THE UNINTENDED (AND COSTLY) EFFECTS DUE TO THE INTRODUCTION OF AN UNRESTRICTED REIMBURSEMENT POLICY FOR ATYPICAL ANTIPSYCHOTIC MEDICATIONS IN A CANADIAN PUBLIC PRESCRIPTION DRUG PROGRAM: 1996/97 TO 2005/06

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ABSTRACT

Background
Due to the increasing costs of pharmaceuticals, drug benefit programs often implement various policies that limit availability of drugs. These policies can have unforeseen consequences.

Objectives
To examine the utilization and expenditures for antipsychotic medications in a provincial government community-based drug program over a 10-year period when atypical antipsychotics were introduced and multiple reimbursement policy changes with respect to these agents were employed.

Methods
Retrospective analysis of the Newfoundland and Labrador Prescription Drug Program (NLPDP) claims database from 1996/97 to 2005/06. Antipsychotic medication utilization and expenditure were measured and effects of changes in reimbursement policies examined. Excess expenditure was measured by subtracting the actual from modelled expenditure under different policies.

Results
Between 1996/97 and 2005/06, the number of prescriptions for antipsychotic medications increased by 75% and expenditures by more than 720% to $7.2 million (peaking at $7.9 million in 2003/04), with atypical agents making up 96% of the total. Expenditure for antipsychotic medications grew by an annual average rate of 26.3%. At the same time, the number of people enrolled in the drug program declined by an annual average rate of 1.13%. The total excess amount of money spent was $266,195 per 1,000 beneficiaries during unlimited access to atypical agents.

Conclusion
There has been a substantial, unintentional, increase in the prescribing of atypical antipsychotics each year in Newfoundland and Labrador over the 10 years, likely due to off-label use following the unrestricted and partial restrictive access policies for these medications. Perhaps restricted access for recognized usage should be enforced.

Key Words: *Drug utilization, provincial drug formulary, drug policy, drug access*

Pharmaceutical drug therapies play an important role in Canada's health care system. As their role in the health care system expands, so does their cost. Total expenditure on drugs was

approximately $3.8 billion in 1985, and is estimated to have reached $25.2 billion in 2006.[1] The extent to which people receive pharmacotherapies is affected by two separate mechanisms: access and utilization. They work together to determine whether a particular drug is used widely in the health care system. Given that prescription drug costs will likely continue to rise in the future, drug benefit programs often implement various access control mechanisms that limit the availability of drugs (e.g. reference drug pricing and special authorization). Drug coverage policy is intended to ensure access to optimal, appropriate, cost-effective pharmacotherapies, and thereby evidence-based and judicious expenditure of public funds. In so doing, it restricts higher cost drugs where evidence demonstrates no meaningful clinical benefit over existing lower-cost therapies.[2] Utilization is more subjective and reflects the degree to which health care services that are available are actually used by the consumer or the extent to which a population 'gains access'.[3] With respect to pharmaceuticals, there are a number of factors that affect utilization such as physician prescribing behaviour and patient adherence to prescribed medications.

Policy decisions concerning which drugs to restrict and how much restriction to impose must consider items such as the expected incremental benefits when compared to other available pharmacological and non-pharmacological treatments, relative cost-effectiveness, and the estimated impact on overall health care costs. These decisions are extremely difficult since information regarding cost-effectiveness, and sometimes comparative clinical effectiveness, is often lacking and there are concerns that policies, such as special authorization, that restrict access, may result in unintended outcomes, including patients switching to less effective treatments or increasing the use of more costly physician or institutional care.[4-6]

Prior to December 23, 1998, the province of Newfoundland and Labrador's Prescription Drug Program (NLPDP), which provides prescription drug coverage for all residents of the province who are either on income support or are aged 65 and older in receipt of the Guaranteed Income Supplement (GIS), relied on a special authorization policy for new, more expensive atypical antipsychotic medications (risperidone (Risperidal®), clozapine (Clozaril®), quetiapine (Seroquel®) and olanzapine (Zyprexa®)) to treat schizophrenia. Reimbursement was based on defined criteria: a diagnosis of schizophrenia and either failure to respond to two adequate trials of conventional agents, or intolerance of conventional agents. The rationale for using prior authorization in this case was based on the assumption that these agents were more expensive than other alternatives, while their increased clinical benefit, based on evidence at that time, was equivocal. It has been suggested that since lowering pharmaceutical expenditures is a valid endpoint in its own right and directly correlates with overall medical cost savings, dispensing of the more expensive agents should require special permission.[7,8]

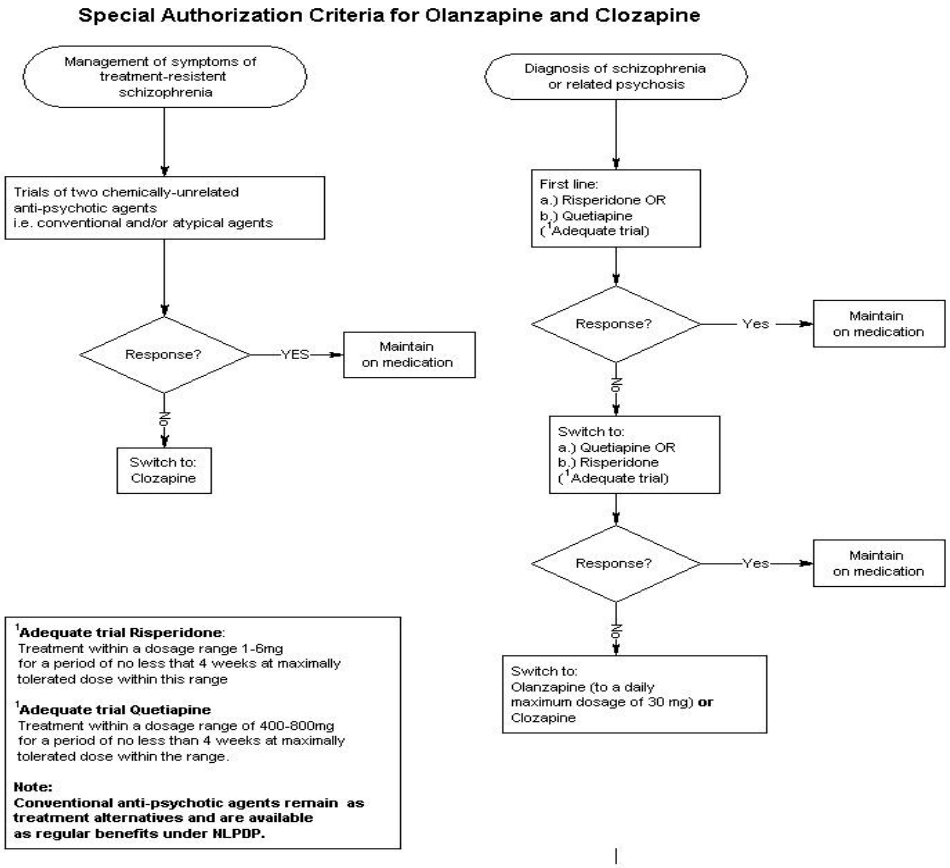
The primary advantage of these atypical antipsychotic medications alleged at that time was the decreased risk of developing extrapyramidal side effects (EPS) such as parkinsonism, akathisia, acute dystonia, and tardive dyskinesia, which may lead to improved adherence with therapy and thus improved effectiveness in clinical practice.[9,10] The value of reduced or absent side effects, and/or enhanced efficacy may have economic implications by reducing the need for hospital admission that may justify the higher drug acquisition costs. Based on these expectations, the Department of Health and Community Services, Government of Newfoundland and Labrador introduced an unrestricted reimbursement policy for these four atypical antipsychotic medications in early 1999.

The findings of an earlier evaluation, designed to measure the impact of the unrestricted access policy on hospital utilization by patients with schizophrenia in the province, were presented to the NLPDP in early 2004. The results have been published elsewhere[11], and in short, the study concluded that the increased access and utilization of atypical antipsychotic medications did not coincide with a reduction in total days in hospital or readmission rates for persons suffering from schizophrenia. Shortly following the release of the initial report to the NLPDP, the drug program made another change to the policy surrounding coverage of these agents. Effective October 1, 2004, the new policy consisted of partial restriction: open benefit status remained in place for risperidone and quetiapine, thereby allowing first line atypical antipsychotic coverage for schizophrenia and other approved indications.

It was noted that this policy was subject to ongoing review and would be amended in the event of inappropriate usage. Olanzapine and clozapine were to be moved from open benefit back to special authorization status and would be considered for coverage where the former have failed (Figure 1). NLPDP beneficiaries who were stabilized on olanzapine and clozapine, if used for the treatment of schizophrenia and related psychosis before October 1, 2004, would continue to be covered for these medications upon receipt of a request for continued coverage that confirmed this diagnosis. This was due to the fact that there were clinical concerns regarding the ability to safely interrupt treatment for patients who had been stabilized on a drug for some time. At the time, the evidence did not unequivocally demonstrate clinical superiority of any particular atypical, particularly if the side effect and safety profile is considered along with the clinical effectiveness profile.[12-19] The only exception is in severely refractory patients, no atypical antipsychotic has consistently been shown to be as effective as clozapine or superior to conventional agents. As such, the two lower cost agents were maintained as open benefit (i.e. risperidone and quetiapine), with restrictions for coverage placed on the two higher cost agents (i.e. olanzapine and clozapine). This partial restriction approach would mean significant savings for this class of medications, while maintaining access to atypicals as first-line medications for the treatment of indicated disorders.

The goal of the current study was to examine variations in utilization of, and expenditure for, atypical antipsychotic medications by the NLPDP during a 10-year period when changes in policy regarding reimbursement for these new agents were occurring.

FIG. 1 Algorithm for Atypical Reimbursement in 2004



METHODS

Source of Data

The NLPDP provided semi-annual claims data for the period April 1996 to March 2006 on the volume of all prescriptions for all therapeutic categories reimbursed by the program and the associated costs (including mark-ups and drug dispensing fees for recipients of the Foundation plan, formerly known as the Income Support Drug Program, but none for recipients of the 65Plus Plan, formerly known as the Senior Citizens Drug Subsidy Program) paid by the program. All antipsychotic medications were extracted from the databases using the appropriate American Hospital Formulary System (AHFS) therapeutic classification (i.e. 28:16.08) and entered into a Microsoft® Office Excel® database. Each antipsychotic medication was grouped as either conventional or atypical. Tablet and liquid formulations of the same drug were combined regardless of dosage strength.

Data Analyses

For each fiscal year, the number of prescriptions reimbursed and the NLPDP expenditure for all antipsychotic drugs was calculated and analyzed by type (i.e. conventional and atypical). To identify which atypical antipsychotic medication gained the largest market share, expenditures for each of the four atypical antipsychotic medications were also analysed separately. Annual values of expenditures were graphed to better illustrate changes.

To ensure that any changes in antipsychotic utilization were not due to changes in the number of beneficiaries eligible for coverage, the number of prescriptions per 1,000 eligible beneficiaries in either the Foundation plan or the 65Plus Plan was determined.

Reimbursement Policy Changes

The effects of the changes in reimbursement policy on expenditures for antipsychotic agents were examined. The data were separated into three discrete time periods: 1) restricted access (April 1996 to March 1999); 2) unrestricted access (April 1999 to March 2004); and 3) partial restriction (April 2004 to March 2006). We constructed an index of each period's average annual rate of growth and compared each one to the growth rate during the period of restricted access. Also, the average annual rate of growth over the entire 10-year study period was calculated. The formula used to calculate the average annual rate of growth was:

$$= (e^{(\ln(\text{value at end of period}) - \ln(\text{value at beginning of period}))/(T-1)}) - 1.$$

Where the constant e equals 2.718, which is the base of the natural logarithm, and T equals the number of years in the period.

Modelling the Impact of Policy Changes

Finally, we modelled antipsychotic expenditure, defined as the cost per 1,000 beneficiaries, if the restricted access policy remained in place and compared it with the actual utilization resulting from the policy changes. To estimate the former, we extrapolated trends in antipsychotic use during restricted access to the end of the study period. We included another year (1995/96) in the calculation of the model since we had access to the data and decided that it would provide extra information to more accurately predict the pattern of utilization. The slope and position of the baseline trends were estimated by linear regression. The excess cost per 1,000 beneficiaries due to the unrestricted policy was then calculated by subtracting the estimated utilization from the actual utilization of antipsychotic medications.

RESULTS

Utilization of, and Expenditure for, Antipsychotic Medications by NLPDP 1996/97-2005/06

In 1996/97, the NLPDP provided reimbursement for 40,238 antipsychotic prescriptions. The atypical antipsychotic agents accounted for a very small share, making up only 5% of the total. Between 1996/97 and 2005/06, prescriptions for antipsychotics grew 75% while expenditures increased by more than 720%. Total NLPDP spending on antipsychotics was approximately $883,000 in 1996/97; however, this therapeutic category exceeded $7.2 million in 2005/06 with the atypical antipsychotic agents making up 96% of this amount. Peak spending occurred in the final year of unrestricted access ($7.9 million) (Figure 2). During this 10-year period, expenditure on antipsychotic medications in the provincial public drug program in Newfoundland

and Labrador grew by an annual average rate of 26.3%, while this growth rate was 42.9% for atypical agents and -7.2% for conventional agents. Consequently, the share of expenditures of atypical antipsychotic medications reimbursed increased from 31.6% in 1996/97 to 95.8% in 2005/06. At the same time, the number of people enrolled in the drug program declined by an annual average rate of 1.13% (Table 1).

FIG. 2 Total NLPDP Antipsychotic Medication Expenditure, by Drug Type between 1996/97 and 2005/06

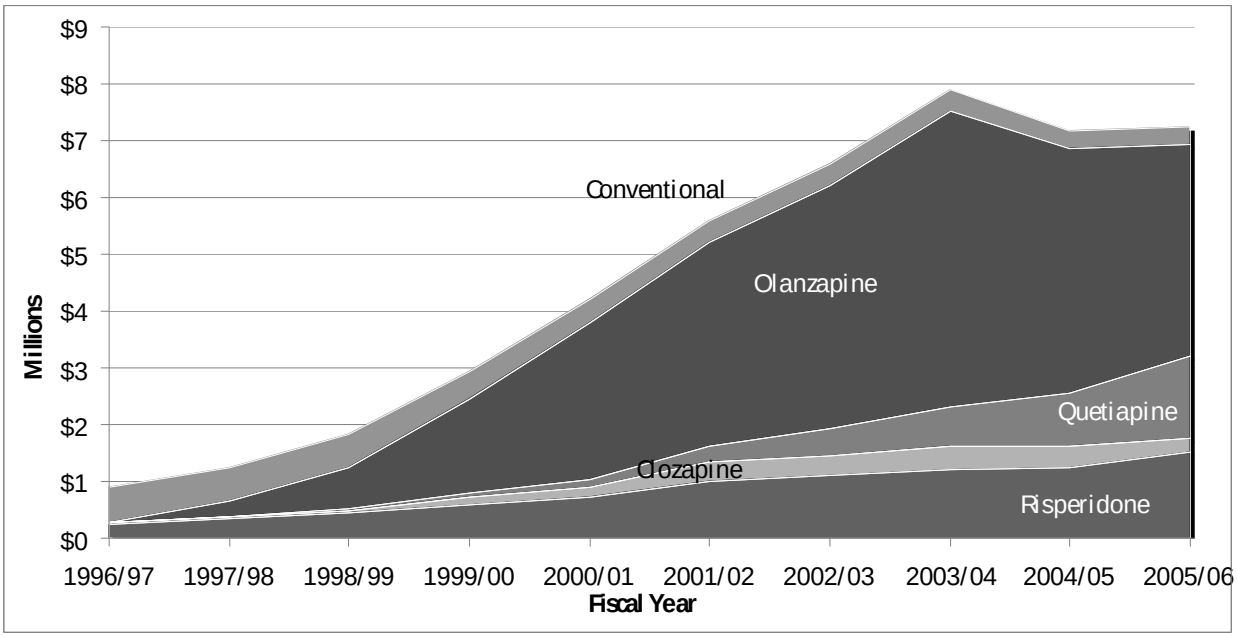


TABLE 1 Number of Beneficiaries by NLPDP Program in each Fiscal Year between 1995/96 to 2005/06

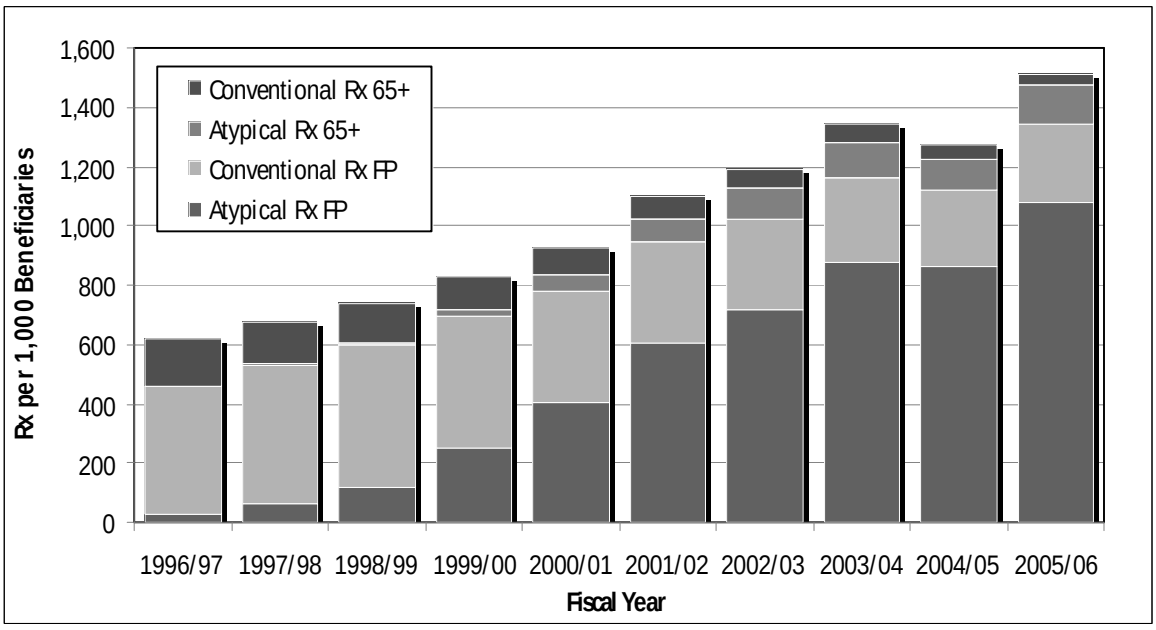
Fiscal Year	Financial Plan Beneficiaries	65Plus Plan Beneficiaries	Total	% change
1995/96	71,357	44,541	115,898	--
1996/97	72,215	45,452	117,667	1.5%
1997/98	67,078	45,160	112,238	-4.6%
1998/99	62,506	45,014	107,520	-4.2%
1999/2000	59,825	44,805	104,630	-2.7%
2000/01	56,481	44,626	101,107	-3.4%
2001/02	52,887	44,602	97,489	-3.6%
2002/03	51,083	45,533	96,616	-0.9%
2003/04	50,483	45,558	96,041	-0.6%
2004/05	48,905	46,906	95,811	-0.2%
2005/06	46,711	46,096	92,807	-3.1%

In the years when there was unrestricted access to atypical antipsychotic medications (i.e. 1999/2000 to 2003/04), the average annual rate of growth of expenditures for antipsychotic medications was 34%. In the final year of this interval, olanzapine dominated the market share with $5.2 million of the total $7.9 million (66%) of all expenditures for antipsychotic medications and risperidone was second, but well behind at 15%.

Once the partial restrictions on olanzapine and clozapine were put in place in 2004, the annual average rate of growth for expenditures for antipsychotic medications decreased to 4.2%. During this time, the share of expenditures for olanzapine decreased by 14 percentage points while quetiapine increased by 11 percentage points (Figure 2).Over the 10-year study period, the number of atypical antipsychotic prescriptions per 1,000 beneficiaries in the Foundation Plan increased by 1,050 from 28 to 1,078 and by 125 from 2 to 127 in the 65Plus Plan. At the same time, prescriptions for conventional antipsychotic medications decreased by 163 per 1,000 beneficiaries in the Foundation Plan, from 429 in 1996/97 to 267 in 2005/06 and by 119 from 157 to 38 in the 65Plus Plan (Figure 3).

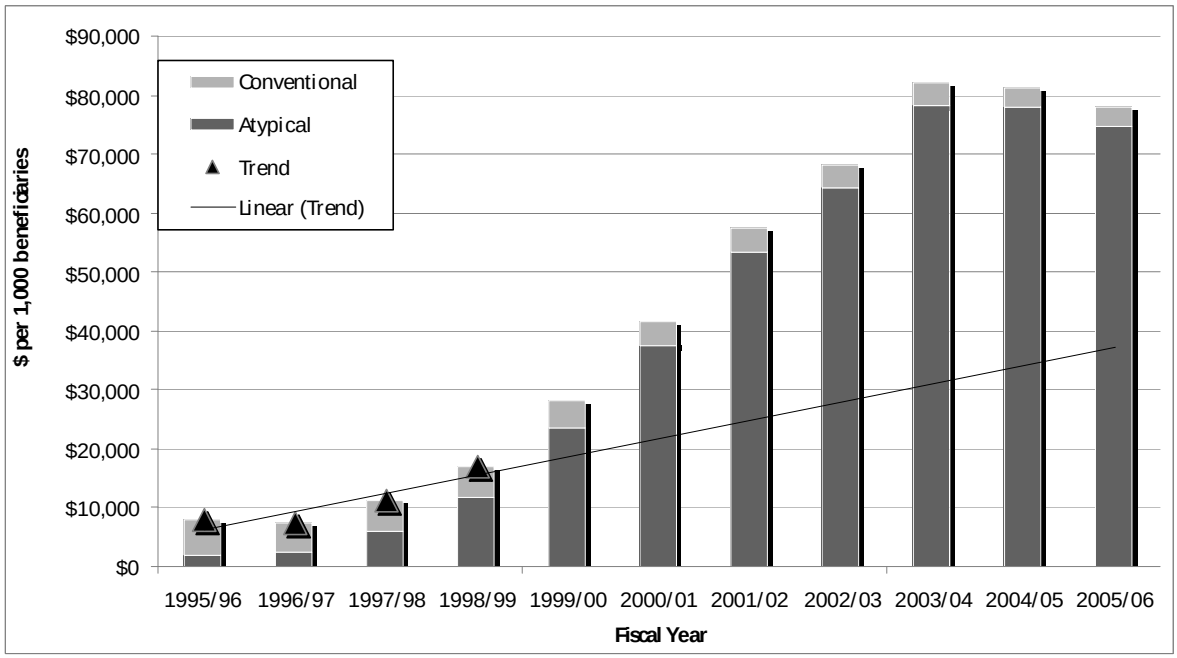
The expenditures per 1,000 beneficiaries increased from $7,883 at the beginning of the restricted access period (i.e. 1995/96) to a maximum of $82,068 by the end of the unrestricted access period (i.e. 2003/04). As illustrated in Figure 4, relative to the trend line created using the annual expenditures for the period of restricted access, the average annual excess expenditure per 1,000 beneficiaries was $38,028 with the excess ranging from $12,767 to a maximum of $54,769 in 2003/04. The total excess amount of money spent was calculated to be $266,195 per 1,000 beneficiaries from 1999/2000 to 2005/06.

FIG. 3 Number of Antipsychotic Medication Prescriptions per 1,000 Beneficiaries Reimbursed by the NLPDP between 1996/97 and 2005/06, by Program



FP =Foundation Plan, Rx = Prescriptions

FIG. 4 Type of Antipsychotic Medication Prescriptions Reimbursed per 1,000 Beneficiaries by NLPDP between 1995/96 and 2005/06



DISCUSSION

This paper documents the trends in use and expenditures for atypical antipsychotic medications from 1996/97 to 2005/06 compared to changes in traditional antipsychotic medications and in relation to changes in reimbursement policies pertaining to the atypical antipsychotic agents in a provincial public drug program. The analysis shows that over the 10-year study period, prescriptions for antipsychotics grew 75% with aggregate spending on atypical antipsychotic medications increasing from $279,000 to $6.9 million, an increase of 2,383%, while spending on conventional agents decreased by only 49%. Total government spending on antipsychotic agents exceeded $7.8 million in 2003/04, the final year of unlimited access, and the four atypical agents accounted for 96% of this amount. At the same time, aggregate spending on traditional antipsychotic medications showed little change. Spending on traditional antipsychotics moved from a level of $604,000 in 1996/97 to $357,000 in 2003/04. After the re-instatement of coverage restrictions for some atypical medications in 2004, the amount of money spent on atypical agents was reduced by $592,000. This dramatic shift towards the prescribing of atypical antipsychotic agents found in this province is similar to results reported in Spain and Australia. Santamaria and colleagues[20] analysed trends in antipsychotic use in Spain over a 6-year period and showed a progressive increase in antipsychotic use. Similarly, a study conducted in Australia showed that between 1995 and 2001, the use of atypical antipsychotics increased from 0.27 to 3.83 defined daily dose/1,000/day.[21] The same patterns were seen in the United Kingdom.[22]

In 2003, Geddes[23] estimated that the value of world sales of these agents increased more than tenfold following the introduction of atypical antipsychotics, from less than $500 million in 1991 to almost $5 billion in the year 2000. The papers did not discuss any policies around reimbursement for these agents or how these drugs were being used in practice but they illustrate the wide acceptance of these medications around the world.

The declining number of people enrolled in the NLPDP over the study period, coupled with the increasing number of prescriptions per beneficiary may suggest that the implementation of an unrestricted reimbursement policy for atypical antipsychotic medications did not merely replace older therapies but expanded the market for use of these agents as a category. The increase in antipsychotic prescriptions may be due to the fact that schizophrenia had long been neglected, by society and by pharmaceutical companies. For most patients, partial remission of symptoms is the best that they can hope for. As a result, patients and their caregivers are always searching for something new. Any new medication, whether substantially better or not, is embraced with great enthusiasm, so it is not surprising that atypical antipsychotics have become synonymous with progress and hope for patients with schizophrenia.

This trend may also reflect an increased use of atypical agents for the treatment and management of disorders other than schizophrenia (i.e. off-label use). While the NLPDP database does not collect information on indication, it is possible to determine a proxy measure of off-label use by analyzing the change in drug costs for atypicals resulting from 2004 policy changes with respect to coverage.

The total cost for all atypicals under the NLPDP for 2003/04 fiscal year, the last full year of open access to all agents, was $7.5 million. Comparing this to data from 2005/06, the first full year of the new coverage policy where risperidone and quetiapine remained open access and the other two agents required special authorization, we see only an 8% decrease in expenditure. This represents a smaller percentage change than one might expect given what was widely believed to be significant off-label use. However, it is important to remember that during this period new indications were approved, which would impact utilization. In addition, any off-label use of olanzapine could simply have shifted to off-label risperidone or quetiapine use as they remained open benefit. To account for these factors, and to get a more precise estimate of the prevalence of off-label use we can compare the olanzapine use during 2003/04 to its use in 2005/06. This comparison demonstrates a 28% decrease in cost. As the only requirement for remaining on olanzapine when the coverage changes were made was confirmation from the prescriber of a diagnosis of schizophrenia, schizoaffective disorder, or psychosis not otherwise specified, this decrease can be reasonably assumed to reflect the extent of off-label use of olanzapine. Whether this rate of off-label use could be applied to the other atypicals would require further study.

One study has shown that more than 70% of prescriptions for atypical antipsychotic medications were being prescribed for conditions other than schizophrenia, such as major depression, bipolar disorder, posttraumatic stress disorder, obsessive-compulsive disorder, and geriatric agitation[24], most of which would be considered off-label use in Canada during the study period. Another study reported that of the 6.3 million antipsychotic prescriptions written by psychiatrists in 2001 in the United States, 43% were for schizophrenia, 22% for bipolar disorder, and 16% for depression.[25] Any off-label use is exacerbated by the fact that atypical antipsychotic medications were, on average, ten times more costly than conventional agents at the time this study was conducted.

At the same time, a review of the controlled trials published on atypical antipsychotic medications since 1998 revealed that data were sparse on the efficacy of novel antipsychotics for off-label uses. For example, while there was conflicting evidence regarding the superiority of quetiapine over placebo in treating dementia[26,27] there was support that risperidone was superior to placebo.[28-30] However, there was no evidence to suggest that risperidone was any better than haloperidol[31] or olanzapine.[32] Similarly, olanzapine has been compared to other active antipsychotic agents for the acute treatment of dementia-related behavioural disturbances and all papers reported no substantive differences in efficacy between the drugs for the treatment of this condition.[32-37]

Despite the fact that there was insufficient evidence to conclude that any of the atypical agents were more effective than older antipsychotic agents at controlling agitation and psychosis in dementia patients, in 1999 risperidone was approved in Canada for the treatment of severe dementia for the acute symptomatic management of inappropriate behaviour due to aggression and/or psychosis.[38] It is important to note however, that the current

licensing system for pharmaceuticals in Canada does not require an assessment of comparative effectiveness or cost effectiveness. For market authorization to be provided Health Canada requires evidence to support a product's safety, efficacy and quality, in accordance with the *Foods and Drugs Act and Regulations*.

Over the period of the current analyses, there was evidence to support that risperidone, olanzapine and quetiapine were as efficacious as other antipsychotic medications in treating patients with acute mania associated with bipolar disorder.[39-49] Risperidone was similar to other agents for the long-term management of mania[50] while one study concluded that olanzapine was actually better than divalproex for the long-term management of this condition.[51] Olanzapine, quetiapine and risperidone were approved in Canada for the acute management of manic episodes associated with bipolar disorder in 2003, 2004 and 2005 respectively.[38,52,53] Olanzapine was also granted approval for monotherapy maintenance treatment in bipolar patients with manic or mixed episodes in 2004.[53]

There was little support for the use of novel antipsychotics in the treatment of autism in children. In short-term studies, risperidone demonstrated a greater improvement in symptoms when compared to placebo.[54-57] However, in the longer term risperidone was shown to be no different than placebo.[58] One study investigated the effectiveness of olanzapine as a treatment for children with autistic disorder by using haloperidol as a standard comparator treatment and found that there was no difference between the two groups.[59]

Olanzapine combination therapy was not shown to be more effective than olanzapine monotherapy or placebo for the treatment of acute or long-term management of depressive episodes in patients with bipolar disorder.[60,53] Two short-term studies demonstrated that the administration of quetiapine resulted in a statistically significant improvement in Montgo mery-Asberg Depression Rating Scale total scores compared to placebo in the treatment of bipolar depression.[61,62]

In patients with treatment-resistant depression there were sparse and conflicting data about the efficacy of augmentation with an atypical antipsychotic agent. One 12-week study found that olanzapine/fluoxetine combination was significantly better than olanzapine monotherapy[63] but others did not come to the same conclusion.[64] An evaluation of risperidone augmentation of serotonin-selective reuptake inhibitor compared to placebo did not demonstrate an improvement in symptoms.[65] Adjunct therapy with quetiapine was found to be better than placebo and lithium.[66]

From 2000 onwards, a number of small, short-term studies were conducted, suggesting that augmentation to a serotonin reuptake inhibitor (SRI) with either risperidone or quetiapine, produced better outcomes than continuing on monotherapy in patients with treatment-refractory obsessive compulsive disorder (OCD).[67-74] At the same time, two studies concluded that there was no additional advantage of adding the atypical antipsychotic in OCD patients who have not had a satisfactory response to an SRI compared with extending the monotherapy trial.[75,76]

Despite the limited evidence in the literature to support the use of atypical antipsychotic medications for other indications besides schizophrenia, off-label use was one of the unintended (and costly) effects of the removal of the coverage restrictions in 1999. Since the 2004 re-introduction of coverage restrictions on two of the four atypicals, costs to the program for atypicals have declined by about 8%. The drug program costs for these agents have likely further declined since risperidone became available in generic form in 2006 and olanzapine in June 2007.

The analyses presented here are not without their limitations. First, the NLPDP database was created primarily for reimbursement purposes and as a result, did not, during the study period, contain any patient-specific information (e.g. age, gender, diagnosis), and it was not possible to link the database with any other information to allow for any inferences about the appropriateness of the prescribing for these drugs in clinical practice and the impact on patient health. Escalating costs to provincial drug formularies strengthens the necessity of determining the appropriateness of drug prescriptions. Inappropriate utilization imposes an economic burden on an already constrained health care budget and this deserves future investigation. Second, the linear trend line calculated was based on 4 years of data; however, we still think this is a reasonable estimate.

Alternative methods to contain pharmaceutical sector costs may be worthy of exploration, such as

spending management by actively negotiating or setting drug prices, or contracting with industry so that the manufacturer shares the financial risk if higher-than-expected expenditures are incurred. Reference-based pricing policies, whereby only the cost of the lowest price drug in a therapeutic group is covered by the drug benefit plan, may also be an option in Newfoundland and Labrador. The reimbursement price is set irrespective of the drug or brand prescribed. If patients wish to have a drug prescribed other than the reference product they must pay the difference out of their own pocket.[8,77] This policy has been implemented in the province of British Columbia for certain therapeutic classes of drugs.

In addition, the development of an electronic medical record with the ability to link with various other health and non-health care sectors would allow for the accurate recording of how drugs are being used and the impact of their use. This would strengthen the evidence with which policymakers can make rational decisions.

In conclusion, the implementation of the unrestricted access policy for atypical antipsychotic medications by the NLPDP resulted in a significant increase in utilization and government expenditure for these drugs. The partial restriction policy reduced the prescribing of the affected atypical antipsychotic agents (i.e. olanzapine and clozapine) and a resulting increase in the remaining two atypical agents (i.e. risperidone and quetiapine).

Reimbursement policies for atypical antipsychotic medications will likely continue to change as more evidence becomes available. For example, a study published in 2005 found that there was no difference between the conventional drug perphenazine and some of the other second generation antipsychotic agents.[78] Another trial concluded that clozapine was superior to other atypical antipsychotic medications after failure of other atypicals (more effective than switching to another atypical).[79] Furthermore, the results of a pragmatic randomized trial refute the hypothesis that the use of atypical antipsychotics is superior to the use of conventional agents in terms of quality of life at 1 year.[80]

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