A POPULATION-BASED COST-EFFECTIVENESS ANALYSIS OF OLANZAPINE AND RISPERIDONE AMONG AMBULATORY PATIENTS WITH SCHIZOPHRENIA

Dan Cooper[1,2], Jocelyne Moisan[1,2], Belkacem Abdous[2,3], Jean-Pierre Grégoire[1,2]

[1]Faculty of Pharmacy, Université Laval, Québec, Canada, [2]Population Health Research Unit, Centre hospitalier *affilié* universitaire de Québec, Québec, Canada, [3]Department of Social and Preventive Medicine, Université Laval, Québec, Canada

Corresponding Author: *Jean-Pierre.Gregoire@pha.ulaval.ca*

ABSTRACT

Background
Olanzapine and risperidone are atypical antipsychotics exhibiting different pharmacological properties that are likely to translate into differences in outcomes, tolerability and safety. As well, their acquisition cost differs. These differences may impact their cost-effectiveness.

Objective
To estimate the incremental cost-effectiveness ratio (ICER) of olanzapine and risperidone in an outpatient population.

Methods
We carried out a cost-effectiveness analysis based on resource utilization data gathered from Quebec's provincial health insurance board databases. Patients previously diagnosed with schizophrenia who received a first prescription of olanzapine or risperidone between 1 January 1997 and 31 August 1999 were followed for 365 days. Absence of hospitalization for mental illness served as the clinical indicator of effectiveness. Direct health care costs for mental illness were considered. Adjusted ICERs were calculated, and their 95% confidence intervals (CI) were assessed using a non-parametric bootstrap.

Results
A total of 6,334 patients were included in the analysis. The ICER for olanzapine was (CA$) 86,918 (95%CI, 27,709 to 237,040) per additional effective treatment per year, among patients hospitalized prior to their treatment. Among those who were not hospitalized prior to their treatment, olanzapine was dominated (95%CI, CA$1.7M to dominated).

Conclusion
Results suggest that, in this population, direct mental health care costs could be minimized by using risperidone instead of olanzapine as the initial treatment.

Key words: *Drugs; antipsychotic; schizophrenia; cost effectiveness; database*

Schizophrenia is a major psychotic disorder that can be highly debilitating. It commonly manifests in late adolescence to young adulthood with a lifetime prevalence of about 1% throughout the world.[1] It is frequently characterized by a chronic recurrent course. In Canada, in 2004, schizophrenia incurred over CA$ 6.8 billion in total health care, non-health care and productivity costs.[2] Hospitalization and acute care were the main health care costs, representing more than 60% of those health care costs. Prescription medications accounted for approximately 7 % of health care costs.[2] The introduction of atypical antipsychotics in the past decade has contributed greatly to improvement in the treatment of schizophrenia. These drugs have bolstered the shift toward ambulatory care. In particular, olanzapine and risperidone have been shown to be

more efficacious, better tolerated and more cost-effective than typical antipsychotics.[3-5] Olanzapine and risperidone exhibit different pharmacological properties[1,6] that are likely to translate into differences in outcomes, tolerability and safety. In addition, their acquisition cost differs, with the acquisition cost of olanzapine higher than that of risperidone.[7-11] These differences may impact the cost-effectiveness of each drug.

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) investigation, Lieberman et al. observed patients initiated on olanzapine to be less likely to be discontinued from their initial treatment than those initiated on risperidone.[12] In a previous population-based study, we also observed patients initiated on olanzapine to be less likely to discontinue their initial treatment than those initiated on risperidone when those medications are used in clinical practice (adjusted hazards ratio= 0.79; 95%CI, 0.74 to 0.84).[13] However, whether this better persistence with olanzapine translates in a favorable cost-effectiveness ratio is unknown.

We identified ten studies where researchers were attentive to the pharmaco-economics of olanzapine and risperidone. In two studies, the authors focused on the in-hospital use of these drugs,[7,11] while in the remaining studies they focused on their ambulatory use.[14-21] Among these eight latter studies, one was a modelization of clinical research[20], another was a modelization of hypothetical data[18], three were observational studies[15-17,19] and two were secondary analyses of clinical trials.[14,21] Of the last six studies, only one[17] was population-based; however, it was limited to a cost comparison of the two drugs and so did not address their cost-effectiveness. Among the nine studies that addressed cost-effectiveness, five showed risperidone to be more cost-effective than olanzapine[11,15,18,19,22] whereas, three reported the opposite[16,20,21] and on[14] reported no difference in quality adjusted life years (QALY) and total health care costs. As study results are divergent, population-based data is limited and data on how the cost-effectiveness of olanzapine and risperidone compare in clinical practice is lacking, we conducted a head-to-head cost-effectiveness study of these drugs. We aimed to estimate their incremental cost-effectiveness ratio (ICER) in ambulatory patients with schizophrenia.

METHODS

This was a population-based cohort study of ambulatory schizophrenic first-time users of olanzapine or risperidone. The economic perspective adopted was that of the Quebec provincial Ministry of Health and Social Services as a public third-party payer for drug therapy and medical care.

Data Source

Hospitalization data came from the Quebec provincial database for hospitalizations administered by the Quebec Ministry of Health and Social Services. Data on both patients use of physician services and prescription drugs came from the Quebec health insurance board (RAMQ) databases. The RAMQ database for prescription claims is known to be accurate[23], and covers all inhabitants of Quebec province for medical care and hospitalizations. Drug plan beneficiaries are welfare recipients, those without access to a private drug group plan and all non-institutionalized persons aged 65 years and over. In 2000, a total of 3.2 million people, out of a population of 7.2 million, were beneficiaries of this drug plan.

Patient Group Studied

To select our study population, we first identified all those drug plan beneficiaries who had received at least one prescription of an atypical antipsychotic (clozapine, olanzapine, quetiapine or risperidone) between 1 January 1997 and 31 August 1999. The date of the first claim of any atypical antipsychotic during this period was defined as the index date.

We then excluded patients who were not beneficiaries of the drug plan for the entire 180-day period preceding the index date. To ensure the inclusion of only new atypical antipsychotic users, we excluded patients who had received any atypical antipsychotic in the 180-day period preceding the index date. Because we were unable to classify them in a particular treatment group, we also excluded those who had received two atypical antipsychotics at the index date. A few drug claims appeared in the drug database with 0-day supply, most likely through error or omission; therefore we also excluded these patients with

only such claims. Since clozapine is usually used to treat more severely ill patients, and quetiapine was made available on the Canadian market only after the start of the study we excluded them as there were few subjects initiated on these drugs. Using data on medical services and hospitalizations, we also excluded patients for whom we did not find a diagnosis of schizophrenic disorder (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 we had complete data for every patient, we excluded those who had moved out of province, became ineligible for the drug plan or died during the 365-day follow-up period. Each remaining patient was then classified in the olanzapine or risperidone treatment group depending on the drug dispensed at the index date.

The *Commission d'accès à l'information du Québec* approved this research. To ensure anonymity, RAMQ assigned a unique encrypted number to each patient.

Variables

Four administrative databases were linked at the patient level using the encrypted number. The RAMQ beneficiary demographic database provided data on patients' age, sex, region of residency (rural or urban, according to the national postal code as defined by Canada Post) and drug plan eligibility. The physician claims database provided data on physician services (type, date and diagnosis) and the cost of each of those services. The prescription claims database provided data on dispensed drugs (drug identification, date of dispensing, days supply, cost and prescriber specialty). The hospitalizations database provided data on hospitalization dates, length of stay, first diagnosis and up to 16 secondary diagnoses.

Using information from the above databases, we assessed the presence of schizophrenic disorder, previous hospitalization for a mental illness, substance use disorder antecedents, previous use of typical antipsychotics, co-morbidity and both persistence with and effectiveness of the drug dispensed at the index date. First, we determined the type of schizophrenic disorder according to ICD-9 codes (295.0 to 295.9) entered in the 180-day period prior to the index date. Second, we classified patients as having been hospitalized for a mental illness (first diagnosis: ICD-9 codes 290 to 319) or not, in the 180-day period preceding the index date. Next, we assessed substance use disorders in the 180-day period prior to the start of treatment using ICD-9 codes 291 (alcoholic psychosis), 292 (drug psychosis), 303 (alcohol dependence syndrome), 304 (drug dependence) and 305 (nondependent abuse of drugs). We also determined previous use of typical antipsychotics in the 180-day period preceding the index date. To assess co-morbidity, we used a chronic disease score with empirically derived weights based on age, sex and prescription claims.[24] This score was assessed using claims for the 180-day period preceding the index date (the higher the chronic diseases score the higher the co-morbidity level). Scores were categorized according to tertile limits. Persistence with treatment was defined as continuously refilling the initial atypical antipsychotic within two times the day supply of the previous dispensing. For claims with a supply of three days or less, patients had to refill their prescription within seven days to be considered persistent.

Finally, we assessed effectiveness and costs. Since hospitalization is a major outcome in schizophrenia, a treatment was considered effective for patients who attained 365 days of follow-up free from any hospitalization for mental illness as first diagnosis. We considered the direct health care costs for mental illness treatment over the first year. Total costs included those for physician services, hospitalizations and drugs (drug acquisition cost plus dispensing fee).

Included in the cost of physician services and hospitalizations were only those costs relevant to care for mental illness or for treatment of adverse effects of atypical antipsychotics (secondary Parkinsonism, other extra-pyramidal reactions and abnormal movement disorders, diabetes, lipid metabolism disorders and abnormal weight gain). Costs of treating schizophrenia-related health problems, such as drug poisoning and toxic effect of alcohol, were also included. Physician services costs, including emergency visits costs, were those reimbursed to physicians by the RAMQ. The daily cost of hospitalization was set at Canadian dollars (CA$) 300, the estimated daily cost for psychiatric care in a Quebec City

psychiatric hospital in year 2000.[25] In the matter of drug costs, we considered those of both atypical and typical antipsychotics used to treat schizophrenia. We also considered mental health-related drug treatments such as antidepressants, anxiolytics, hypnotic-sedatives and mood stabilizers (carbamazepine, valproic acid, vigabatrin, lamotrigine, topiramate, gapapentin and lithium). As well, we included the costs of drugs used to treat adverse effects of atypical antipsychotics (antiparkinson drugs, anti-diabetics and serum lipid reducing agents). Anti-diabetics and lipid lowering agents were considered as being used for the treatment of adverse atypical antipsychotics effects if they were first prescribed after the index date (i.e. there was no claim for these drugs in the 180-day period preceding the index date). Drug costs were those claimed by pharmacists to RAMQ.

Statistical Analysis

Baseline characteristics for patients in the two treatment groups were described. For both atypical antipsychotics and among patients who persisted with the drug, the mean daily dose with its 95%CI was assessed at day 365. We compared mean daily doses with their respective defined daily dose (DDD). The DDD is the adult average maintenance dose per day for a drug used in its main indication. The olanzapine and risperidone DDDs are 10mg and 5mg, respectively.[26]

The adjusted risk of hospitalization was estimated using a binomial regression with the SAS genmod procedure with binomial distribution and a log link. For this, we first checked if age, sex, type of schizophrenic disorder, region, co-morbidity, prior hospitalization for mental illness, previous substance use disorders, previous use of typical antipsychotics, beneficiary type and physician's specialty were modifying the association between study drugs and hospitalization for mental illness. To this end, we used the interaction terms method[27] and observed that none of these variables were causing interaction. We also compared the mean of each treatment costs using covariance analysis. As they were skewed, we transformed costs to the natural log (ln) scale. We built our models using the same steps and procedures as those used in the above-mentioned models for comparing the risk of hospitalization for mental illness. As prior hospitalization for mental illness interacted significantly ($p<0.05$) with study drug and costs, the study population was stratified by prior hospitalization for mental illness status in the estimates of study drug effect on hospitalizations and costs. As residuals were normally distributed and homoscedasticity of the variance was respected on the log scale model, we retransformed the predicted values to the dollar scale using the smearing estimate as proposed by Duan.[28]

To adjust for differences in baseline characteristics between the two treatment groups, both effectiveness and cost models included the following variables: age, sex, type of schizophrenic disorder, region, co-morbidity, previous substance use disorders, previous use of typical antipsychotics, beneficiary type and physician's specialty. We used the incremental cost-effectiveness ratio (ICER), which is defined as:

$$\frac{\text{mean total cost}_{(\text{olanzapine})} - \text{mean total cost}_{(\text{risperidone})}}{\text{mean effectiveness}_{(\text{olanzapine})} - \text{mean effectiveness}_{(\text{risperidone})}}$$

We calculated one adjusted ICER in each stratum of prior mental illness hospitalization. To calculate ICERs' 95%CI we used the bootstrap method.[29,30] For this, we generated 1,000 new random samples of equal size, with replacement, from the original data for each comparison. Uncertainty was summarized using cost-effectiveness acceptability curves. We also performed univariate sensitivity analyses on key parameters.

First, as older patients generally receive lower doses, and since this may affect drug acquisition costs, we assessed the effect of age on the cost-effectiveness comparison by restricting the analyses to patients aged less than 65. Second, we varied the daily hospitalization cost. For this, we used the hospitalization costs as evaluated by the Quebec Ministry of Health and Social Services. In 1997, the daily costs of hospitalization, in long-term facilities and in short-term hospital care were CA$179.53 and CA$479.53 respectively. Analyses of baseline characteristics and regression models were performed using SAS version 9.1.3 (SAS institute, Inc, Cary, North Carolina).[31]

TABLE 1 Characteristics of patients with schizophrenia, initiated on olanzapine or risperidone at the index date

	Study Drugs		Total
	Risperidone N = 2,694 (42.5%)	**Olanzapine N = 3,640 (57.5%)**	**N = 6,334 (100.0%)**
Age (years)			
0-24	216 (8.0)	281 (7.7)	497 (7.8)
25-44	1,248 (46.3)	1,915 (52.6)	3,163 (49.9)
45-64	856 (31.8)	1,172 (32.2)	2,028 (32.0)
65+	374 (13.9)	272 (7.5)	646 (10.2)
Sex			
Women	1,238 (46.0)	1,476 (40.5)	2,714 (42.8)
Men	1,456 (54.0)	2,164 (59.5)	3,620 (57.2)
Type of schizophrenic disorder			
Paranoid	1,067 (39.6)	1,434 (39.4)	2,501 (39.5)
Acute	58 (2.2)	58 (1.6)	116 (1.8)
Residual	138 (5.1)	177 (4.9)	315 (5.0)
Schizo-affective	378 (14.0)	551 (15.1)	929 (14.7)
Other*	1,053 (39.1)	1,420 (39.0)	2,473 (39.0)
Beneficiary type			
Welfare recipients < 65 years	1,931 (71.7)	2,929 (80.5)	4,860 (76.7)
Others < 65 years	397 (14.7)	443 (12.2)	840 (13.3)
Welfare recipients ≥ 65	256 (9.5)	190 (5.2)	446 (7.0)
Others >65	110 (4.1)	78 (2.1)	188 (3.0)
Region of residency			
Rural	401 (14.9)	495 (13.6)	896 (14.1)
Urban	2,292 (85.1)	3,144 (86.4)	5,436 (85.8)
Undisclosed	1 (0.0)	1 (0.0)	2 (0.0)
Co-morbidity (CDS[b])			
Low (<2,780)	1,007 (37.4)	1,104 (30.3)	2,111 (33.3)
Medium (2,780-4,663)	844 (31.3)	1,267 (34.8)	2,111 (33.3)
High (>4,663)	843 (31.3)	1,269 (34.9)	2,112 (33.3)
Hospitalized for a mental illness in the 180-day period prior to the index date			
Yes	937 (34.8)	1,248 (34.3)	2,185 (34.5)
No	1,757 (65.2)	2,392 (65.7)	4,149 (65.5)
Substance use disorder[c]			
Yes	200 (7.4)	267 (7.3)	467 (7.4)
No	2,494 (92.6)	3,373 (92.7)	5,867 (92.6)
Previous use of typical antipsychotics[d]			
Yes	1,802 (66.9)	2,743 (75.4)	4,545 (71.8)
No	892 (33.1)	897 (24.6)	1,789 (28.2)
Prescriber's specialty			
Psychiatrist	1,779 (66.0)	2,750 (75.6)	4,529 (71.5)
General practitioner	760 (28.2)	675 (18.5)	1,435 (22.7)
Other	37 (1.4)	48 (1.3)	85 (1.3)
Undisclosed	118 (4.4)	167 (4.6)	285 (4.5)

[a]Other types of schizophrenic disorders include simple, disorganized, catatonic, latent, undifferentiated and other types of schizophrenia.
[b] Chronic disease score (CDS) assessed for the 180-day period prior to the index date, using empirically derived weights as published by Clark et al.[23] Substance use disorder assessed for the 180-day period prior to the index date using ICD-9 codes 291 (alcoholic psychosis), 292 (drug psychosis), 303 (alcohol dependence syndrome), 304 (drug dependence) and 305 (non-dependent abuse of drugs).[d]Previous use of typical antipsychotic assessed in the 180-day period prior to the index date.

RESULTS

A total of 6,334 patients were included in the study: 3,640 olanzapine users and 2,694 risperidone users. Baseline characteristics of study patients are presented in Table 1. In the group of patients who had previously been hospitalized for a mental illness, the mean daily dose among patients persisting on olanzapine (n= 501) or risperidone (n= 273) after 365 days of follow-up was 13.mg (95%CI, 12.8 to 13.9) and 4.2mg (95%CI, 3.9 to 4.5), respectively. In the group of patients not previously hospitalized for a mental illness, the mean daily dose of olanzapine, among persistent users (n=1,059), was 12.8mg (95%CI, 12.4 to 13.2) and that of risperidone, among persistent users (n= 624), was 4.2mg (95%CI, 4.1 to 4.4). In both strata, the mean daily dose of risperidone was lower than its DDD ($p<0.0001$); whereas, the mean daily dose of olanzapine was higher than its DDD ($p<0.0001$).

Among individuals previously hospitalized for a mental illness, the adjusted risk of hospitalization in the first year following treatment initiation was 32% and 28% for risperidone and olanzapine, respectively. The corresponding mean number of hospitalizations was 0.6 (median=0, sd=1.1) and 0.6 (median=0, sd=1.2) and the mean duration of hospitalization was 18.0 days (median=0, sd=38.5) and 16.9 days (median=0, sd=37.3), respectively. In both groups, 5% of patients were hospitalized more than once. Among patients not previously hospitalized for a mental illness, the adjusted risks of hospitalization were lower (18% and 19% for risperidone and olanzapine, respectively). The corresponding mean number of hospitalizations was 0.2 (median=0, sd=0.6) and 0.2 (median=0, sd=0.6) and the mean duration of hospitalization was 5.9 days (median=0, sd=22.6) and 6.5 days (median=0, sd=23.3), respectively. In both groups, 10% of patients were hospitalized more than once. Table 2 shows the mean crude annual costs of treatment per cost type, per patient and per year, stratified for drug dispensed at the index date and for prior mental illness hospitalization. The adjusted results of the incremental cost-effectiveness analysis are presented in Table 3.

TABLE 2 Mean and median costs per patient per year (CA$) among patients with schizophrenia initiated on olanzapine or risperidone according to prior hospitalization for mental illness (N = 6,334)

	Mean Costs[a]						
Hospitalized for mental illness in the 180-day period prior to the index date	**Antipsychotics**		**Other drugs[b]**	**Physician services**	**Hospitalizations**	**Total**	
	Atypical	**Typical**				**Mean**	**Median**
Yes							
Risperidone (n = 937)	1,205 ±1,015	76 ±169	393 ±460	931 ±1,182	5,423 ±11,543	8,027 ±12,305	3,135
Olanzapine (n = 1,248)	2,473 ±1,631	90 ±192	411 ±567	931 ±1,130	5,134 ±11,329	9,039 ±11,919	4,756
No							
Risperidone (n = 1,757)	1,170 ±1,062	120 ±238	315 ±456	612 ±842	1,787 ±6,826	4,005 ±7,492	2,006
Olanzapine (n = 2,392)	2,230 ±1,592	146 ±316	332 ±489	667 ±835	1,959 ±7,006	5,334 ±7,597	3,435

[a] Values are mean ± one standard deviation. [b] Other drugs: antidepressants, anxiolytics, hypnotic-sedatives, mood stabilizer drugs (carbamazepine, valproic acid, vigabatrin, lamotrigine, topiramate, gapapentin and lithium), anti-Parkinson drugs, anti-diabetics and serum lipid reducing agents.

TABLE 3 Incremental cost-effectiveness analysis using the mean adjusted costs (CA$) obtained from the smearing estimate for retransformed data (CA$) and the mean adjusted probability of effective treatments

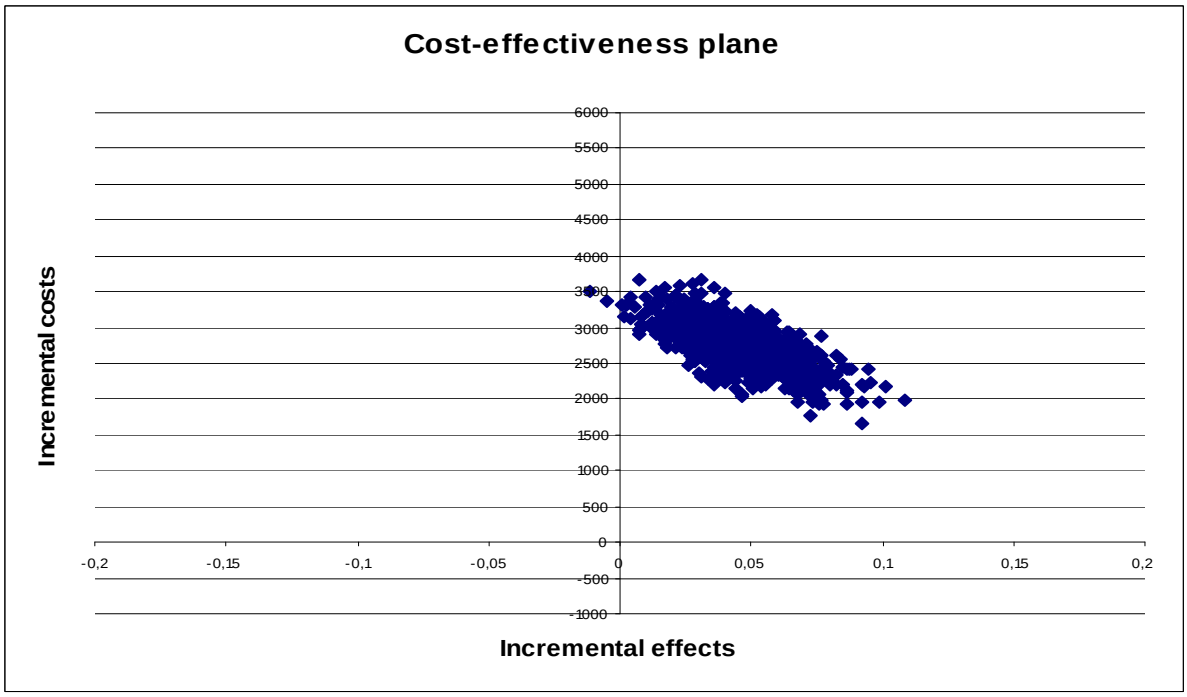
Hospitalized for mental illness in the 180-day period prior to the index date	Mean adjusted[a] costs[b] (per patient per year)		Adjusted[a] risk of effective treatments[c]		Adjusted incremental cost-effectiveness ratio	
	CA$	95%CI[d]	%	95%CI[d]	CA$	95%CI[d]
Yes						
Risperidone (n = 937)	7,129	(6,720-7,561)	68	(60-77)	-----	-----
Olanzapine (n = 1,248)	9,880	(9,347-10,398)	72	(64-82)	-----	-----
Incremental costs and effects	2,751	(2,153-3,341)	5	(1-8)	86,918	(27,709 - 237,040)
No						
Risperidone (n = 1,757)	3,704	(3,531-3,867)	82	(76-89)	-----	-----
Olanzapine (n = 2,392)	5,648	(5,426-5,889)	81	(75-87)	-----	-----
Incremental costs and effects	1,944	(1,734-2,152)	-1	(-2-1)	dominated	(1.7M$-dominated)

[a] Both costs and effectiveness estimates adjusted for age, sex, type of schizophrenic disorder, region, co-morbidity, previous substance use disorders, previous use of typical antipsychotics, beneficiary type and physician's specialty. [b] Mean adjusted costs (CA$) obtained using the smearing estimate to retransform data from the log scale. [c] A drug was considered to be effective if the entire 365-day period of follow-up was hospitalization-free for mental illness. [d] 95%CI obtained by bootstrap.

Treatment costs for patients on risperidone were lower than for those on olanzapine. Among patients previously hospitalized for a mental illness, mean total costs were CA$7,129 (95%CI, 6,720 to 7,561) for risperidone and CA$9,880 (95%CI, 9,347 to 10,398) for olanzapine; while, they were respectively CA$3,704 (95%CI, 3,531 to 3,867) and 5,648 (95%CI, 5,426 to 5,889) among those who were not previously hospitalized. For both drugs, mean total costs were lower among those patients not previously hospitalized for mental illness than among those who had been previously hospitalized.

Among those patients previously hospitalized for mental illness, olanzapine was both more effective and more costly than risperidone. The adjusted ICER was in the upper right hand quadrant of the cost-effectiveness plane (Figure 1) and was CA$ 86,918 (95%CI, 27,709 to 237,040) per year for each additional effective treatment with olanzapine. The cost-effectiveness acceptability curve shows that, compared with risperidone, the probability that olanzapine is cost-effective is not higher than 32% when the ICER threshold is CA$50,000 per effective treatment gained (Figure 2). Among those patients who had not been previously hospitalized for mental illness, olanzapine was dominated (less effective and more costly). The adjusted ICER (dominated, 95%CI, CA$1.7M to dominated) was in the upper left hand quadrant of the cost-effectiveness plane (Figure 3). The acceptability curve shows that the probability of olanzapine being cost-effective, as compared with risperidone, is less than 10% even at ICER thresholds up to CA$1,000,000 (Figure 4). Cost-effectiveness results were not sensitive to variations in age or in hospitalization costs.

FIG. 1



1000 bootstrap re-samples of the incremental cost-effectiveness ratio (ICER) among patients hospitalized for mental illness in the 180-day period prior to the index date. A drug was considered to be effective if the entire 365-day period of follow-up was hospitalization-free for mental illness. Costs (in CA$) were retransformed from the log scale after correction for skewness. Adjusted differences in costs and effectiveness were computed as olanzapine minus risperidone values.

FIG. 2 Acceptability curve of the cost-effectiveness ratio among patients hospitalized for mental illness in the 180-day period prior to the index date

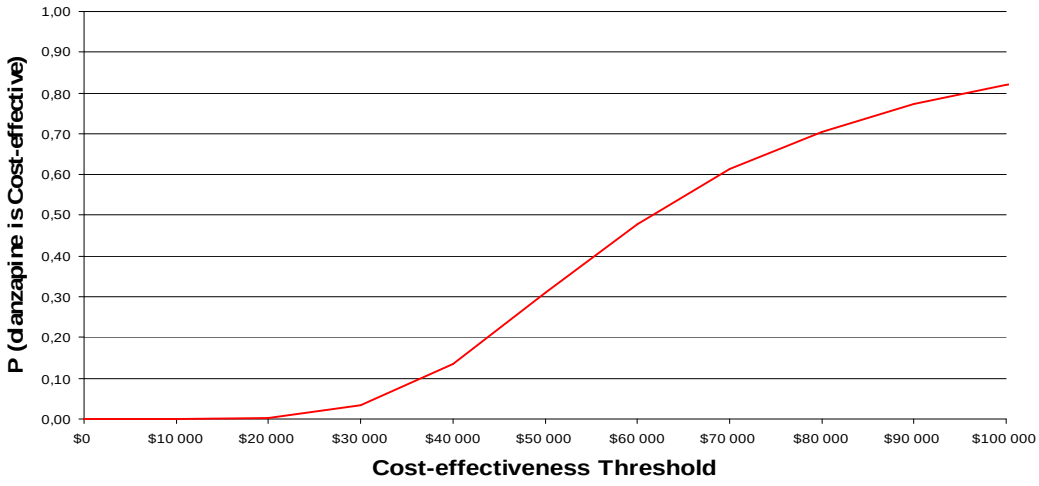
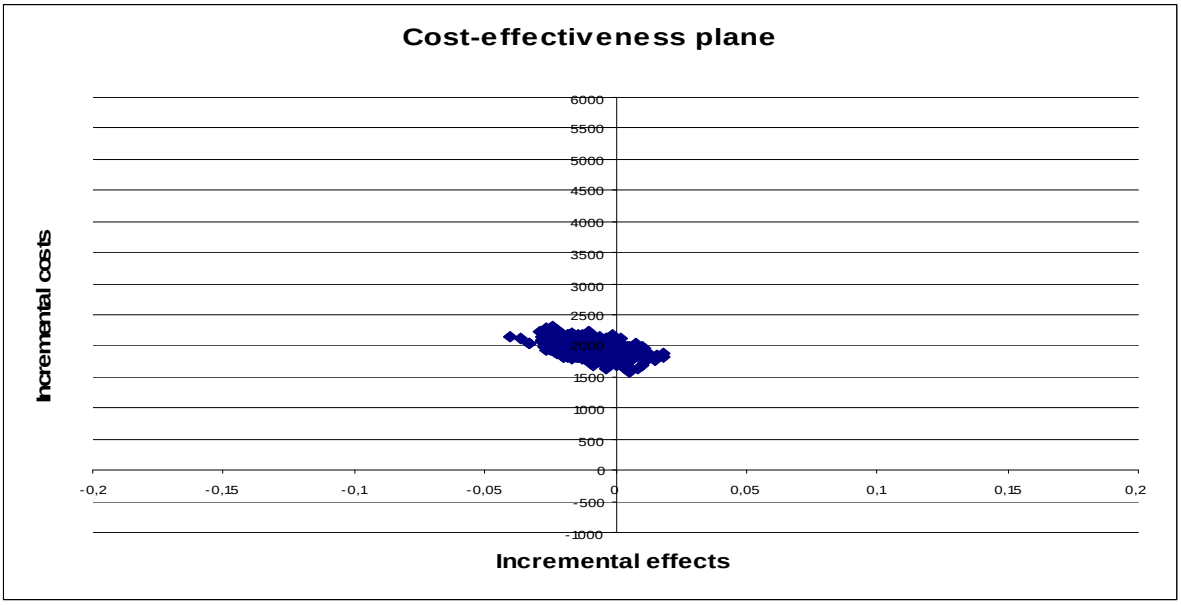
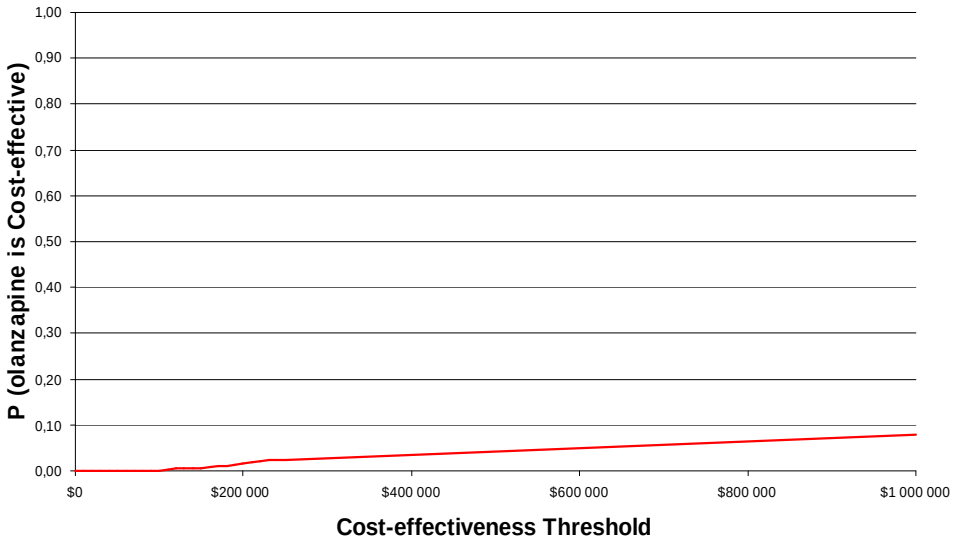


FIG. 3



1000 bootstrap re-samples of the incremental cost-effectiveness ratio (ICER) among patients not hospitalized for mental illness in the 180-day period prior to the index date. A drug was considered to be effective if the entire 365-day period of follow-up was hospitalization-free for mental illness. Costs (in CA$) were retransformed from the log scale after correction for skewness. Adjusted differences in costs and effectiveness were computed as olanzapine minus risperidone values.

FIG. 4 Acceptability curve of the cost-effectiveness ratio among patients not hospitalized for mental illness in the 180-day period prior to the index date



DISCUSSION

Two important findings emerged after conducting a population-based cost-effectiveness comparison of olanzapine and risperidone using clinical practice data. First, the risk of hospitalization in the first year following treatment initiation between the two treatment groups differs slightly depending if patients were previously hospitalized or not. Second, olanzapine was associated with higher direct health care costs for mental illness than was risperidone.

Using continuation of the initial atypical antipsychotic as a primary measure of effectiveness, investigators of the CATIE trial have observed olanzapine to be more effective than risperidone.[12] However, this did not translate into a better outcome as measured by QALY ratings.[14] In a prior study of a similar population, we have also observed individuals initiating an antipsychotic treatment with olanzapine to be less likely to discontinue their drug treatment than those initiated with risperidone.[13] The results of our study suggest this better persistence with olanzapine does not translate clearly into a lesser risk of hospitalization for mental illness in the first year following treatment initiation. In the present study, olanzapine was associated with higher direct health care costs for mental illness than was risperidone. Our findings are concordant with results from other studies.[15,17,19] However, some researchers have reported opposite results.[16,21] In a secondary analysis[21] of a randomised, double-blind, prospective study[32] in which mean doses used for both drugs were higher (17.7+/-3.4mg/day for the olanzapine treatment group and 7.9+/-3.2mg/day for the risperidone treatment group) than those used in usual clinical practice, total direct costs were lower for patients on olanzapine than for those on risperidone; although, the observed difference was not statistically significant. Moreover, in a retrospective database study comparing 985 risperidone users and 348 olanzapine users with previously diagnosed schizophrenia, Zhao[16] observed lower direct total health care costs, as well as lower mental health care costs, with olanzapine than with risperidone over a one year period. However, when considering schizophrenia-related costs only, the difference between the two drugs was not statistically significant. The difference between our findings and those of Zhao is likely attributable to difference in mean daily doses of olanzapine used by patients. Indeed, in the Zhao study, mean daily doses of olanzapine received by patients were 25% lower than those we observed in our study, whereas the mean daily doses of risperidone were similar to ours.

Among patients not previously hospitalized for a mental illness, we have observed that olanzapine was dominated; yet, the 95%CI around the ICER overlaps the effectiveness difference null value on the cost-effectiveness plane. Among patients previously hospitalized, olanzapine was both more effective and more costly than risperidone. In both groups of patients, 95%CIs around the ICERs were in the upper half of the cost-effectiveness plane. This illustrates that risperidone was less costly than olanzapine.

The ICERs of risperidone and olanzapine have been assessed twice in the past.[18,20] Both studies, on this issue, used clinical decision analysis models that generated opposite results. In one study[20], olanzapine at a daily dose of 10mg dominated risperidone at a daily dose of 6mg; although, when the daily dose of olanzapine used in the comparison was 15mg, olanzapine was no longer dominating risperidone. Our results are however in line with those of the study[18] in which olanzapine at a daily dose of 10mg, was dominated by risperidone at a daily dose of 5mg. Conflicting results between the two studies[18,20] may be at least partly explained by differences in mean daily doses used. Daily doses of 6mg for risperidone and 10mg for olanzapine are respectively higher and lower than those used in clinical practice. The relative cost-effectiveness of risperidone is liable to be underestimated, as drug acquisition costs are sensitive to doses used. Since our study was population-based, our estimates were based on doses used in clinical practice. These doses were similar to those observed in recent studies conducted in clinical practice settings.[2,7,9-11,19]

Evidence emerging from recent studies suggests that olanzapine users would be more at risk of developing diabetes[33-35] or dyslipidemia[35-37] than risperidone users. Compared with risperidone, olanzapine was also recently associated with greater increases in glycosylated hemoglobin, total cholesterol and triglycerides.[12] Such adverse effects may have important long-

term consequences on health, quality of life and consequently, on total costs incurred. Our results, based on a 365-day period of follow-up, may not have captured all the long-term consequences of these adverse effects which are likely to impact on the cost-effectiveness of olanzapine and risperidone.

Our study has some limitations, mainly inherent in the analysis of administrative databases. First, we assumed that the drugs dispensed were actually used. Second, the RAMQ drug insurance plan does not cover the Quebec population under age 65 with access to a private drug plan. On the other hand, one may assume that most people suffering from schizophrenia are covered by the RAMQ program given that very few patients with schizophrenia remain employed[38] and thus with the possibility of access to a private drug group plan.

We used actual as opposed to constant costs of drugs and medical services. This could have introduced bias in the cost comparison analysis if costs varied during the study period. However, the likelihood of bias remains low. Although the cost of a few medical services did increase slightly (less than 5%) during the study period, this had a limited effect on total medical service costs. In addition, olanzapine and risperidone costs reimbursed to pharmacists did not vary between 1997 and 2000 and were therefore constant. As drug cost is one of the main drivers of total direct costs considered in this study, not using medical service 1997 costs had no effect on the cost-effectiveness comparison between the two drugs.

As clinical information on disease severity, reduction of symptoms and adverse effects is not available in the databases, hospitalization for mental illness during the 365-day follow-up served as an indicator of treatment effectiveness. However, the decision to admit somebody to a hospital may not be due only to a lack of drug effectiveness but to an array of factors, for example accessibility to outpatient services, family support, etc. Although hospitalization is a major negative outcome of schizophrenia, it is possible that a different clinical indicator of effectiveness would generate different ICERs than those observed. In clinical practice, physicians do not randomly prescribe drug treatments to patients. To minimize indication bias, we included only those patients suffering from schizophrenic disorders that were newly treated with an atypical antipsychotic, and we adjusted both effectiveness and costs measures for potential confounding variables. We also stratified our results for prior hospitalization for mental illness.

Since we did not have access to the data on some components of direct costs such as psychological care, community nursing care, social services and drugs used in hospital, the total direct health care costs for mental illness may have been underestimated. Although there is no reason to believe this underestimation would be differential, it cannot be ruled out.

As we used hospitalization as a measure of effectiveness, one may express concerns of double counting in the assessment of the ICERs. Indeed, hospitalizations were taken into account both in the numerator and in the denominator of the ICER. Although double counting is not recommended when an ICER is expressed in terms of cost per life-year saved or cost per quality-adjusted life-year saved, it is less clear whether it should be avoided when expressed in terms of cost per event avoided like we did.[39] For those who remain concerned by this double counting issue, our analysis could still be interpreted as a cost-minimization analysis. For a similar effectiveness, olanzapine is associated with higher direct health care costs for mental illness than risperidone.

CONCLUSION

Our current findings suggest that, in this population, direct mental health care costs could be minimized by using risperidone instead of olanzapine as the initial treatment. As generic versions of risperidone and olanzapine are now available on the Canadian market at 57% and 75%, respectively of the cost of the patent versions[40], the gap in direct mental illness health care costs between the two drugs is likely to remain in favour of risperidone.

On the other hand, depending on the hospitalization status in the 180-day period prior to the index date, ICERs appeared in two different quadrants of the cost-effectiveness plane. These results suggest that olanzapine could be a cost-effective drug for particular subgroups of patients. For example, olanzapine could perhaps be more efficiently used by patients who are more prone to

hospitalization. This should be explored in future studies. Moreover, our study results should be interpreted cautiously with regards to study limitations, particularly, possible residual confounding by indication.

Thus far, cost-effectiveness studies comparing atypical antipsychotics have for the most part, been based on clinical trials data. There is a need for more population-based studies based on clinical practice data, as was this study. Further studies should however try to incorporate comprehensive clinical information and extend the comparison over other available atypical antipsychotics and over a longer period of time so that the costs of adverse events such as diabetes and dyslipidemia could be more accurately captured.

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