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Comparative effectiveness and safety of antipsychotic drugs in schizophrenia treatment: a real-world observational study

Vanasse A, Blais L, Courteau J, Cohen AA, Roberge P, Larouche A, Grignon S, Fleury M-J, Lesage A, Demers M-F, Roy M-A, Carrier J-D, Delorme A. Comparative effectiveness and safety of antipsychotic drugs in schizophrenia treatment: a real-world observational study.

Objective: The objective was to compare, in a real-world setting, the risk of mental and physical health events associated with different antipsychotic drugs (clozapine, olanzapine, risperidone, quetiapine and first-generation antipsychotics) in patients with SZ.
Methods: This is a retrospective cohort study using administrative data. Outcome measures included any mental health event (suicide, hospitalization or emergency visit for mental disorders) and physical health event (death other than suicide, hospitalization or emergency visit for physical disorders). Cox proportional hazard models were used to estimate the hazard ratios of the events associated with the use of the different antipsychotic drugs.
Results: The cohort included 18 869 adult patients living in the province of Quebec (Canada) with SZ and starting antipsychotic drugs between January 1998 and December 2005. Results show that quetiapine and not using any antipsychotics were associated with an increased risk of mental and physical health events as compared to other drugs. The second finding is the confirmation of better performance of clozapine. The results were robust across sensitivity analyses.
Conclusion: Both findings call for an international public health and drug agencies surveillance of 'real-world' antipsychotic medication to ensure the optimal choices in treatment guidelines for SZ.

A. Vanasse[1,2], L. Blais[3], J. Courteau[2], A. A. Cohen[1,2], P. Roberge[1,2], A. Larouche[2], S. Grignon[4], M.-J. Fleury[5], A. Lesage[6], M.-F. Demers[7,8], M.-A. Roy[8], J.-D. Carrier[2], A. Delorme[9]

[1]Département de médecine de famille et de médecine d'urgence, Université de Sherbrooke, Sherbrooke, QC, [2]PRIMUS Group, Centre de recherche du CHUS, Université de Sherbrooke, Sherbrooke, QC, [3]Faculté de Médecine, Université de Montréal, Montréal, QC, [4]Département de Psychiatrie, Université de Sherbrooke, Sherbrooke, QC, [5]Douglas Mental Health University Institute, McGill University, Montréal, QC, [6]Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, QC, [7]Faculté de pharmacie, Université Laval, Québec, QC, [8]Centre de recherche de l'Institut universitaire en santé mentale de Québec (CRIUSMQ), Québec, QC, and [9]Direction de la santé mentale, Ministère de la santé et des services sociaux du Québec, Québec, QC, Canada

Key words: real-world study; schizophrenia; antipsychotic drugs; relative effectiveness; safety; discontinuation

Alain Vanasse, Département de médecine de famille et de médecine d'urgence, Université de Sherbrooke, 3001, 12th Avenue North, Sherbrooke, QC J1H 5N4, Canada.
E-mail: Alain.Vanasse@Usherbrooke.ca

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Significant outcomes

- In this real-world study, quetiapine was associated with worse outcomes as compared to first-generation antipsychotics, but initial doses seemed to be suboptimal.
- Clozapine and Olanzapine performed slightly better than first-generation antipsychotics.
- Clozapine, quetiapine, olanzapine and risperidone were all associated with a lower risk of stopping or changing their medication as compared to first-generation antipsychotics.

Limitations

- This observational study was limited to public drug insurance beneficiaries.
- This study was based on administrative data so that reasons for prescription or disease severity were not directly available; thus, there are still possible residual confounding factors.
- Quetiapine was a new drug during the study period (1998–2005). It is thus unclear whether its poor performance is due to the molecule itself or to the suboptimal doses prescribed during that time.

Introduction

Antipsychotic (AP) drugs are used to treat and manage symptoms for several psychiatric disorders including schizophrenia. APs are commonly categorized into first generation (FGA) (developed in the 1950s) and second generation (SGA) (developed in the 1990s), the main difference being that FGA drugs block dopamine D2 receptors and SGA drugs block dopamine D2 receptors with faster dissociation and also affect serotonin levels (1). Whether or not all APs are equally effective is still in debate. Recent studies have attempted to provide comparative effectiveness of different APs (2–5). Two meta-analyses of randomized controlled trials (RCTs) (2, 5) with direct comparison between FGAs and SGAs concluded that SGAs performed generally better than FGAs, except for tolerability (e.g. weight gain). However, another review found few differences of clinical importance for outcomes of effectiveness between them in studies also using direct comparison (4). In 2013, a meta-analysis (3) of 212 RCTs using direct and indirect comparisons of AP drugs reported pairwise comparisons between 15 available APs, mainly SGAs, regarding efficacy [change in Positive and Negative Syndrome Scale (6)], acceptability (discontinuation) and tolerability (weight gain, extrapyramidal side-effects, sedation, etc.). Clozapine, a SGA, was ranked first in terms of efficacy and also performed well regarding discontinuation and extrapyramidal side-effects, but has been associated with weight gain and sedation. Some RCTs were excluded from the analysis (3), in particular those conducted in patients with concomitant medical illness. However, in clinical practice, an important proportion of patients with schizophrenia can experience these conditions. For example, it has been reported that schizophrenia is associated with substantial chronic medical burden (7, 8), particularly regarding the association with the development of diabetes mellitus (9–11), which can be partially explained by the use of AP but also by poor health behaviours of patients with schizophrenia, and also by the involvement of a systemic inflammatory component in both diseases that may contribute to their co-occurrence (12, 13).

The findings from RCTs are often limited in terms of generalizability (exclusion of older adults, patients with comorbidities or co-medications) (14); for instance, up to 87% of patients with schizophrenia were ineligible to participate in pivotal RCTs (15). For this reason, observational 'real-world' studies can bring complementary information in comparative effectiveness research (16). Such studies have been infrequent, probably due to difficult access to linked administrative health databases in a single private or public managed care system covering the population of a state or country. However, one such study was conducted in Finland by Tiihonen et al. (17). They reported outcomes in terms of reduced life expectancy and found significantly better outcomes with clozapine, and worst with quetiapine, compared to perphenazine, a FGA, and better outcomes with APs in general, compared to no AP, for people diagnosed with schizophrenia. This study was, however, largely criticized by De Hert et al. (18), raising a number of methodological and conceptual issues including survivorship bias due in part to the prevalent-user design of the Tiihonen study (17); the exclusion of a large proportion of deaths occurring during hospitalization; and also strong and systematic differences in illness duration across the treatment groups. However, one way to limit such bias is to use a new-user design (19), that is to identify all patients in a defined population who initiate a course of treatment with the study medication by setting a minimum period of non-use prior to its initiation.

Aims of the study

The main objective of this study was to measure and compare, using a new-user design in a real-world setting, the risk of mental health events and the risk of physical health events for patients with schizophrenia or schizoaffective disorder initiating different APs, taking into account their gender, age and comorbidities.

Methods

Design and data sources

In Quebec, as in the rest of Canada, health and social services (except medication) are free and equally accessible to all. This is a retrospective cohort study with a new-user design using administrative data obtained from the *Régie de l'assurance maladie du Québec* (RAMQ). The RAMQ owns and manages health administrative databases including a hospital discharge register (MED-ECHO), patients' demographic information, physicians' reimbursement claims and the provincial drug insurance plan. The mortality database, provided by the *Institut de la statistique du Québec*, includes dates and causes of deaths (ICD-9 before 2000, ICD-10 since 2000). MED-ECHO contains information on dates of acute care hospitalizations, interventions and main and secondary

diagnoses (according to ICD-9 before 1 April 2006, and to ICD-10 thereafter) encountered during hospitalizations. The RAMQ demographic database provides information on patients' age, gender, eligibility for the public drug insurance plan and, for those eligible, receipt of welfare or supplement. The physician reimbursement claims database provides the date and the diagnosis (according to ICD-9) associated with the service provided. The drug database contains information on the drugs claimed from community pharmacies by individuals covered by the public drug insurance plan and also contains the specialty of the prescribing physician. This drug database does not contain information on in-patient drug treatment. The public drug insurance plan covers about 90% of residents aged ≥65 years, all welfare recipients, and any person under 65 years who does not have access to a private plan. In 2006, 42% of the Quebec population (including the elderly) were beneficiaries of the public drug insurance plan (20). However, prior assessment of our database indicates that as many as 75% of adult patients diagnosed with schizophrenia were registered to the public drug insurance (data not shown). Using a unique encrypted identifier, patient files were linked to provide demographic characteristics, medical and drug information. A recent report from Quebec's public health agency provides details on the population coverage, validity studies and content of the databases (21). For the present project, we obtained access to the linked databases through a grant from the Canadian Institutes of Health Research, after clearance from the *Commission d'accès à l'information* (Quebec's data privacy commissioner) and the Research Ethics Board Committee of the *Université de Sherbrooke*.

Study cohort

The study cohort includes all adult patients living in Quebec and starting at least one AP drug (with a clearance baseline period of 6 months without any APs) between January 1998 and December 2005, with a prior diagnosis of schizophrenia or schizoaffective disorder (SZ) (ICD-9: 295) reported in the administrative database within 2 years prior to the index date (i.e. date of the first occurrence of AP claim) (Fig. 1). Patients not covered by the public drug insurance plan during the 6-month baseline period, pregnant women and those with an outcome event (death, hospitalization, or emergency department (ED) visit for mental or physical disorders) at the index date or the day after were excluded. The 18 869 new AP users included were followed until an event occurred, the end of

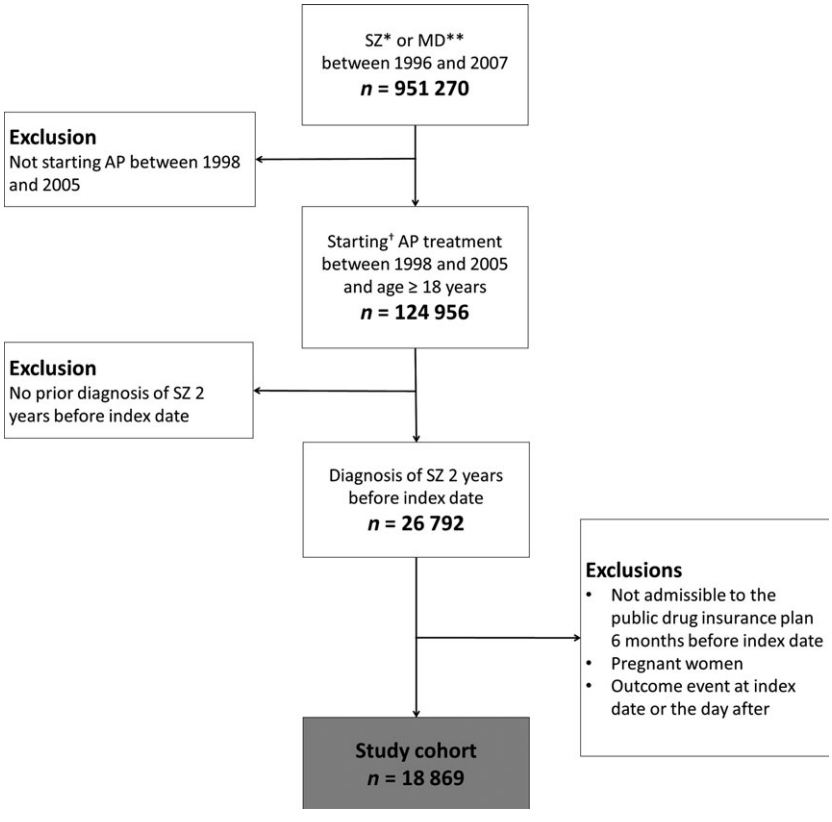


Fig. 1. Selection criteria of the study cohort. *one diagnosis of schizophrenia (SZ) during a hospitalization or during a medical visit. **one diagnosis of mood disorders (MD) during a hospitalization or two diagnosis of MD within one year during a medical visit. †With a clearance period of 6 months.

eligibility to the public drug insurance plan (in the case of the current use analysis – see Statistical analyses) or to the end of follow-up period of 2 years, whichever came first.

Main outcomes

Effectiveness was measured by the occurrence of mental health events, and safety by the occurrence of physical health events. Mental health events refer to the first occurrence of any of the following within 2 years after the index date: suicide (CIM-9 accidental cause: 950–959; ICD-10: X60-X84, Y87.0), hospitalization or ED visit with a main diagnosis related to mental disorders (ICD-9: 290–319; ICD-10: F00-F99). Physical health events refer to the first occurrence of any of the following non-mental health events within 2 years after the index date: death other than suicide, hospitalization or ED visit with a main diagnosis not related to mental disorders.

Secondary outcomes were as follows: AP discontinuation (if the patient did not claim any APs at a community pharmacy for at least 90 consecutive days); switch/add-on AP treatment (if the patient changed AP or added an AP during the follow-up period); and a composite outcome combining discontinuation and switch of AP. Discontinuation is often considered to be an indicator of inefficacy or intolerability in the literature (2, 5, 22–25).

Drug exposure

The following SGA drugs were available during the study period and were considered separately in the analyses: olanzapine, risperidone, quetiapine and clozapine. All FGAs were pooled in a single category. All patients who claimed medication from more than one of these categories were included into a multiple-treatment category (MULT). At the index date, each patient was exposed to one of these six AP categories. A patient was considered exposed to the drug from the date (s)he claimed a prescription at a community pharmacy and for the duration of the drug delivered. As long-acting injectable SGA drugs were not available during the inclusion period (1998–2005), we did not differentiate oral vs. long-acting injectable APs. Also, dosage was not taken into account at this stage. Nonetheless, these issues were addressed in sensitivity analyses.

Covariates

The following covariates were assessed at the index date or during the baseline period (6 months before and including the index date): gender; age; index year; elapsed time between the diagnosis of SZ and initiation of AP treatment; poor financial status (defined as receiving social assistance, or guaranteed income supplement); specialty of the prescribing physician (psychiatrist, general practitioner, any medical resident, and unknown); use of lithium, divalproex, antidepressants, benzodiazepines; prior hospitalization for schizophrenia or psychosis; prior hospitalization for another mental disorder; prior substance abuse (reported during a hospitalization or during an ambulatory medical visit); prior hospitalization for a non-mental health reason; physical comorbidity index (categorized as: 0, 1–2, ≥3); and, because of the high risk of metabolic syndrome in patients with SZ (26), prior hospitalization for cardiovascular disease, and prior diagnosis of diabetes, hypertension or dyslipidemia. The comorbidity index was based on the Charlson score, as adapted by D'Hoore et al. (27). to better suit the Quebec administrative database; it is a weighted score of comorbid physical chronic conditions calculated using the diagnoses reported in MED-ECHO and in the physicians' claims registry.

Statistical analyses

Cox proportional hazard models were used to estimate the hazard ratios (HR) (with their 95% confidence intervals) of the outcome events associated with the use of the different AP categories with FGAs as the reference group. Two approaches were considered for the definition of AP exposure: an intent-to-treat (ITT) and a 'current use' approach (28, 29). As the exposure to AP treatment refers to the initial AP category claimed on the index date in the ITT analysis, there is a possible misclassification of treatment due to the fact that patients may either stop or change AP during follow-up. To overcome this, a 'current use' approach was proposed; in this case, the AP exposure refers to the AP drug taken by the patient just before the event (including the possibility of no treatment). ITT was analysed with a Cox model without time-dependent variables, and outcomes were censored at the end of follow-up (index date + 730 days). The 'current use' approach was analysed using a Cox model with time-dependent AP exposure. In this case, outcomes were censored at the date of ineligibility to the public drug insurance plan or the end of follow-up. All models were adjusted for the covariates mentioned above. An adjustment strategy using the selected covariates instead of a propensity score analysis was preferred considering the sufficient number of events per

confounder (30). Analyses were performed using SAS 9.4.

Sensitivity analyses were performed to see whether the results were robust. To see whether the initial dosage had an effect on the results, we stratified initial AP use as higher or lower initial dose using the 3rd quartiles as thresholds. We also performed an ITT analysis on patients who initiated an oral AP treatment only, as patients on long-acting injectable APs may behave differently from those on oral APs. Other stratified analyses were also performed: by gender, age (<35, 35–54, ≥55), financial status (poor, wealthy), history of hospitalization for psychosis, comorbidity index (0, ≥1) and finally by index year (1998–1999, 2000–2005) as utilization of SGAs was more prevalent in the latest period (Fig. S1).

Results

Nearly 125 000 adult patients from our database started an AP between 1998 and 2005. Of these, only 26 792 had received a prior diagnosis of SZ (Fig. 1). As the case definition of SZ has been previously validated and showed a high sensitivity (31), this suggests that most APs are prescribed either for off-label use or for bipolar disorders. After exclusions, the study cohort included 18 869 patients. At initiation of treatment, only 8.0% of them received more than one class of drugs; 28.5% received only FGAs (phenothiazines: 40.8%, haloperidol: 34.5%, thioxanthenes: 13.4%, long-acting injectable: 38.8%); 63.4% received a SGA in monotherapy – olanzapine 29.3% (median daily dose: 10 mg), risperidone 26.4% (median daily dose: 2 mg), quetiapine 6.0% (median daily dose: 100 mg) and clozapine 1.7% (median daily dose: 400 mg) (Table 1). Characteristics of the study cohort differed somewhat widely according to the AP exposure category, especially regarding clozapine. Clozapine was most often prescribed by a psychiatrist, and patients initiating clozapine were more often male, younger, poorer, received divalproex more often and were hospitalized for psychosis prior to AP initiation in a greater proportion than the other exposure categories. However, they were in better physical health and were less diagnosed or treated for other mental health disorders, particularly when compared to patients initiating quetiapine (Table 1).

During the follow-up period (maximum of 2 years), 9502 patients (50.4%) were reported as having a mental health event, among which 0.6% (114) died from suicide, 35.3% (6654) had a hospitalization for a mental disorder, and 45.5% (8583) consulted an ED for a mental health disorder. Also, 10 532 (55.8%) suffered from a physical health event, among which 4.4% (825) died from another cause than suicide, 19.9% (3758) had a hospitalization for a non-mental disorder, and 52.3% (9863) consulted an ED for a non-mental health disorder (Table 1). An important proportion of patients (67.7%) discontinued or switched/added-on their AP treatment (Table 1).

First, exposure assessment differs in ITT analyses as compared to 'current use' analyses as an important proportion of patients changed or stopped their treatment during follow-up, making 'current use' a better indicator of actual AP exposition. Nonetheless, the results reveal that ITT quetiapine use was associated with an increased risk of mental and physical health events as compared to FGAs (Fig. 2) or to oral FGAs only (Fig. S2b, d). More specifically, patients using quetiapine and those not using any APs at event time were at an increased risk of mental health events (HR = 1.38, 95% CI: 1.24–1.54, $P < 0.0001$ and HR = 1.54, 95% CI: 1.44–1.65, $P < 0.0001$, respectively) (Fig. 2b), and also of physical health events (HR = 1.24, 95% CI: 1.12–1.37, $P < 0.0001$ and HR = 1.24, 95% CI: 1.17–1.32, $P < 0.0001$, respectively), as compared to FGAs (Fig. 2d). Similar results regarding quetiapine were observed when looking at specific elements of the effectiveness composite outcome, including hospitalizations and ED visits for mental health (Fig. S3a, b).

Clozapine and olanzapine performed slightly better than FGAs, while risperidone and FGAs did not seem to differ significantly from each other regarding the risk of mental and physical health events (Fig. 2b, d). Looking deeper, clozapine was associated with reduced risk of physical health events in ITT analysis (Fig. 2c), but associated with an increased risk of death or urgent hospitalization for physical health in 'current use' analysis (Fig. S3f). Regarding hospitalization for physical health or serious physical health events, APs other than clozapine did not differ significantly from each other (Fig. S3d, f). Suicides in this cohort were too rare to draw meaningful conclusions.

Overall, FGAs were associated with the highest risk of discontinuation or switch (Fig. 3). Patients initiating clozapine had, by far, less chance of discontinuing their treatment than all other AP categories (Fig. 3a). Quetiapine was associated with the least chance of switching or adding AP (Fig. 3b).

Stratified analyses by initial daily dose (Fig. S2a, c) show little differences in the results. However, patients receiving quetiapine as the first AP treatment seemed to be prescribed non-optimal initial doses. Results were similar when stratified by

Table 1. Characteristics of the study cohort by AP category* (n = 18 869)

	Total	FGAs	OLAN	RISP	QUE	CLOZ	MULT	P-value†
Total, n (%)	18 869	5379 (28.5)	5528 (29.3)	4989 (26.4)	1139 (6.0)	324 (1.7)	1510 (8.0)	–
Initial Daily Dose, Q_1, median, Q_3 (mg)	–	–	5, 10, 10	1, 2, 3	50, 100, 200	160, 400, 500	–	–
Long-acting injectable AP, n (%)	–	2087 (38.8)	0 (0.0)	7 (0.1)	0 (0.0)	0 (0.0)	–	–
Gender, n (%)								<0.0001
Women	8634 (45.8)	2576 (47.9)	2358 (42.7)	2465 (49.4)	534 (46.9)	112 (34.6)	589 (39.0)	
Men	10 235 (54.2)	2803 (52.1)	3170 (57.3)	2524 (50.6)	605 (53.1)	212 (65.4)	921 (61.0)	
Age, mean (SD)	45.2 (17.4)	47.6 (15.8)	41.8 (78.5)	47.2 (19.7)	44.2 (17.5)	40.8 (10.8)	43.3 (14.9)	<0.0001
Days since SZ diagnosis, mean (SD)	97 (167)	140 (192)	78 (154)	74 (147)	124 (193)	84 (138)	74 (133)	<0.0001
Index year, n (%)								<0.0001
1998–1999	7856 (41.6)	3577 (66.5)	1964 (35.5)	1641 (32.9)	118 (10.4)	111 (34.3)	445 (29.5)	
2000–2002	6487 (34.4)	1307 (24.3)	2030 (36.7)	2025 (40.6)	377 (33.1)	138 (42.6)	610 (40.4)	
2003–2005	4526 (24.0)	495 (9.2)	75 (23.2)	1323 (26.5)	644 (56.5)	75 (23.2)	455 (30.1)	
Poor financial status, n (%)	13 515 (71.6)	4112 (76.4)	3752 (67.9)	3394 (68.0)	781 (68.6)	277 (85.5)	1199 (79.4)	<0.0001
Prescriber speciality, n (%)								<0.0001
Psychiatrist	11 305 (59.9)	3087 (57.4)	3474 (62.8)	2848 (57.1)	681 (59.8)	226 (69.8)	989 (65.5)	
GP	5426 (28.8)	1791 (33.3)	1381 (25.0)	1498 (30.0)	324 (28.4)	75 (23.2)	357 (23.6)	
Other	2138 (11.3)	501 (9.3)	673 (12.2)	643 (12.9)	134 (11.8)	23 (7.1)	164 (10.9)	
Lithium, n (%)	1739 (9.2)	508 (9.4)	527 (9.5)	399 (8.0)	127 (11.2)	35 (10.8)	143 (9.5)	0.0067
Divalproex, n (%)	2193 (11.6)	540 (10.4)	701 (12.7)	460 (9.2)	137 (12.0)	79 (24.4)	276 (18.3)	<0.0001
Antidepressant, n (%)	5062 (26.8)	1114 (20.7)	1568 (28.4)	1458 (29.2)	555 (29.2)	52 (16.0)	315 (20.9)	<0.0001
Benzodiazepines, n (%)	9606 (50.9)	2817 (52.4)	2663 (48.2)	2501 (50.1)	657 (57.7)	125 (38.6)	843 (55.8)	<0.0001
Prior Hosp. SZ-psychosis, n (%)	6567 (34.8)	1340 (24.9)	2158 (39.0)	1847 (37.0)	258 (22.6)	163 (50.3)	801 (53.0)	<0.0001
Prior Hosp. other mental dis., n (%)	3279 (17.4)	609 (11.3)	1181 (21.4)	955 (19.1)	307 (27.0)	13 (4.0)	214 (14.2)	<0.0001
Prior substance abuse, n (%)	4220 (22.4)	862 (16.0)	1437 (26.0)	1190 (23.8)	289 (25.4)	47 (14.5)	395 (26.2)	<0.0001
Prior Hosp. physical health, n (%)	1975 (10.5)	584 (10.9)	471 (8.5)	659 (13.2)	141 (12.4)	11 (3.4)	109 (7.2)	<0.0001
Prior Hosp. diabetes, HBP, DLP, n (%)	1946 (10.3)	568 (10.6)	458 (8.3)	644 (12.9)	145 (12.7)	22 (6.8)	109 (7.2)	<0.0001
Comorbidity index (≥ 1), n (%)	4467 (23.7)	1109 (20.6)	1264 (31.8)	1480 (29.7)	277 (24.3)	35 (10.8)	302 (20.0)	<0.0001
Outcomes								
Mental health event, n (%)	9502 (50.4)	2489 (46.3)	2953 (53.4)	2477 (49.6)	639 (56.1)	147 (45.4)	797 (52.8)	<0.0001
Suicide‡	114 (0.6)	–	–	–	–	–	–	–
Hosp. for mental disorder	6654 (35.3)	1678 (31.2)	2091 (37.8)	1744 (35.0)	424 (37.2)	113 (34.9)	604 (40.0)	<0.0001
ED visit for mental disorder	8583 (45.5)	2238 (41.6)	2703 (48.9)	2210 (44.3)	594 (52.2)	124 (38.3)	714 (47.3)	<0.0001
Physical health event, n (%)	10 532 (55.8)	2965 (55.1)	3012 (54.5)	2892 (58.0)	741 (65.1)	147 (45.4)	775 (51.3)	<0.0001
Death (other than suicide)‡	825 (4.4)	–	–	–	–	–	–	–
Hosp. for non-mental disorder	3758 (19.9)	1116 (20.8)	932 (17.3)	1121 (22.5)	269 (23.6)	59 (18.2)	261 (17.3)	<0.0001
ED visit for non-mental disorder	9863 (52.3)	2747 (51.1)	2836 (51.3)	2708 (54.3)	712 (62.5)	132 (40.7)	728 (48.2)	<0.0001
Discontinuation of any AP, n (%)	9071 (52.3)	3015 (56.0)	2892 (52.3)	2539 (50.9)	572 (50.2)	53 (16.4)	–	<0.0001
Switch/Add AP, n (%)	6502 (37.5)	2130 (39.6)	2102 (38.0)	1814 (36.4)	327 (28.7)	129 (39.8)	–	<0.0001
Discontinuation or switch/add, n (%)	11 750 (67.7)	3922 (72.9)	3685 (66.7)	3273 (65.6)	726 (63.7)	144 (44.4)	–	<0.0001

AP, antipsychotics; CLOZ, clozapine; DLP, dyslipidemia; ED, emergency department; FGAs, first-generation APs; GP, general practitioner; HBP, high blood pressure; MULT, Multi APs; OLAN, olanzapine; Q1, 1st quartile; Q3, 3rd quartile; QUE, quetiapine; RISP, risperidone; SZ, schizophrenia or schizoaffective disorder.

*AP initiated at index date.

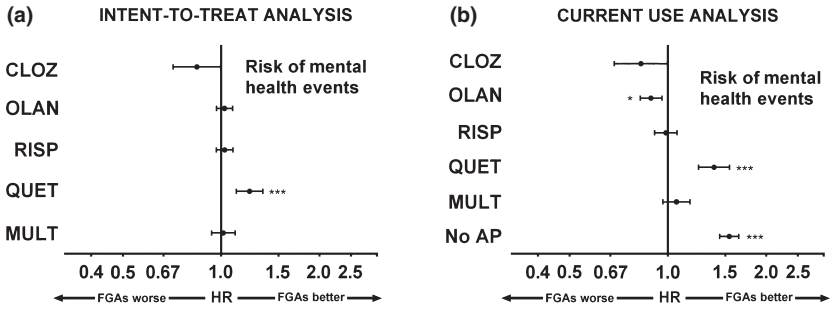
†Kruskal–Wallis test (continuous variables); chi-squared test (categorical variables).

‡Results by AP categories are not presented due to small numbers in some categories.

gender (Fig. 4a, c), but showed differences in effectiveness between age groups (Fig. 4b, d); for example, clozapine performed better than first-generation APs in younger patients (<35), but not in older ones (35–54, ≥55). Nonetheless, not taking any APs or current use of quetiapine was still associated with an increased risk of mental and physical health events for all age groups. Other stratified analyses (Figs S4–S5) produced essentially similar results, but the gap between quetiapine and FGAs was reduced between 1998–1999 and 2000–2005.

Discussion

This study aimed to compare effectiveness and safety among different AP treatment categories using a real-world observational new-user design, including a large cohort of patients with SZ who are typically excluded from RCTs (older people, patients with comorbidities). The main finding of this study was the poorer performance of quetiapine and a slightly better performance of clozapine regarding effectiveness when compared to FGAs. Additionally, not taking any APs at event time was also associated with an increased risk of health events. A poorer performance of quetiapine regarding physical health events was also found, especially on ED visits for physical conditions. Comparing the main non-mental diagnoses reported at EDs between quetiapine patients and the others, we observed an increased number of ED visits with diagnoses falling in the category



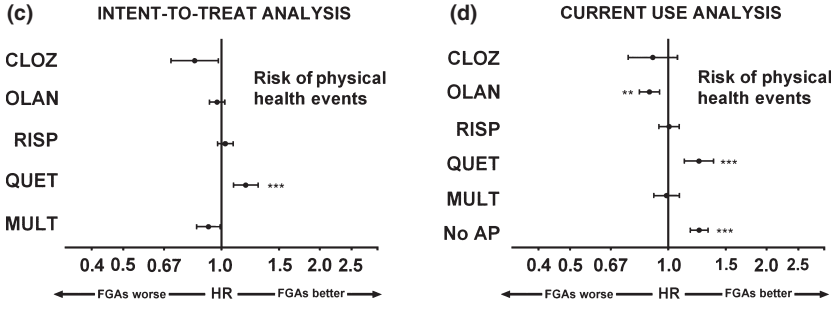


Fig. 2. Relative effectiveness and safety of antipsychotic drugs as compared to FGAs according to the exposure definition: Intent-to-treat analysis (left) and current use analysis (right). *$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$.

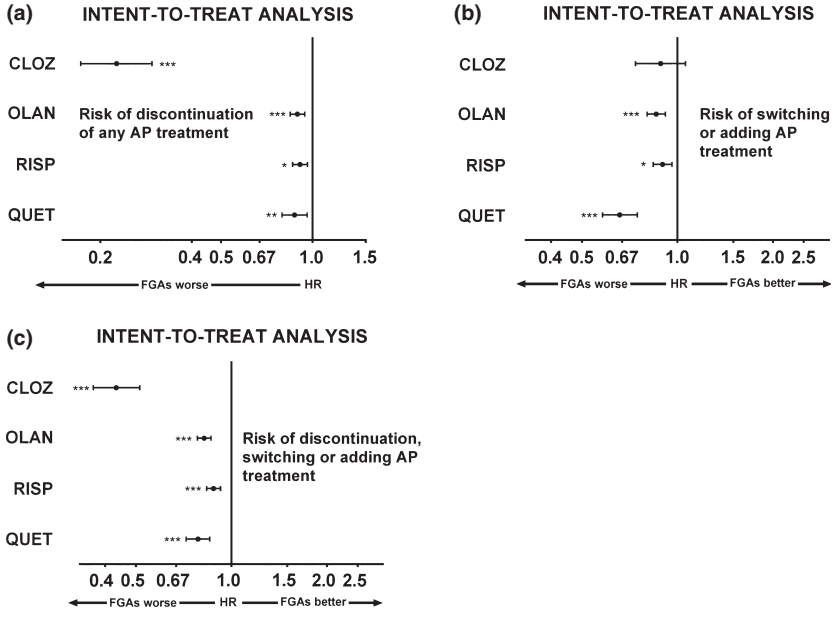


Fig. 3. Discontinuation and switch (initial antipsychotic drugs) as compared to FGAs. *$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$.

'injury or poisoning' and, to a much lesser extent, in the category 'infectious and parasitic diseases'. More studies are needed to better understand the reasons associated with the increased risk of physical ED visits in the quetiapine group.

Despite clear results, we cannot tell whether the poorer performance of quetiapine is due to the product itself, to suboptimal prescription (in terms of non-optimal dosage for instance), or to residual bias (e.g. being unable to control for indication bias – the tendency for the arrival of a new drug is to use it in the most severe cases). If the poorer performance is due to the product itself, it can raise clinical issues as quetiapine is increasingly prescribed in Canada, but most of this increase was attributed to another indication (mood disorders) or off-label indication (anxiety, sleep disturbances) with a moderate increase for psychotic disorders between 2005 and 2012 (32). Nonetheless, the fact that the increased risk associated with quetiapine was reduced between 1998–1999 and 2000–2005 (Fig. S4a) may indicate an improvement in the prescription pattern of quetiapine as the drug was gradually integrated into clinical practice [from 1.4% of patients in 1998 to 20.0% in 2007 (Fig. S1)]; however, initial dosage did not increase

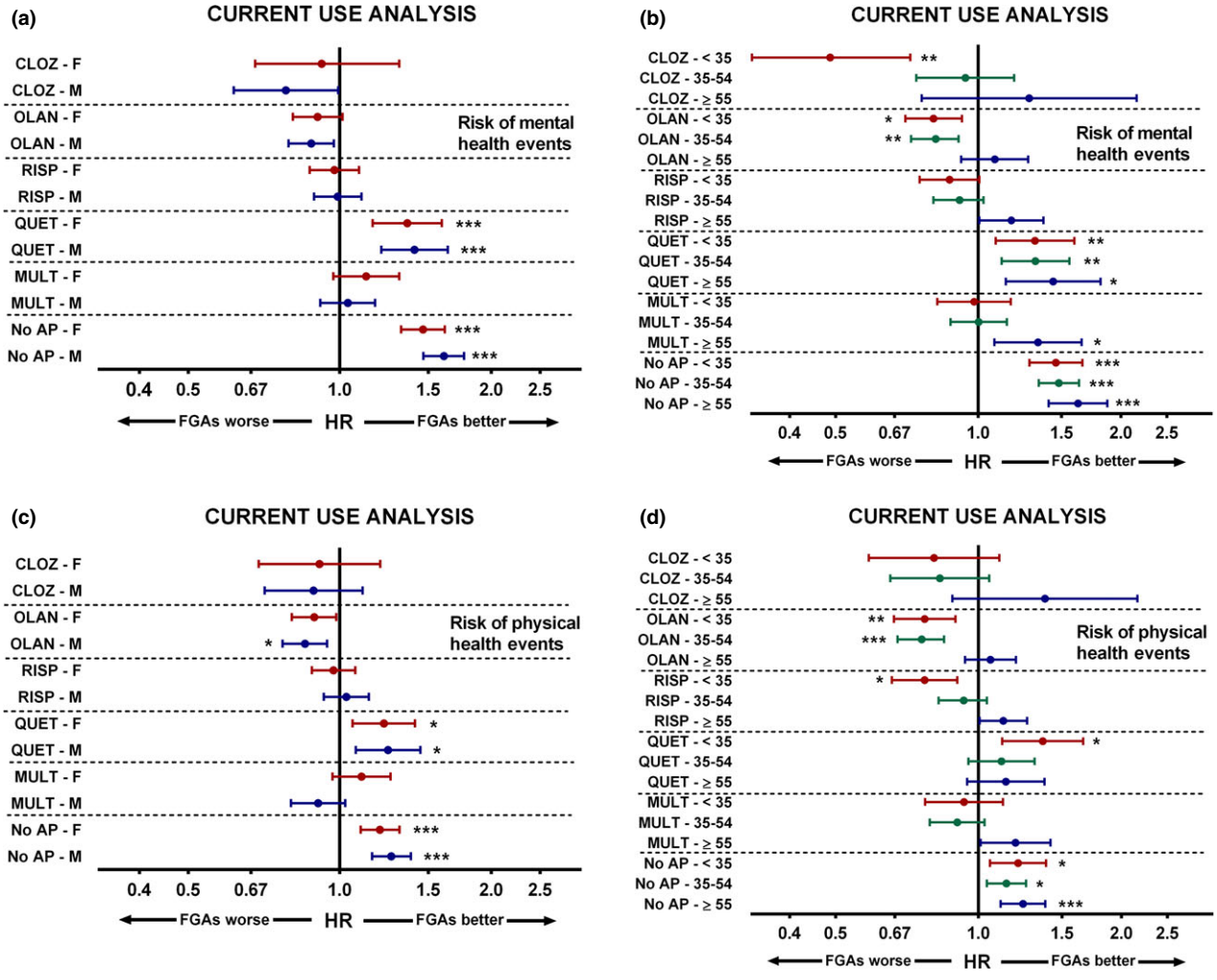


Fig. 4. Relative effectiveness and safety of antipsychotic drugs as compared to FGAs by gender and age. *$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$.

within those years (data not shown). Further studies are needed to better understand the impact of dosage in the effectiveness of APs, particularly regarding quetiapine, as it seemed to be prescribed with non-optimal initial doses.

Our findings regarding effectiveness of APs are in agreement with Tiihonen's (17) in providing an AP ranking similar to the one proposed in Leucht et al. (3)., with clozapine the most and quetiapine the least effective. Other studies have also shown less effectiveness for quetiapine among SGAs in the treatment of SZ (16, 33) More specifically, Asmal et al. (33) proposed an extensive review of RCTs on the effect of quetiapine compared with other SGAs in the treatment of schizophrenia or psychosis. In their review, quetiapine was associated with an increased risk of rehospitalization compared to olanzapine and risperidone, but no statistically significant differences regarding risk of death.

Our results clearly support greater effectiveness for clozapine in younger patients (<35), which was observed despite the fact that patients using clozapine had the highest rate of prior hospitalization for psychoses. Although this could partially be explained by a lower rate of discontinuation in clozapine patients, superiority of clozapine is also suggested by prior studies. In a meta-analysis, Davis et al. (34). showed that clozapine produced the best response among all studied SGAs when compared to FGAs, followed by amisulpride, risperidone and olanzapine; the remaining SGAs, including quetiapine, did not significantly differ from FGAs. Finally, clozapine has been shown to reduce the risk of suicide better than olanzapine in schizophrenia patients (35).

In our study, an important proportion of patients (67.7%) discontinued or switched their treatment during the 2-year follow-up. This rate is higher than what was found in one study

conducted over a longer follow-up period (3 years) (25), but lower than others (36, 37). We found that SGAs performed better regarding all-cause discontinuation than FGAs, as did Leucht et al. (3) and Haro et al. (25). Quetiapine seemed to be well tolerated as it was associated with the lowest risk of switching or adding AP drugs than the other AP categories. In turn, clozapine was associated with the lowest risk of discontinuation among all APs, as found in other observational studies (24, 36).

Strengths

Our study has many strengths, such as the large number of patients included (n = 18 869) and its representativeness (good external validity) – the study population includes a high number of patients who are generally underrepresented in RCTs (14, 15) and is more representative of the real-world situation. We also chose a 'new-user' design (i.e. we included only patients initiating an AP drug); this eliminates prevalent-user biases: prevalent users are 'survivors' of the early period of pharmacotherapy, and their inclusion precludes controlling for disease risk factors which may be altered by exposure to the drugs under study (19).

Limitations

One limitation is the study period (1998–2005) considered. However, the molecules available during that period are still largely used today so that the results remain relevant. There are also several limits associated with the use of administrative databases. First, this study is limited to public drug insurance beneficiaries. However, this is mitigated by our preliminary work showing that as much as 75% of adult patients diagnosed with SZ are registered under the public drug insurance programme. There is also a risk of information bias related to the quality of the information included in administrative databases, which may suffer from missing data or coding errors when used for clinical observational studies; fortunately, the Quebec prescription claims database has been found to include accurate information (38). Second, although we used a new-user design with a 6-month washout period, we were unable to establish whether patients had ever used APs before that period, so that we did not differentiate incident AP users from those who stopped their AP for at least 6 months before resuming AP drug treatment. Furthermore, no data on reason for prescription or disease severity are directly available in this database. However, we tried to reduce indication bias by controlling for several covariates, some of which are proxies of the severity of the disease, such as prior hospitalization for psychosis or for other mental health disorders, prior substance abuse, physical health problems and concomitant use of some specific drugs. Despite adjustment for these covariates, it is still possible that patients on quetiapine were more severely impaired on average compared to users of other AP drugs. Our results could thus theoretically be partly biased by confounding factors, although the large effect sizes, the robustness of our findings across sensitivity analyses and the convergence of findings with other studies suggest that the effect observed for quetiapine users is unlikely to be due solely to residual confounding.

In conclusion, the findings of this study call for surveillance of 'real-world' AP medication from international public health and drug agencies, to ensure real-world validity of guidelines and recommendations for the treatment of schizophrenia or schizoaffective disorder, particularly in the context where excess mortality of psychiatric patients becomes a public health issue and a measure for the performance of healthcare systems (39).

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Declaration of interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution of initial antipsychotic drugs among ten annual cohorts of patients with SZ initiating AP treatment (from 1998 to 2007).

Figure S2. Relative effectiveness and safety of antipsychotic drugs as compared to FGAs by initial dose (a, c) and among oral AP users only (b, d).

Figure S3. Relative effectiveness and safety of antipsychotic drugs as compared to FGAs by specific elements of the composite outcomes.

Figure S4. Relative effectiveness and safety of antipsychotic drugs as compared to FGAs by period and financial status.

Figure S5. Relative effectiveness and safety of antipsychotic drugs as compared to FGAs by history of hospitalization for schizophrenia/psychosis (HHSZ) and Charlson comorbidity index (CCI).