37 to 1.91
65 y or over	340 (9.6)	86 (9.0)	1.66	1.27 to 2.16	1.77	1.32 to 2.36
Gender						
Female	1485 (42.0)	397 (41.3)	1.00			
Male	2049 (58.0)	564 (58.7)	0.97	0.84 to 1.12		
Welfare recipient or receiving guaranteed income supplement						
No	471 (13.3)	190 (19.8)	1.00		1.00	
Yes	3063 (86.7)	771 (80.2)	1.60	1.33 to 1.93	1.33	1.09 to 1.63
Region						
Rural	495 (14.0)	122 (12.7)	1.00			
Urban	3039 (86.0)	838 (87.2)	0.89	0.72 to 1.11		
Missing	0 (0.0)	1 (0.1)				
Prescriber specialty						
Psychiatrist	2610 (73.9)	699 (72.7)	1.00			
General practitioner or other	775 (21.9)	211 (22.0)	0.98	0.83 to 1.17		
Missing	149 (4.2)	51 (5.3)				
Previous[d] hospitalization for a mental disorder						
No	2362 (66.8)	602 (62.6)	1.00			
Yes	1172 (33.2)	359 (37.4)	0.83	0.72 to 0.97		
Previous[d] no. of physician claims						
Fewer than 8	1766 (50.0)	468 (48.7)	1.00			
8 or more	1768 (50.0)	493 (51.3)	0.95	0.82 to 1.10		
First atypical antipsychotic prescribed						
Olanzapine	2012 (56.9)	525 (54.6)	1.00		1.00	
Risperidone	1309 (37.0)	402 (41.8)	0.85	0.73 to 0.99	0.91	0.78 to 1.07
Clozapine	125 (3.5)	12 (1.3)	2.72	1.49 to 4.95	4.43	2.37 to 8.26
Quetiapine	88 (2.5)	22 (2.3)	1.04	0.65 to 1.68	1.29	0.78 to 2.13
Intensity of antipsychotic treatment at day 30[e]						
Low	869 (24.6)	239 (24.9)	1.00		1.00	
Medium	1342 (38.0)	319 (33.2)	1.16	0.96 to 1.40	1.31	1.08 to 1.60
High	1121 (31.7)	205 (21.3)	1.50	1.22 to 1.85	1.82	1.47 to 2.27
No treatment at day 30	202 (5.7)	198 (20.6)				
Previous[d] use of typical antipsychotic						
No	761 (21.5)	377 (39.2)	1.00		1.00	
Yes	2773 (78.5)	584 (60.8)	2.35	2.02 to 2.74	2.03	1.66 to 2.49
Comorbidity index[f]						
Low (less than 4146)	1530 (43.3)	585 (60.9)	1.00		1.00	
High (4146 and over)	2004 (56.7)	376 (39.1)	2.04	1.76 to 2.36	1.39	1.14 to 1.68
Type of schizophrenic disorder						
Paranoid	1388 (39.3)	381 (39.7)	1.00			
Acute	54 (1.5)	24 (2.5)	0.62	0.38 to 1.01		
Residual	189 (5.4)	36 (3.8)	1.44	0.99 to 2.09		
Schizoaffective	532 (15.1)	130 (13.5)	1.12	0.90 to 1.40		
Other[g]	1371 (38.8)	390 (40.6)	0.97	0.82 to 1.13		
Substance-use disorder[d]						
No	3329 (94.2)	875 (91.1)	1.00		1.00	
Yes	205 (5.8)	86 (9.0)	0.63	0.48 to 0.81	0.71	0.54 to 0.95

[a]Data shown as N (%).
[b]Compliance defined as having at least 80% of the follow-up period covered by an atypical antipsychotic.
[c]Model adjusted for variables retained in a stepwise procedure including all characteristics with a statistical entrance level of 0.10 and an exit level of 0.15.
[d]Number of physician claims, hospitalization diagnosed with a mental disorder (ICD-9 codes 290 to 319), previous use of typical antipsychotics and substance-use disorder (ICD-9 codes 291, 292, 303, 304, 305) were computed in the 180-day period prior to the index date.
[e]Daily doses according to tertiles of the distribution: Low intensity: lower than or equal to 9.7 mg for olanzapine, 1.9 mg for risperidone, 300.0 mg for clozapine, and 100.0 mg for quetiapine. Medium intensity: higher than 9.7 mg and lower than or equal to 10.0 mg for olanzapine, higher than 1.9 mg and lower than or equal to 4.0 mg for risperidone, higher than 300.0 mg and lower than or equal to 425.0 mg for clozapine, higher than 100.0 mg and lower than or equal to 300.0 mg for quetiapine. High intensity: higher than 10.0 mg for olanzapine, 4.0 mg for risperidone, 425.0 mg for clozapine, and 300.0 mg for quetiapine.
[f]Comorbidity score computed in the 180-day period prior to the index date, using empirically derived weights.[25]
[g]Other type of schizophrenic disorder includes simple, disorganized, catatonic, latent, undifferentiated, and other specified types of schizophrenia.

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treated patients. A third of patients do not persist for 1 year with the atypical antipsychotic treatment, yet clinical guidelines suggest a treatment duration of at least a year following a first episode.[1] Moreover, among those patients who are still on treatment after a year, 1 in 5 is not compliant with the treatment.

We observed that 67.5% of those initiating an atypical antipsychotic drug treatment are still on the therapy after a year. Other studies have shown that persistence with these medications varies between 34%[12] and 85%.[10] This wide variation could be explained in part by methodological differences.

For instance, persistence is likely to be lower when the focus of the study is on the initial medication as opposed to the antipsychotic treatment. In a previous analysis of this cohort,[12] for example, we observed that 39.5% of those who initiated atypical antipsychotic drug treatment with risperidone or olanzapine stayed on the initial medication during a 1-year follow-up period. In a recent clinical trial, Lieberman et al.[11] observed persistence with the initial atypical antipsychotic drug to be as low as 26% for an observation period of 18 months.

Furthermore, persistence is likely to decrease as the duration of the observation period increases. For instance, in clinical trials, persistence with the initial atypical antipsychotic drug was observed to be around 70% after 28 weeks,[6] down to 44% after 9 months[7] and to 26% after 18 months.[11] Nevertheless, as mentioned above, the decision to assess persistence 1 year after the initiation of treatment was based on the fact that clinical practice guidelines for schizophrenia suggest 1 year as the minimal treatment duration for a first episode.[1] Had we chosen a shorter observation period, the proportion of persistent individuals would have been greater than what we observed.

In our study, 21.4% of persistent users were not compliant, i.e., had a CMA lower than 80%. Other researchers have assessed the CMA among individuals taking atypical antipsychotic drugs,[8,10,16–19] and the CMAs observed in these studies varied between 42%[16] and 86%,[19] but none of the studies measured CMA among individuals still being treated 1 year after treatment initiation. It is therefore difficult to compare our results with those reported in the above-mentioned studies.

We identified 7 determinants of persistence. As observed in other studies,[7,9,13] clozapine users had better persistence. This result was expected, as individuals treated with clozapine are strictly monitored to ensure that their white blood cell counts remain within normal levels in order to minimize occurrence of agranulocytosis, a serious adverse event related to clozapine. Individuals initiated on risperidone treatment were less likely to be persistent than those initiated on olanzapine treatment. This finding is consistent with recent observations from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).[11]

Regardless of the atypical antipsychotic received, patients on medium or high intensity treatment at day 30 were also more likely to persist with their treatment. Exposure to a higher dose may contribute to a better control of the symptoms, which is therefore likely to facilitate persistence. On the other hand, patients with a lower dosage may receive suboptimal treatment.

Individuals who used typical antipsychotics in the 6 months prior to the index date were also more likely to persist with atypical antipsychotics. In fact, individuals who took a typical antipsychotic in the past had been being treated for a longer period of time than the others. Hence, one can hypothesize that patients who have remained in the health care system are likely to persist with their drug treatment.

Individuals who were initially prescribed their atypical antipsychotic by a psychiatrist, as opposed to another physician, were more likely to persist with their antipsychotic treatment. In Quebec, consulting a psychiatrist usually requires referral from a general practitioner. It might, therefore, be assumed that patients under a psychiatrist's care are more severely ill than others, and consequently they may receive a closer follow-up. One might also assume that patients who are referred to a psychiatrist and who do show up to their appointments are more likely to persist with treatment because they have exhibited persistence with appointments.

Patients on welfare or receiving GIS, when compared to the others, were more likely to be persistent. As mentioned above, this could be explained by their better economic access to prescription drugs since their copayments (the contribution that the individual patients pay themselves) are lower than those of the latter group. This result is in line with what has been observed in the field of hypertension.[27]

Individuals with a history of substance-use disorder were at greater risk of treatment discontinuation. This could be explained by what might be seen as the disorganized lifestyle of such individuals. Another hypothesis, suggested by Elbogen et al.,[28] is that patients with psychotic disorders may substitute drugs or alcohol for antipsychotics as a form of self-medication for psychological distress and mood or psychotic symptoms. In our study, we also looked at individuals with a history of substance abuse. If it is assumed that those who abused drugs in the past are more likely to repeat such behavior, then such a hypothesis might contribute to the explanation as to why these individuals were at greater risk of treatment discontinuation.

We identified 7 determinants of compliance. Among them, 5 were also determinants of persistence. Age and comorbidity were 2 variables not predictive of persistence but predictive of compliance. On the one hand, patients aged 35 years or more, compared to those aged less than 35, were more likely to comply with the treatment. These

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patients may be more aware of the importance of taking their antipsychotic regularly. As hypothesized by Gilmer et al.,[17] who measured adherence to antipsychotics using the CMA method among both persisting and nonpersisting individuals, younger patients with a shorter duration of illness may not have had sufficient time to develop an awareness of the consequences of nonadherence. On the other hand, individuals with a higher level of comorbidity were also more likely to comply with treatment. Since comorbidity was measured on the basis of the number of concurrent medications, it is likely to be correlated to the number of pills taken daily. In a study on the determinants of compliance among patients persisting with their antihypertensive treatment, self-reported compliance was shown to be better among those taking 4 or more pills daily.[29] Patients who remained on treatment after 1 year may have passed through an earlier and possibly more critical stage for treatment compliance and have developed means to better manage their treatment for the long term.

As mentioned earlier, other researchers have tentatively examined the determinants of better treatment compliance with atypical antipsychotics, yet none has measured compliance among persistent users only. However, although focusing on both persistent and nonpersistent users, the researchers in some of those studies have observed determinants similar to those we have identified.

For example, Valenstein et al.[18] observed that being treated with clozapine (compared to conventional or to other atypical antipsychotics), being aged 45 to 65 (compared to those aged less than 45), and having received at least 1 antipsychotic high-dose fill (doses exceeding 1000 mg chlorpromazine equivalents for conventional antipsychotics and exceeding 6 mg for risperidone, 20 mg for olanzapine, 750 mg for quetiapine, and 900 mg for clozapine) were 3 factors associated with a CMA of 80% or more.

In the study by Gilmer et al.,[17] being treated with clozapine (compared to conventional or to other atypical antipsychotics), increasing age, and a lack of substance-use disorder were 3 factors associated with a CMA of between 80% and 110%.

In our study, patients who were initially prescribed their atypical antipsychotic by a psychiatrist and patients who received olanzapine (as opposed to risperidone) were more likely to be persistent. In contrast, these variables were not associated with compliance among those who were still on treatment after 1 year. These results suggest that being treated by a psychiatrist or being initiated on olanzapine treatment may be important for long-term persistence with drug treatment, but, for those who persist, these are not factors that predict compliance.

Our study has some limitations inherent in the use of administrative databases. First, we assumed that drugs dispensed were actually used. In so doing, we possibly overestimated both persistence and compliance. On the other hand, as the leftover duration of a dispensing was not counted when patients had overlapping consecutive refills, we may have underestimated both persistence and compliance. Second, the RAMQ drug insurance plan does not cover the Quebec population below age 65 who have access to a private group drug insurance plan. However, given that very few schizophrenic patients are employed[30] and thus have access to a private drug insurance group plan, most people suffering from schizophrenia are covered by the RAMQ drug plan. Third, information on many clinical and demographic characteristics is lacking. Consequently, we were not able to take into consideration some potential determinants previously identified in other studies, e.g., attitude toward drug use,[31,32] social support,[31,32] family situation,[17,31] living conditions,[17,31] and race.[17]

Moreover, as the in-hospital use of medication is not recorded in the prescription claim database, those patients who were hospitalized in the final 45 days of the follow-up period may have been erroneously considered as nonpersistent. However, there were only 7 patients hospitalized during this period and thus considered nonpersistent. Excluding them from the analysis did not alter the results concerning the determinants of persistence (data not shown).

Despite these limitations, we were able to study a large population of ambulatory-treated adults with schizophrenia in a naturalistic setting and observe patterns of use over a 1-year period. We analyzed persistence and compliance as 2 different components of treatment adherence. Recent research in hypertension[29] has shown that some determinants of persistence and of compliance may be different. Our current findings in schizophrenia give further credence to the rationale for studying persistence and compliance separately. In addition, prior studies have described persistence and compliance with the initial atypical antipsychotic prescribed, whereas we focused on persistence and compliance with any atypical antipsychotic treatment, not with the initial drug only. Such an approach is relevant in terms of potential impact on clinical outcomes, since it is important that schizophrenic patients be exposed to an antipsychotic treatment in order to prevent relapses.

CONCLUSION

Since schizophrenia is a chronic condition requiring long-term and continuous treatment, persistence and compliance with atypical antipsychotic medications are important elements in the successful management of schizophrenic patients in routine clinical practice. This study suggests that many patients treated with atypical antipsychotics show erratic treatment behaviors, thereby potentially reducing treatment effectiveness. Further studies specifically designed to develop and assess interventions so as to optimize the use of atypical antipsychotic medications are needed.

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Drug names: clozapine (FazaClo and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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