**Trends in utilization and cost of antipsychotics among older Ontarians from 2007 to 2013: the effects of the introduction of newer agents and changes in generic status**

P D Foster, BSc

X Camacho, MMath

S Vigod, MD, MSc, FRCPC

Z Yao, MD, MS

D N Juurlink, MD PhD

J M Paterson, MSc

M M Mamdani, PharmD MA MPH

Diana Martins, MSc

T Gomes, MHSc

**Affiliations**: Schulich School of Medicine and Dentistry, Western University (PF), The Institute for Clinical Evaluative Sciences (XC, SV, ZY, DNJ, JMP, MMM, DM, TG); Applied Health Research Center, St. Michael's Hospital (PF, TG, MMM), Women's College Hospital and Research Institute (SV), Department of Medicine, Sunnybrook Health Sciences Centre (DNJ) and St. Michael's Hospital (MMM); Departments of Medicine (DNJ, MMM), Psychiatry (SV) Pediatrics (DNJ), Institute of Health Policy, Management, and Evaluation (SV, DNJ, JMP, MMM, TG), and the Leslie Dan Faculty of Pharmacy (MMM, TG) at the University of Toronto; Department of Family Medicine, McMaster University (JMP)

**Correspondence:**
Tara Gomes
30 Bond St.
Toronto, ON
M5B 1W8
GomesT@smh.ca
416-864-6060 x77046

**Word Count** Manuscript: 1860

**Funding Acknowledgement:** This study was supported by the Ontario Drug Policy Research Network which is funded by grants from the Ontario Ministry of Health and Long-Term Care Health System Research Fund.This study was also supported by the Institute for Clinical

Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

**Data Source Acknowledgement:** These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

**Conflicts of Interest:** Dr. Mamdani has served as an advisory board member for AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Glaxo Smith Kline, Hoffman La Roche, Novartis, Novo Nordisk and Pfizer. Dr. Vigod received one-time consulting fees from MDH consultants for the development of continuing education activities related to perinatal mental health (2012). No other authors have conflicts of interest to report.

**ABSTRACT:**

***Background:*** Recently, there have been several new atypical antipsychotics introduced in Ontario; however the impact of these agents on prescribing rates and costs is unknown.

***Methods:*** We performed a population-based cross-sectional study of adults aged 65 and over using atypical antipsychotics in Ontario from 2007 to 2013. We conducted time-series analysis to assess the impact of the introduction of new atypical antipsychotics on atypical antipsychotic utilization rates and expenditures.

***Results:*** Rates of atypical antipsychotic use increased following the introduction of new agents in 2009, from 27.6 users per 1000 population in Q3 2009 to 29.1 users per 1000 population in Q1 2013 (p=0.04). Although prescribing rates for the newer atypical agents (aripiprazole, ziprasidone, and paliperidone) remained low relative to their older counterparts (olanzapine, risperidone, quetiapine), rates of aripiprazole use rose to 1.0 users per 1000 population by the end of the study period. The proportion of prescriptions that were for brand-name agents fell from 57.5% in Q2 2007 to 6.1% in Q2 2009, before rising to 11.7% by Q1 2013 following introduction of new drugs. At the end of the study period, new atypical antipsychotic agents were used by 4.3% of atypical antipsychotic users, but accounted for 14% ($1.2M of $8.5M) of publicly funded atypical antipsychotic expenditures.

***Conclusions:*** Although their overall prevalence of use remains low, the introduction of new atypical antipsychotic agents has led to increased prescribing of this class of drugs in the elderly. Given the potential cost implications, further monitoring of these trends would be prudent.

**BACKGROUND:**

Antipsychotic drug therapy is a mainstay in the treatment of psychosis and related disorders. Since the introduction of atypical antipsychotics in the 1990s, the utilization and costs associated with these drugs has increased substantially (1-6). This was driven primarily by prescriber preference for atypical (or second-generation) antipsychotics(1,2), higher costs of newer agents compared with typical (or first-generation) antipsychotics(1), and a widening range of on- and off-label uses (3-5,7-9). The increase in use of atypical antipsychotic medications has been particularly significant in older adults with dementia (8,10-12). Since the early 2000s, there has been a growing appreciation for antipsychotic-related adverse effects among older persons with dementia, prompting warnings from the manufacturers and Health Canada regarding the safety of these products (2). Although concerns around safety slowed the growth of antipsychotic prescribing, rates of use continued to increase between 2000 and 2007 (2).

Between 2007 and 2013, several changes to antipsychotic availability and funding would affect the costs of these drugs. Introduction of generic versions of risperidone, quetiapine and olanzapine between 2006 and 2008 resulted in substantially lower prices for these products. Furthermore, in 2010, the Ontario government reduced generic drug prices from 50% of the brand-name equivalent to 25% (13). Although these events would be expected to decrease costs associated with antipsychotic drug therapy in Ontario, soon, three new medications -- paliperidone, ziprasidone, and aripiprazole -- would receive regulatory approval and be added to the ODB formulary (14-16). The impact of the competing forces of high relative cost and potential for rapid uptake of newer, brand-name agents (17-20) and the greater availability and

lower prices of generic drugs is uncertain. Accordingly, we sought to investigate the impact of the introduction of the newer brand name atypical antipsychotics (starting with paliperidone in 2009) on atypical antipsychotic prescribing rates, prevalence of brand-name antipsychotic utilization, and related drug benefit expenditures.

**METHODS:**

We conducted a population-based serial cross-sectional time series analysis of Ontario residents aged 65 and older who were dispensed an antipsychotic between Jan 1 2007 and March 31 2013. These patients have universal access to physician services, hospital care, and publicly funded drugs. This study was approved by the Research Ethics Board of the Sunnybrook Health Sciences Centre, Toronto, Ontario.

**Data Sources**

We used large population-based administrative databases to conduct this study. These databases were linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences. The Ontario Drug Benefit (ODB) database contains records of all prescriptions dispensed to public drug plan recipients in Ontario. This database was used to identify the number and cost of all prescriptions for atypical antipsychotics dispensed over our study period. The The Ontario Health Insurance Plan (OHIP) Registered Persons Database (RPDB) contains basic demographic information (including date of birth, sex, and date of death) for all residents of Ontario who have ever received a health card. Finally, the Contact Database combines OHIP registration data and health care usage data to maintain a list of individuals eligible for physician and hospital care services in Ontario. It was used to determine the size of the population of Ontario Health Insurance Plan (OHIP)-eligible individuals over our study

period. The Contact Database was unavailable for the last quarter of the study period; therefore we generated a quadratic least-squares regression model in order to obtain population estimates for this final time point ($R^2 = 0.997$).

**Rates of Atypical Antipsychotic Use**

We examined the use of all atypical antipsychotics that were listed on the ODB formulary over the study period, namely quetiapine, olanzapine, risperidone, paliperidone, ziprasidone, and aripiprazole. In each calendar quarter of the study period, we identified all individuals aged 65 years or older who filled at least one prescription for an atypical antipsychotic, and reported the number of people who used atypical antipsychotics, overall and stratified by atypical antipsychotic agent. Rates of atypical antipsychotic use were calculated as a percentage of the population of OHIP-eligible Ontario residents aged 65 and older and alive at the beginning of each quarter.

**Prevalence of Brand-name Agents, and Antipsychotic Expenditures**

For each quarter, we determined the total quarterly cost to the provincial drug plan of atypical antipsychotic prescriptions dispensed to patients aged 65 and older, and estimated the average cost per prescription. This analysis was conducted overall, and stratified by each atypical antipsychotic agent. To estimate the quarterly market share of brand-name prescriptions, we then classified all atypical antipsychotic prescriptions according to their generic status and found the proportion of prescriptions that were for brand-name agents.

### Statistical Analyses

We conducted time series analysis using interventional autoregressive integrated moving-average (ARIMA) models to examine the impact of the introduction of new brand name atypical antipsychotics on overall rates of atypical antipsychotic use. Due to close temporal relation of the new agents' introduction, we chose the marketing of the first new agent as our main intervention point in the model (paliperidone, Q3 2009). We used the correlograms depicting autocorrelation, partial autocorrelation, and inverse autocorrelation functions to guide initial model selection. We assessed autocorrelation at various lags using the Ljung-Box Chi-square statistic and stationarity using the augmented Dickey-Fuller test. Our intervention was modeled as a step function in the regression model. A p-value <0.05 was considered statistically significant. All analyses were conducted using SAS software version 9.2.

## RESULTS

### Overall Atypical Antipsychotic Use and Choice of Agent

Over the study period, we identified 235 267 older adults who were prescribed an atypical antipsychotic in Ontario. On average, atypical antipsychotic users were aged 79 years (standard deviation 8.9), and 39.6% (N=93 200) were male. Risperidone was the most commonly used agent at the beginning of the study period (13.0 users per 1000 older adults, Q1 2007; N=23 107), followed by quetiapine (9.3 users per 1000 older adults, Q1 2007; N=16 436) and olanzapine (7.6 users per 1000 older adults, Q1 2007; N=13 570; Figure 1). Over the subsequent six years, quetiapine use rose to become the most commonly used atypical antipsychotic in the first quarter of 2013, with a prevalence of 15.1 users per 1000 older adults (N=32 532).

Following their introduction in Q3 2009, use of new brand name agents increased, reaching a high of 1.5 users per 1000 older adults in Q1 2013 (N=3,132; Figure 1). This rise was driven largely by aripiprazole use, which reached a rate of 1.0 users per 1000 older adults (N=2,120; Figure 1). Overall, the introduction of brand name agents in Ontario led to a small, but statistically significant increase in the overall rate of atypical antipsychotic use, from 27.6 users per 1000 older adults (Q3 2009) to 29.1 users per 1000 older adults (Q1 2013; Figure 2; p=0.04).

**Market Share of Brand Name Agents and Atypical Antipsychotic Expenditures**

Following the introduction of generic versions of olanzapine and quetiapine between the start of our study period (Q1 2007) and Q2 2009, the prevalence of brand name antipsychotic agents decreased considerably from 57.5% to 6.1% (Figure 3). However, following the introduction of new agents in the third quarter of 2009, the prevalence of branded agents began to rise, reaching 11.7% by the end of the study period.

The costs for atypical antipsychotics were also greatly influenced by the introduction of generic formulations early in the study period as well as the decrease in government reimbursement for generic drugs in Q3 2010. Following these changes, the average cost per atypical antipsychotic prescription fell from $26.46 (Q1 2007) to a low of $14.00 (Q4 2010; Figure 3). However the costs rose 17.6% from Q4 2010 to Q1 2013, from a mean of $14.00 per prescription to a mean of $16.39 per prescription.

In the first quarter of 2013, the newly introduced medications (aripiprazole, ziprasidone, and paliperidone) were used by only 4.3% of atypical antipsychotic users (Figure 1), but accounted for 16.3% of total atypical antipsychotic expenditures ($1.4M of $8.8M). This was driven by the large differential in the average quarterly costs per person for these branded and

generic agents. In the first quarter of 2013, average quarterly costs per user for paliperidone, ziprasidone and aripiprazole were $953.76, $362.64, and $349.60, respectively. In comparison, the mean quarterly costs per patient for generic atypical agents at this time were $104.59 for quetiapine, $110.40 for risperidone and $152.75 for olanzapine.

**DISCUSSION:**

Over the study period, we found large shifts in atypical antipsychotic prescribing preferences and drug costs among seniors in Ontario, and an overall increase in the rate of atypical antipsychotic prescribing following the introduction of new brand name agents to the public drug formulary. As expected, we observed a marked decrease in expenditures corresponding with the introduction of generic agents, and a reversal of this trend with the arrival of novel atypical agents. Although newer branded agents were used by less than 5% of patients treated with atypical antipsychotics in early 2013, these agents accounted for over 15% of atypical antipsychotic drug costs. Furthermore, the growth of aripiprazole use shows no sign of slowing, and due to its high price compared to generic formulations, it is likely that costs for atypical antipsychotic agents will continue to rise in the near future.

Several limitations of this study warrant emphasis. First, we are unable to access in-hospital medication records, and thus our study is restricted to atypical antipsychotic use in community-dwelling seniors and long-term care residents. Second, due to the close proximity of the introduction of new antipsychotic agents and generic versions of existing agents, we were unable to assess the independent impact of each new antipsychotic agent on drug expenditures using time series analysis.

Previous studies have found expanding off-label prescribing and potential overuse of atypical antipsychotics, suggesting that the rising rate of use of these products after the introduction of new agents should be further monitored and explored to assess the appropriateness of these prescribing practices (1,2,7,8). Furthermore, the safety of antipsychotic use in older patients has been questioned, particularly for the symptomatic treatment of behavioural and psychological symptoms of dementia (2,12). Adverse effects observed include extrapyramidal symptoms and increased risk of diabetes, hip fracture, and all-cause mortality (6,21-23). Notably, Health Canada and Janssen Inc. have recently agreed to limit risperidone use in dementia to short-term symptomatic treatment of behavioural or psychological symptoms of severe Alzheimer type dementia, citing a higher risk of cerebrovascular adverse events (24). However, previous studies have found safety warnings to be ineffective at reducing the use of antipsychotics among the older population in Canada and Europe, and our findings indicate that, while prescribing preferences have shifted within the class as product availability has changed, atypical antipsychotics are increasingly a mainstay of geriatric psychiatry, despite these safety concerns (2,12).

**CONCLUSION:**

The results of this study suggest that the introduction of new atypical antipsychotic agents, which are more aggressively marketed than generic therapies (25-27), led to a small but significant increase in the overall use of these medications in Ontario. Furthermore, we demonstrated that, despite a drop in atypical antipsychotic costs following the introduction of several generic formulations, expenditures related to these drugs are once again rising. Further monitoring of these trends and their impact on patient outcomes and health sector

expenditures would be prudent as they have the potential to have considerable impacts on quality of care and drug formulary budgets.

**REFERENCES**


1. Rapoport M, Mamdani M, Shulman KI, Herrmann N, Rochon PA. Antipsychotic use in the elderly: shifting trends and increasing costs. Int J Geriatr Psychiatry. 2005 Aug;20(8):749–53.

2. Valiyeva E, Herrmann N, Rochon PA, Gill SS, Anderson GM. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis. CMAJ. 2008 Aug 26;179(5):438–46.

3. Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS. Increasing off-label use of antipsychotic medications in the United States, 1995-2008. Pharmacoepidemiol Drug Saf. 2011 Feb;20(2):177–84.

4. Leslie DL, Mohamed S, Rosenheck RA. Off-label use of antipsychotic medications in the department of Veterans Affairs health care system. Psychiatr Serv. 2009 Sep;60(9):1175–81.

5. Chen H, Reeves JH, Fincham JE, Kennedy WK, Dorfman JH, Martin BC. Off-label use of antidepressant, anticonvulsant, and antipsychotic medications among Georgia medicaid enrollees in 2001. J Clin Psychiatry. 2006 Jun;67(6):972–82.

6. Maher AR, Maglione M, Bagley S, Suttorp M, Hu J-H, Ewing B, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. JAMA. 2011 Sep 28;306(12):1359–69.

7. Rochon PA. Exploring the variation in Ontario nursing home prescribing rates for antipsychotics. Healthc Q. 2007;10(4):20–2.

8. Rochon PA, Stukel TA, Bronskill SE, Gomes T, Sykora K, Wodchis WP, et al. Variation in nursing home antipsychotic prescribing rates. Arch Intern Med. 2007 Apr 9;167(7):676–83.

9. Spielmans GI, Berman MI, Linardatos E, Rosenlicht NZ, Perry A, Tsai AC. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. PLoS Med. 2013;10(3):e1001403.

10. Dewa CS, Remington G, Herrmann N, Fearnley J, Goering P. How much are atypical

antipsychotic agents being used, and do they reach the populations who need them? A Canadian experience. Clin Ther. 2002 Sep;24(9):1466–76.

11. Chen Y, Briesacher BA, Field TS, Tjia J, Lau DT, Gurwitz JH. Unexplained variation across US nursing homes in antipsychotic prescribing rates. Arch Intern Med. 2010 Jan 11;170(1):89–95.

12. Schulze J, van den Bussche H, Glaeske G, Kaduszkiewicz H, Wiese B, Hoffmann F. Impact of safety warnings on antipsychotic prescriptions in dementia: nothing has changed but the years and the substances. Eur Neuropsychopharmacol. 2013 Sep;23(9):1034–42.

13. Law MR, Ystma A, Morgan SG. The short-term impact of Ontario's generic pricing reforms. PLoS ONE. 2011;6(7):e23030.

14. Update K, Ontario Drug Benefit No. 41 [Internet]. [cited 2015 Jan 12]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/formulary/41_update_k_20090805.pdf

15. Update U, Ontario Drug Benefit No. 41 [Internet]. [cited 2015 Jan 12]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/formulary/41_update_k_20090805.pdf

16. Update AB, Ontario Drug Benefit No. 41 [Internet]. [cited 2015 Jan 12]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/formulary/41_update_ab_20111014.pdf

17. Drake R, Skinner J, Goldman HH. What explains the diffusion of treatments for mental illness? Am J Psychiatry. 2008 Nov;165(11):1385–92.

18. Liu Q, Gupta S, Venkataraman S. The dynamics of competitive drug detailing. 2007. Available from: http://www.chicagobooth.edu/research/workshops/marketing/docs/Liu-jobpaper.pdf

19. Hoffman MN. Pharmaceutical Detailing Is Not for Everyone: Side Effects May Include Sub-Optimal Prescribing Decisions, Compromised Patient Health, and Increased Prescription …. Journal of Legal Medicine. 2012.

20. Spurling GK, Mansfield PR, Montgomery BD, Lexchin J, Doust J, Othman N, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review. PLoS Med. 2010 Oct;7(10):e1000352.

21. Schneider LS, Dagerman KS, Insel P. Risk of Death With Atypical Antipsychotic Drug Treatment for Dementia: Meta-analysis of Randomized Placebo-Controlled Trials. JAMA. American Medical Association; 2005 Oct 19;294(15):1934–43.

22. Gill SS. Antipsychotic Drug Use and Mortality in Older Adults with Dementia. Ann Intern

Med. 2007 Jun 5;146(11):775.

23. Jalbert JJ, Eaton CB, Miller SC, Lapane KL. Antipsychotic Use and the Risk of Hip Fracture Among Older Adults Afflicted With Dementia. Journal of the American Medical Directors Association. 2010 Feb;11(2):120–7.

24. Janssen Inc. Risperidone - Restriction of the Dementia Indication [Internet]. Toronto, ON; 2015. Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/43797a-eng.php

25. Oldani MJ. Thick prescriptions: toward an interpretation of pharmaceutical sales practices. Med Anthropol Q. 2004 Sep;18(3):325–56.

26. Liu Q, Gupta S, Venkataraman S. An Empirical Model of Drug Detailing: Dynamic Competition and Policy Implications. Available at SSRN …. 2013.

27. Adair RF, Holmgren LR. Do drug samples influence resident prescribing behavior? A randomized trial. The American Journal of Medicine. 2005 Aug;118(8):881–4.

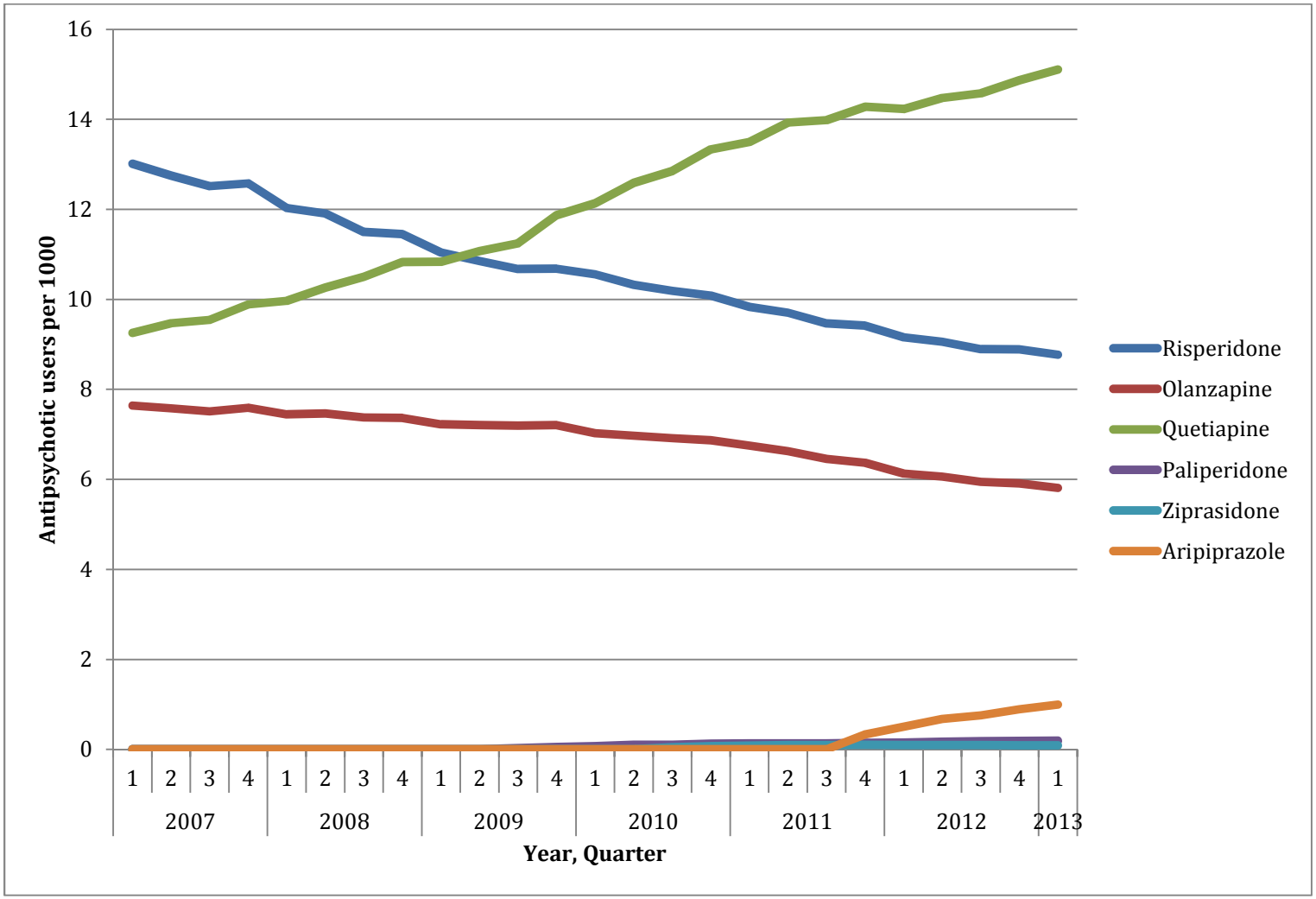


**Figure 1: Prevalence of Atypical Antipsychotic Use among Seniors in Ontario, by Drug.**

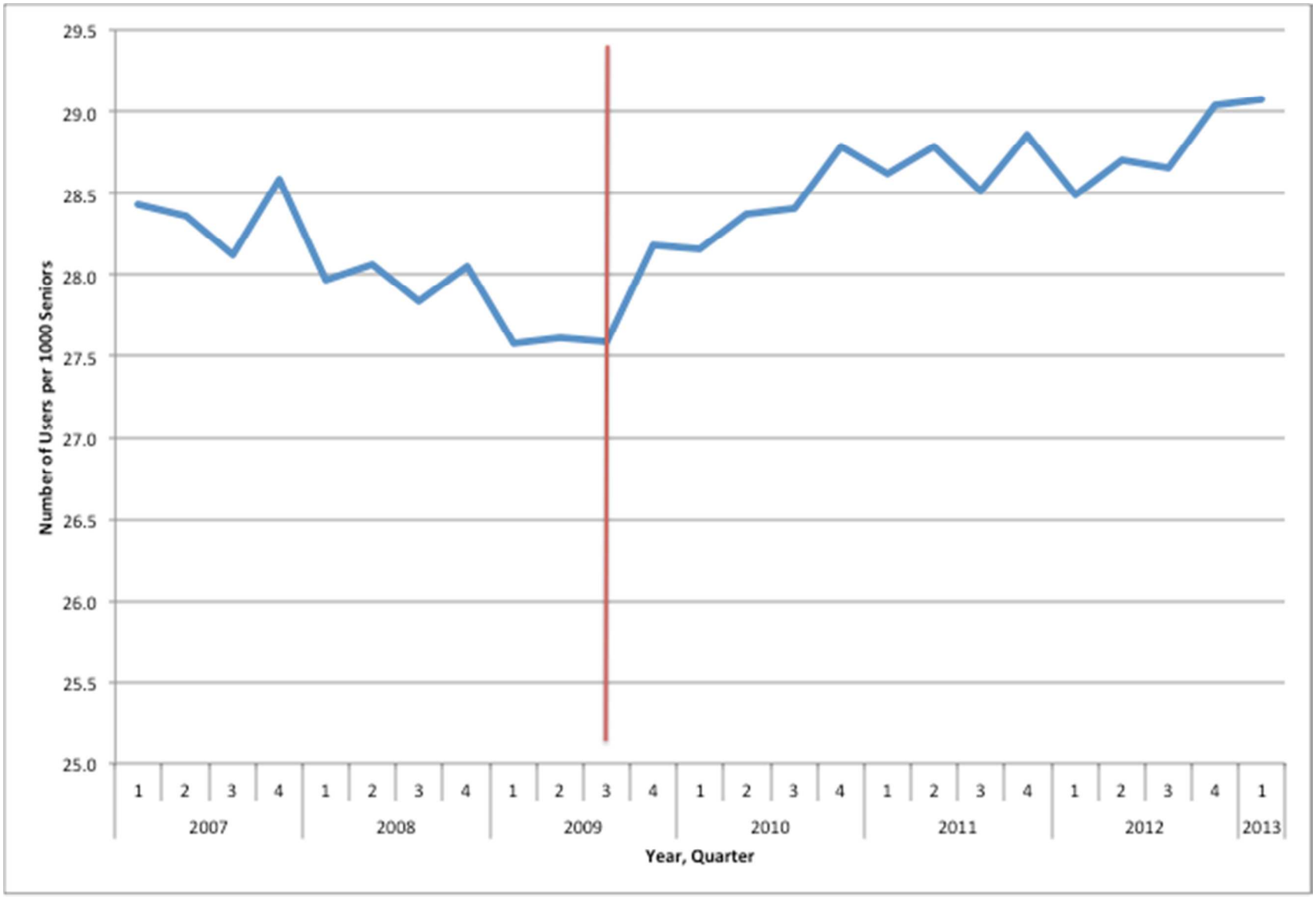


**Figure 2: Rate of Atypical Antipsychotic Prescribing per 1000 older adults in Ontario**

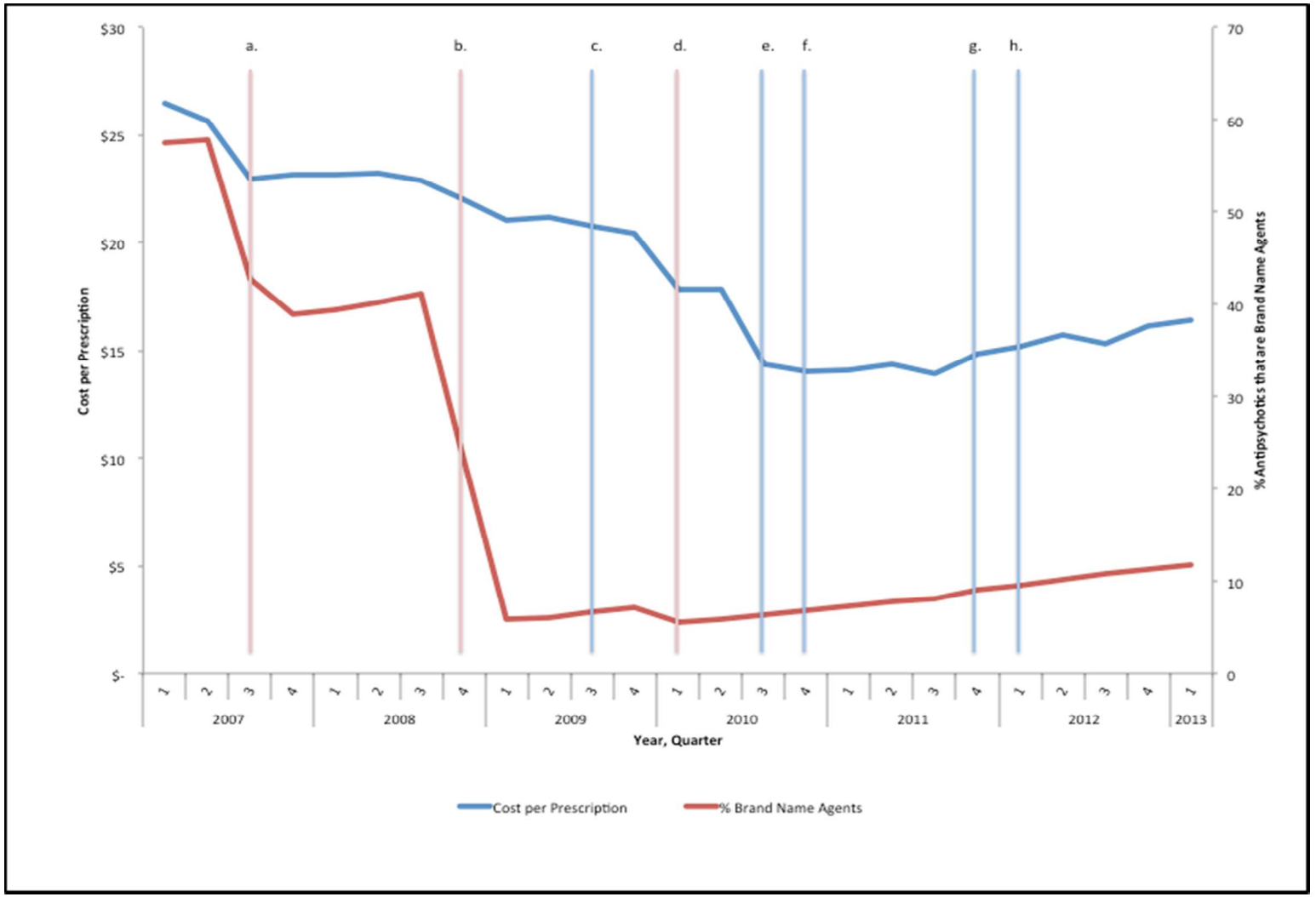


**Figure 3: Cost per antipsychotic prescription and prevalence of branded atypical antipsychotic agents.**

**Legend**

a. Olanzapine patent expiry
b. Quetiapine patent expiry
c. Paliperidone added to formulary
d. Olanzapine rapid dissolve patent expiry
e. Quetiapine extended release added to formulary
f. Ziprasidone added to formulary
g. Aripiprazole added to formulary
h. Injectable paliperidone added to formulary