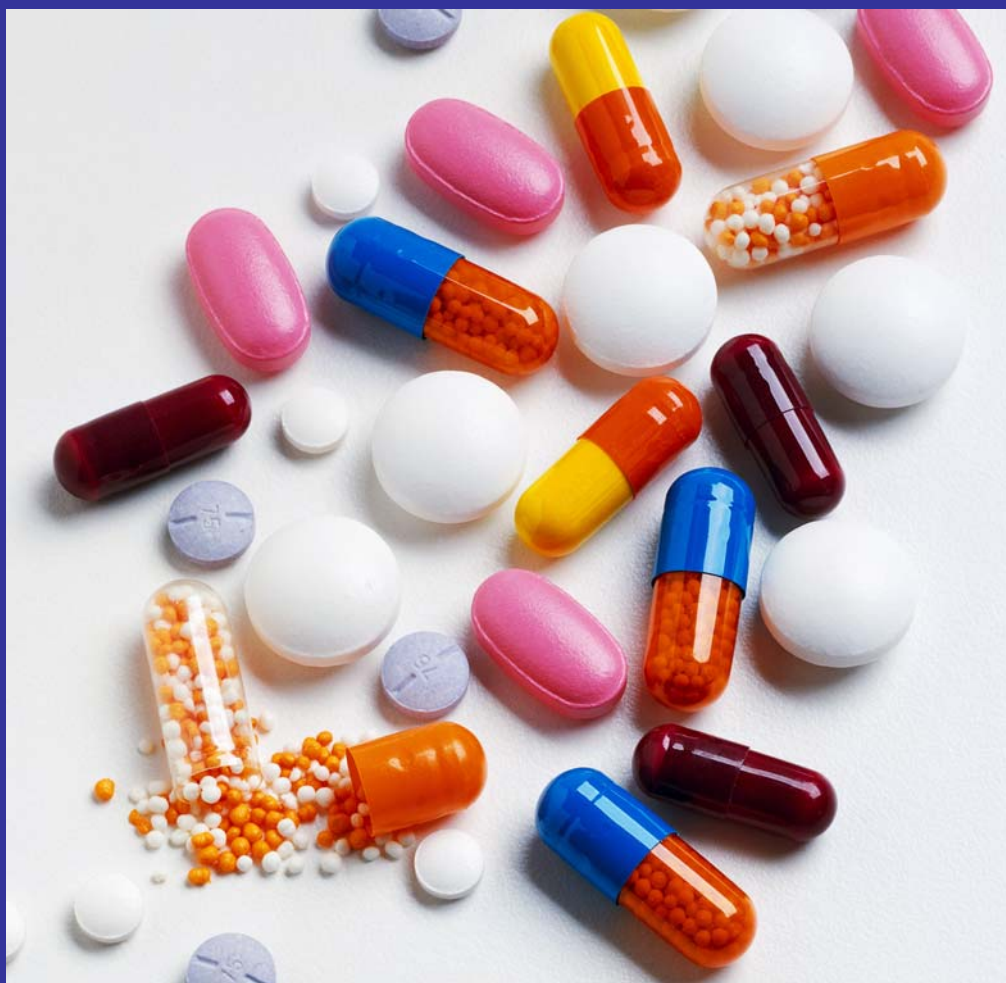


Incorporating Pharmacosurveillance in Provincial Drug Formulary Decision-Making



Investigative Report

June 2005

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ICES—Ontario's resource for informed health care decision-making

ICES (Institute for Clinical Evaluative Sciences) is an independent, non-profit organization that conducts health services evaluations on a broad range of topical issues to enhance the effectiveness of health care for Ontarians. Internationally recognized for its innovative use of population-based health information, ICES knowledge provides evidence to support health policy development and changes to the organization and delivery of health care services.

Unbiased ICES evidence offers fact-based measures of health system performance; a clearer understanding of the shifting health care needs of Ontarians; and a stimulus for discussion of practical solutions to optimize scarce resources.

Key to ICES' work is our ability to link anonymous population-based health information on an individual patient basis, using unique encrypted identifiers that ensure privacy and confidentiality. This allows scientists to obtain a more comprehensive view of specific health care issues than would otherwise be possible. Linked databases reflecting 12 million of 30 million Canadians allow researchers to follow patient populations through diagnosis and treatment, and to evaluate outcomes.

ICES brings together the best and the brightest talent under one roof. Many of our faculty are not only internationally recognized leaders in their fields, but are also practising clinicians who understand the grassroots of health care delivery, making ICES knowledge clinically-focused and useful in changing practice. Other team members have statistical training, epidemiological backgrounds, project management or communications expertise. The variety of skill sets and educational backgrounds ensures a multi-disciplinary approach to issues management and creates a real-world mosaic of perspectives that is vital to shaping Ontario's future health care.

ICES collaborates with experts from a diverse network of institutions, government agencies, professional organizations and patient groups to ensure that its findings are relevant.

Therapeutics Initiative

The Therapeutics Initiative (TI) was established in 1994 by the Department of Pharmacology and Therapeutics, in cooperation with the Department of Family Practice, at the University of British Columbia to provide up-to-date, evidence-based, practical information on rational drug therapy. The TI is an independent organization, which is at arms length from government, the pharmaceutical industry, and other vested interest groups. It is funded by a grant from the BC Ministry of Health to the University of British Columbia.

The Evaluation Working Group of the TI conducts research on: the appropriateness of prescription drug utilization; the population health impact of prescription drug therapy; the population health and health services utilization impact of drug coverage policies; and the impact of the TI's educational interventions upon prescribing, health services use, and health outcomes in BC.

Centre for Health Services and Policy Research

Based at the University of British Columbia, the Centre for Health Services and Policy Research (CHSPR) was formally established in 1990 as a key partner in health care policy and planning in British Columbia (BC). CHSPR's mission is to stimulate scientific enquiry into issues of health in population groups and ways in which health services can best be organized, funded, and delivered. Its researchers carry out a diverse program of applied health services and population health research under this agenda. CHSPR is also home to the BC Linked Health Database, one of only a small number of data resources in the world where longitudinal research on an entire population can be carried out.

CHSPR receives core funding from the BC Ministry of Health Services to support research with a direct role in informing policy decision-making and evaluating health policy reform, as well as for ongoing development of the BC Linked Health Database. The Centre is also funded by competitive external grants from provincial, national, and international agencies, including the Michael Smith Foundation for Health Research, the Canadian Institutes of Health Research, and the Commonwealth Fund.

Contents

Executive Summary	1
Issue	1
Study	1
Key findings	2
Implications	2
Introduction	3
Policy context	3
Background	4
Findings	7
Baseline interviews with drug plan executives and advisors	7
Interprovincial drug utilization (Level I) studies	8
Closing interviews with provincial drug plan executives in Ontario and BC	10
12 Lessons on Pharmacosurveillance Evidence for Formulary Decision-Making	11
List of Exhibits	15
Appendix A. How the Research was Done	40
Analyses	40
Appendix B. Canadian Network of Centres of Excellence in Pharmacosurveillance.....	43
References.....	44

Executive Summary

Issue

Provincial prescription drug plan managers seek real world evidence regarding the safety and effectiveness of drugs and drug coverage policies. University-based pharmacoepidemiologists with access to routinely gathered health administrative data could help to meet these information needs.

Pharmacoepidemiology, and its application to the study of outcomes in the real world, rather than experimental settings, is referred to as post-market surveillance or pharmacosurveillance.

The key objectives of this research project were:

- To work with formulary decision-makers in Ontario and British Columbia (BC) to identify pharmacosurveillance information needs;
- To develop and refine techniques for producing evidence, and to share those techniques with research teams in both provinces; and,
- To assess the impact of pharmacosurveillance on decision-making.

Study

Relationships were established with provincial drug plan managers in Ontario and BC, and research teams were comprised of investigators and analysts in both provinces. Information about use of evidence and key drugs of interest was collected through 30 semi-structured interviews with drug plan managers and advisors in BC, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia, Newfoundland, and Yukon Territories.

To help streamline communication across the project teams and with stakeholders, a hierarchical classification scheme was developed to describe the types of pharmacosurveillance information this study aimed to produce.

- *Level I* studies examine temporal trends in drug utilization, claimants, and costs, and can be used to compare patterns of use across jurisdictions.
- *Level II* studies examine prior medical history and concurrent drug use for individuals exposed to specific drugs. These provide information about appropriateness of use and can be used to test the validity of assumptions made in cost-effectiveness or budget impact analyses.
- *Level III* studies consider outcomes associated with drug exposures, and can be used to test hypotheses about specific drug safety or effectiveness issues.

Separate analyses of BC and Ontario administrative data were conducted to study drugs of interest using jointly developed computer programs and analytic plans. Monthly or quarterly data were extracted on prescriptions from, and costs paid by, the provincial drug plans, and information on prescriptions paid by private insurers or patients (from BC's PharmaNet database) was added. Results were pooled for discussion with provincial drug plan managers.

Closing interviews with drug plan managers (2 in BC and 2 in Ontario) included a request for feedback on the usefulness/impact of studies done for the drug plans in the preceding 3 years, including those undertaken for this research project.

Key findings

In terms of **drugs of interest**, provincial drug plan managers were most interested in 5 classes of drugs:

1. Newer, more expensive nonsteroidal anti-inflammatory drugs (NSAIDs) (celecoxib, rofecoxib, valdecoxib, and meloxicam), collectively known as coxibs;
2. Newer neuroleptic drugs (antipsychotics);
3. Cytokine inhibitors (infliximab, etanercept, and anakinra);
4. Statins; and,
5. Proton pump inhibitors.

These categories represent blockbuster drugs and reflect situations in which drug coverage was substantially different (e.g., coxibs) and similar (e.g., statins) in BC and Ontario. With one exception (cytokine inhibitors), the analyses showed consistently higher rates of drug use in Ontario, even when public drug coverage was similar. The BC PharmaNet data illustrated the marked impact public drug plan policy can have on drug utilization and costs to private payers.

In terms of techniques for **developing and producing pharmacosurveillance evidence**, this project demonstrated that it is possible for university-based researchers and drug plan managers in different provinces to agree upon priority areas and to undertake research using common methods. However, gaining plan manager input into the research plan and access to some data sources is a challenge. Because information timeliness is critical for effective policy-making, dedicated time with plan staff and resources and mechanisms to guarantee rapid access to complete data is critical.

Interprovincial sharing of ideas and methods, rather than data, builds local research capacity and improves efficiency. Separate data analysis addresses privacy and logistical issues; further, local researchers have established relationships with their provincial drug plans, access to core administrative databases, and are familiar with the data.

In terms of **impact of pharmacosurveillance evidence**, the study found that research was deemed most useful when it was: designed to inform/evaluate a specific decision or policy; available at the time of decision-making; and, easy to apply.

Implications

Existing health administrative databases can provide useful information, but they do not capture many important patient characteristics and outcomes.

The analyses raised important questions about:

- Factors that could contribute to different rates of drug use;
- The characteristics of drug users; and,
- Effects on patient and population health, some of which cannot be answered using administrative data.

To permit better characterization of therapies, patients, and outcomes, the development of new ways to fund, collect, and link information from patients and medical records to administrative data is critical.

Introduction

Escalating provincial health budgets have forced provincial drug plans to seek new ways to encourage appropriate prescription drug utilization, and thereby control costs. Access to good information is vital for responsible decision-making to balance efficacy and safety issues with budgetary constraints in drug plan management.

The key objectives of this research project were:

- To work with formulary decision-makers in Ontario and BC to identify pharmacosurveillance information needs;
- To develop and refine techniques for producing such evidence, and to share those techniques with research teams in the two provinces; and,
- To assess the impact of pharmacosurveillance on decision-making.

Policy context

Evidence for drug regulatory vs. drug coverage decisions: time for a new approach?

Although the concept of explicitly incorporating evidence into decision-making is attractive at a theoretical level, there are few public policy processes with formal mechanisms tying research to policy-making. One example is licensing of pharmaceutical products. Mandatory presentation of evidence in a clear and structured format is a well-accepted part of the process for drug licensing, and clearly defined research methods for producing evidence on drug safety and efficacy are the basis for licensing decisions.

Evidence used in drug-licensing decisions has an accepted framework involving the use of specific methods for obtaining particular types of evidence. Phase 1 to 3 studies each have agreed-upon protocols, and each has an explicit role in the regulatory process. In particular, Phase 3 trials involve the use of a randomized controlled design that provides evidence on efficacy with strong internal validity and inherent protection against bias, and there is agreement between drug manufacturers and the federal government on acceptable methods for analysis. To similarly streamline communication within and across the project teams and with decision-makers, a hierarchical classification scheme for the research was developed.

Developing a well-defined and accepted framework for producing and using evidence has been extended from drug licensing at the national level to the inclusion of drugs on provincial drug benefit formularies. In this context, evidence is not limited to safety and efficacy, but also measures relative efficacy, cost-effectiveness, and budget impact. Provincial governments have structures that allow decision-makers to obtain evidenced-based expert advice to determine which drugs to list on their formularies, as well as conditions of coverage.¹⁻³

Randomized controlled trials and cost-effectiveness analyses are not the only types of research relevant to appropriate prescription drug funding policy. Research that applies sophisticated methods drawn from epidemiology to study the impact of drugs in non-experimental or observational settings has grown.⁴ Pharmacoepidemiology, and its application to the study of outcomes in the real world, rather than experimental settings, is referred to as post-market surveillance or pharmacosurveillance. Research methods are well accepted, and pharmacosurveillance studies have provided compelling evidence on the use and effects of prescription drugs in the real world.⁵⁻¹²

A logical extension of the role of evidence in drug policy decision-making is a move from the present pre-market analysis of safety, efficacy and cost-effectiveness toward a more systematic approach to production and application of pharmacosurveillance evidence. Federal and provincial governments in the First Ministers' Meeting Communiqué recognized the importance of pharmacosurveillance as part of a comprehensive approach to pharmaceutical management on health in September 2000.¹³ Stakeholder

input from across Canada resulted in the June 2001 report *Listening for Direction: A National Consultation on Health Services and Policy Issues*. The report identified health care evaluation, and particularly evaluation of new drugs, as a primary research theme;¹⁴ a theme that has since been echoed in reports by Michael Kirby¹⁵ and Roy Romanow.¹⁶

A successful pharmacosurveillance system requires the application of sound and systematic scientific methods to provide evidence on outcomes associated with drugs after licensing, and a process to link evidence to drug management policy. Although systems exist for passive collection and reporting of adverse drug events, and independent research groups examine drug safety and effectiveness issues, a well-developed model for systematic collection of pharmacosurveillance data and linkage of evidence to drug policy does not exist. Such a model would provide an area for federal and provincial governments to work together to develop standards and to share information.

Background

Use of pharmacosurveillance evidence by provincial drug plans in Canada

Canadian studies of prescription drug utilization began in the late 1970s and early 1980s, with development of provincial population-based health care administrative databases.¹⁷⁻¹⁹ Since then, the data and analytical methods have grown in sophistication, but relationships between researchers and provincial drug plans have remained underdeveloped.

Provincial drug plans have acted largely as insurance agencies: essentially reimbursing pharmacies for certain prescription drugs for eligible individuals, most commonly people over the age of 65. Traditionally, plan managers have made use of drug insurance claims to monitor program activities, such as drug utilization and cost, through in-house health ministry data analysts. This has allowed them to determine cost, by individual drug and drug category, and to estimate the potential budget impact of new drugs being considered for formulary inclusion.

Cost control options include removing old drugs from the formulary, tightening existing listing criteria, or refusing to fund newer, more expensive therapies that lack good evidence of superior cost-effectiveness. British Columbia has had recent success with restrictive drug funding policies. Although limited to certain classes of drugs, evidence to date suggests the province's drug management programs have successfully limited growth of provincial spending on prescription drugs without compromising patient health.^{3,20} Establishing and defending these policies has strengthened relationships between BC drug plan managers and the university-based researchers participating in this project, and laid a foundation for incorporating research-based information into drug policy decision-making. As a policy option, refusing to fund new, more expensive drugs has had variable application across Canada.²¹

More common approaches to drug plan management have been efforts to restrict medications to patients considered most appropriate on the basis of clinical or cost-effectiveness criteria.²² These "special authority", "prior authorization", or "limited use" criteria have generally required physicians to seek plan approval for coverage, and advocate patients with specific needs. As a result, plan managers are interested in determining whether patients reimbursed under such mechanisms actually meet criteria for coverage; whether limiting funding to only these patients, and not others, results in harm; and whether those covered achieve benefits predicted from pre-market trials. These analyses have typically been beyond the mandate or capacity of government administrations.

Academic researchers in several provinces have conducted studies of the impact of provincial drug plan policies on drug utilization and population health. Studies of reference-based pricing policies in BC, for example, measured population health parameters and outcomes associated with the reference pricing of ACE (angiotensin converting enzyme) inhibitors^{23,24} and nitrate drugs.²⁵ Marshall et al. studied the effect of BC's reference pricing for histamine-2 receptor antagonists and restricted access to proton pump inhibitors on drug utilization and costs.²⁶ Tamblin and colleagues assessed the impact of a new cost-sharing policy on the use of drugs and health services in Quebec.²⁷ In all instances, the research was published years after the policies were implemented.

Types and production of pharmacosurveillance evidence

Traditionally, Canadian pharmacoepidemiological research has relied on rich health administrative data in BC, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia.²⁸ These provinces have a set of 4 core health administrative databases (Exhibit 1):

1. A registered persons database that provides basic demographic information about those eligible for provincial health insurance coverage;
2. A provincial drug insurance claims database that stores information about each outpatient prescription dispensed and financed by the province, including the chemical entity, date and quantity dispensed, and cost;
3. A medical service claims database that provides fee-for-service billing data for ambulatory and hospital-based care; and,
4. A hospital discharge abstract database that stores more detailed information collected by the Canadian Institute for Health Information (CIHI) about each episode of hospital-based care.

These databases are linkable at the patient and physician level via unique encrypted identifiers. The provincial drug plan databases have been particularly well characterized and found to be complete and accurate.²⁹⁻³¹ BC and Manitoba also have databases that store information about outpatient prescriptions financed through private insurance or paid by patients.

Exhibit 2a provides an overview of pharmacosurveillance research designs possible using health administrative data. Exhibit 2b gives examples of specific research questions that could be asked of such designs, using selective cyclooxygenase-2 inhibitors (coxibs) as the study subject.

Studying use of evidence in public health policy decision-making

Evaluative research on decision-making processes in general, and in particular on the use of evidence in decision-making, is complex. One approach, taken by Singer and colleagues,⁴¹⁻⁴⁴ used qualitative methods and grounded theory to describe how hospitals and government programs set priorities for coverage of new drugs and technologies, and evaluated those processes using a conceptual framework for priority setting in health care—Daniels' and Sabin's "accountability for reasonableness". This framework argues that, in the absence of consensus on the principles that should govern priority setting, an overarching goal should be a fair decision-making process defined by:

- Transparency about the grounds for decisions;
- Appeals to rationales that all can accept as relevant to the decision-making context;
- Procedures for revising decisions in light of challenges to them; and,
- A voluntary or regulatory mechanism to ensure that these conditions are met.⁴⁵

Applying the framework to several Ontario settings taught Singer et al. several lessons:

- Elements of the framework are familiar and acceptable to Ontario decision-makers;
- Refinements are possible (in fact preferable) in some settings; and,
- The framework can be useful to promote fairer decisions.

Findings relevant to Ontario hospital⁴³ and provincial⁴⁴ formulary decision-making include:

- A general lack of clarity about overarching goals;
- Lack of patient or community representation;
- Poor access to reasons for decisions; and,
- Lack of clarity about and mechanisms to ensure accountability for decisions.

A second approach used to evaluate health policy decision-making builds upon the work of Knott and

Wildawsky⁴⁶ and Landry et al.⁴⁷ This work describes the utilization of evidence in decision-making as a series of sequential stages—transmission, cognition, reference, effort, influence, and application. Since these stages are sequential, they can be used to define a scale: the higher the stage reached, the greater the impact of evidence on decision-making. More recently, Lavis,⁴⁸ Hanney⁴⁹ and colleagues focused on identifying conditions under which research is, and is not, used to inform health policy. Key considerations are clear accounts of the context for decisions, and methods for characterizing and measuring the ways in which research (and other factors) can influence decision-making.

Together, these perspectives informed the evaluation strategy for this study.

Findings

Baseline interviews with plan executives and advisors

Information use and needs

In response to questions about information used by drug plans before and after coverage decisions, 4 themes emerged:

- All provincial/territorial drug plans use clinical and economic evidence (based largely on Phase 3 randomized controlled trials) before listing;
- Most provincial/territorial drug plans conduct at least some post-market monitoring, but this is limited mainly to budget impact, rarely safety issues, and virtually never health outcome;
- Few studies have evaluated health outcomes associated with specific formulary policies, for example, reference pricing in BC and cost-sharing in Quebec; and,
- Lack of resources and expertise are common reasons for not doing more.

These findings are largely consistent with those of West et al. who surveyed 5 provincial drug plans (BC, Alberta, Ontario, Quebec and New Brunswick) in 2000. In their work, 3 provinces reported that systematic follow-up to evaluate the impact (economic, outcome) of listing decisions was done 40–70% of the time, while 2 provinces reported that it was rarely done (< 40%). Two plans reported that drug utilization review to evaluate the quality of drug use was done 40–70% of the time, 1 reported rarely (< 40%), and 2 responded “never”. When staff were asked whether drugs were ever listed with the understanding that a cost-effectiveness study would be done after its use was established, 2 stated “rarely” and 3 stated “no”. All provinces reported removing drugs from the formulary and switching drugs to restricted status in the past 5 years. Further, the survey respondents confirmed that collaboration among provinces was minimal, and that the decisions of other plans had little or no impact on their own.

Drugs groups of interest

Five drug groups were consistently cited as important from the perspectives of population health impact or plan cost.

1. Coxibs: celecoxib (Celebrex[®]), rofecoxib (Vioxx[®]), valdecoxib (Bextra[®]), meloxicam (Mobicox[®]);
2. Atypical neuroleptics: olanzapine (Zyprexa[®]), risperidone (Risperdal[®]), quetiapine (Seroquel[®]);
3. Cytokine inhibitors: infliximab (Remicade[®]), etanercept (Enbrel[®]), anakinra (Kineret[®]);
4. Statins: and,
5. Proton pump inhibitors (PPIs).

Reasons given by provincial drug plan executives for the level of interest in these products are as follows.

Provincial drug plan executive on **coxibs**:

“Fifty percent of the prescriptions are COX-2s. So seniors are paying a whack of money for the COX-2s. It didn’t affect us. But seniors are certainly getting hit with it, which doesn’t make us happy. But you know what? It was one of those categories that was out of control before you could do anything about it.”

Three plan executives on **atypical neuroleptics**:

“We are concerned about olanzapine because it’s being used for everything.”
“The problem with these drugs: we’ve totally lost control.”
“Basically, once it came on the market, its use exploded.”

Plan executive on **cytokine inhibitors**:

“The only problem is that once you put a drug on the list, it’s hard to go back and make changes that tighten things up... But, I think we’re into an era exemplified by the biologics. So that, because of cost and safety concerns of these drugs, in the future it’s going to be required that we enter into some form of follow-up monitoring and evaluation of these drugs, to try to understand... Have they performed as the clinical studies said they should? What’s happened with costs, utilization, appropriateness, and so on?”

Interprovincial drug utilization (Level I) studies

NSAIDs and coxibs

Celecoxib, rofecoxib, and meloxicam were approved by Health Canada's Therapeutics Products Directorate (TPD) in April 1999, October 1999 and October 2000 respectively. For coxibs to be paid by the BC Ministry of Health Services (BCMOHS), physicians must complete a Special Authority (SA) request, describing why their patients require a coxib, and these must be approved by the BCMOHS prior to reimbursement (for details, see Exhibit 3). Celecoxib and rofecoxib were listed on the BC formulary in October 2000, followed by meloxicam in April 2001. In Ontario, celecoxib and rofecoxib were granted Limited Use (LU) status in April 2000, which means that they are reimbursed if physicians indicate on a special prescription pad that their patients had a previously documented peptic ulcer or gastrointestinal bleed, or had failed 3 conventional NSAIDs (Exhibit 3). Meloxicam was granted General Benefit status (reimbursed and available without restriction) in March 2001.

Throughout the study period, there was a small but steady decrease in the number of NSAID prescriptions reimbursed by the BCMOHS (Exhibit 5). In Ontario, the number of NSAID prescriptions per senior was considerably higher than in BC even before the coverage of coxibs, and this more than doubled (from 0.10 to 0.24) between the first quarter of 2000 and the third quarter of 2002, after coxibs were covered on a limited basis. The cost of NSAID prescriptions reimbursed by the BCMOHS increased only slightly between the first quarter of 2000 and the third quarter of 2002 (from \$1.43 to \$1.50 per senior), while the cost reimbursed by the Ontario Ministry of Health and Long-Term Care (OMOHLTC) more than doubled (from \$4.52 to \$10.95 per senior; Exhibit 6). In BC, the number of NSAID prescriptions paid by non-provincial drug plans and patients increased considerably after the TPD approval of celecoxib and rofecoxib, and by the end of the study, exceeded that reimbursed by the BCMOHS (Exhibit 5). However, the total number of prescriptions paid by the BCMOHS, other drug plans, and patients themselves, was still only half the number paid by the OMOHLTC. Data for prescriptions paid by private insurers and patients were not available for Ontario.

Neuroleptics

Typical neuroleptics such as haloperidol and chlorpromazine have been available for many years. Risperidone, the first atypical neuroleptic, received TPD approval in April 1993, followed by olanzapine (October 1996) and quetiapine (December 1997). In Ontario, risperidone was approved as a General Benefit in 1994, olanzapine in August 1997 and quetiapine in December 1998. In BC, access to atypical neuroleptics was restricted to SA until risperidone was granted General Benefit status in August 1999, followed by quetiapine in November 2000. Not surprisingly, the per senior OMOHLTC reimbursement for neuroleptics was considerably higher than reimbursement by the BCMOHS, especially after the TPD approved risperidone for the treatment of behavioural and psychological symptoms of dementia, in the second quarter of 2000 (Exhibit 7). However, even after risperidone and quetiapine became General Benefits in BC, the utilization and costs of neuroleptics remained relatively lower in BC.

Cytokine inhibitors

Tumor necrosis factor (TNF)- α is a pro-inflammatory cytokine thought to have a role in such disorders as rheumatoid arthritis (RA) and Crohn's Disease (CD). Recently, several TNF- α antibody therapies (cytokine inhibitors) have emerged that show promise in patients with severe RA and CD unresponsive to traditional therapies, but these agents are expensive (\$1,000–\$5,000 per month) and risky in terms of

safety and effectiveness. Since their introduction, the currently licensed cytokine inhibitors, etanercept (Enbrel[®], approved December 2000), infliximab (Remicade[®], approved June 2001), and anakinra (Kineret[®], approved November 2002) have been available to Ontarians only through the Individual Clinical Review (Section 8) mechanism (Exhibit 3), and financed through 1 of 3 drug programs depending on the patient's age, health status, and income (Exhibit 4). Cytokine inhibitors have been similarly financed in BC, but are available through the relatively less restrictive SA process.

Data on etanercept and infliximab prescriptions are presented in Exhibit 8. (Anakinra prescriptions were excluded due to small numbers.) The exhibit suggests relatively higher utilization of both agents and a greater rate of growth for etanercept in BC. However, behind these data are several important considerations. Though limited, the available information suggests that pre-notice of compliance and pre-formulary use of these products (through Health Canada's Special Access Program and manufacturer-sponsored programs) may have differed in the 2 provinces.

1. Since 50% of patients cannot tolerate or are unresponsive to cytokine inhibitor therapy, if a greater proportion of Ontario residents had access to these products before listing, this would selectively reduce the pool of Ontarians eligible for therapy after provincial coverage.
2. Because infliximab is given intravenously and is typically prepared and administered in hospital, before the OMOHLTC formally announced coverage, an unknown number of early infliximab prescriptions were financed through hospital global budgets. Whether this occurred in BC is not known.
3. Until September 2003, Ontario pharmacies could submit prescription claims for infliximab using a generic, rather than product-specific, identifier. As noted in the exhibit, these prescriptions are lost to analysis.
4. The size, timing, and mechanics for processing non-senior drug benefit deductibles differ in the 2 provinces (Exhibit 4), which could lead to differential loss to the analysis of some prescriptions, and would definitely contribute to cost variance between the 2 provincial drug plans.
5. An unknown number of non-seniors receive cytokine inhibitors financed through private insurance.

Statins

Over the last decade, statins have been among the fastest growing and costliest medications for provincial drug plans in Canada. Unlike the other products analyzed, statins had General Benefit status in both provinces throughout the course of study. Lovastatin (Mevacor[®]), the first to receive regulatory approval, was licensed June 1988. Since then, 7 agents joined the class, 4 with generic formulations. Despite identical reimbursement status, statin use in Ontario has been consistently higher than in BC (nearly twice as high in 1997) and remained that way over the subsequent 5 years (Exhibit 9). By the third quarter of 2002, prescription rates per 100 seniors were 32.4 in Ontario versus 19.2 in BC. This translated to per senior costs of \$38.18 and \$26.87, respectively.

Proton pump inhibitors

Proton pump inhibitors (PPIs) are extremely effective, but their widespread and growing use means huge costs to public and private drug plans. The Ontario Drug Benefit (ODB) program, for example, spent over \$110 million (roughly 5% of its budget) on PPIs in 2002. These costs have continued to grow at annual rates of 15–20%, despite efforts to channel PPIs to those for whom the drugs represent good value. Omeprazole (Losec[®]), the first PPI to market, received TPD approval in 1989, and was immediately listed on the ODB formulary as a Non-Formulary Benefit. This coverage option no longer exists. When it did, such products were accessed through a process similar to BC's current SA mechanism (Exhibit 3). Subsequent PPIs were similarly listed in August 1996 (lansoprazole) and August 1997 (pantoprazole). In December 1998, the entire drug class was reclassified as LU, until July 2002, when rabeprazole (Pariet[®]) was listed at close to half the cost of its competitors and became the only PPI with General Benefit status.

The timing of PPI formulary listings was similar in BC: the SA process for omeprazole was introduced in October 1995, and was later extended to lansoprazole and pantoprazole. The main difference between

Ontario and BC policy relates to rabeprazole, added to the BC formulary in July 2003, a year later than Ontario. Rather than list rabeprazole as a General Benefit, BC PharmaCare required patients new to PPI therapy to start with rabeprazole. Under the policy, SA approvals for prior PPI therapy remained valid until expiration or January 14, 2004 (whichever came first), after which SA for rabeprazole was automatic, and patients who chose to remain with a different PPI assumed responsibility for the full cost.

Before the introduction of Ontario's LU policy, utilization of PPIs in Ontario was 50–100% higher than in BC (e.g. 3.3 versus 2.0 prescriptions per 100 seniors in December 1998) and exhibited roughly similar rates of growth (Exhibit 10). Once the LU policy was implemented, utilization in Ontario fell sharply, such that, for several months, the rate of PPI use in BC exceeded that in Ontario. From that point forward, utilization growth accelerated in Ontario. Between January 1999 and July 2003, PPI use grew in Ontario by 0.14 prescriptions per 100 seniors per month compared to 0.04 in BC, representing a 4-fold greater growth rate in Ontario. In combination with BC's income-based deductibles (introduced April 2003), these PPI use rates translated to July 2003 plan costs of \$8.85 per senior in Ontario versus \$2.80 in BC (Exhibit 11).

This study underlines the potential challenges of interpreting even Level I interprovincial analyses, particularly when carried out in sub-populations that have uneven drug benefits coverage across provinces.

Closing interviews with provincial drug plan executives in Ontario and BC

Exhibits 12a and 12b summarize feedback from the drug plans regarding the impact of our research on decision-making. Together with supplementary comments, the responses led to 3 main conclusions.

1. The questions of greatest interest to plan managers cannot be answered by analyses of simple, even interprovincial, drug claims data. More sophisticated methods and linkage of multiple provincial health administrative databases are required.
2. The impact of the research was greatest when it was: a) designed to inform or evaluate a specific decision or policy; b) available at the time of decision-making; and, c) presented in a manner that made application easy. Studies with the greatest impact were those linking drug utilization with patients' characteristics or treatment, such as is required to determine the proportion of patients meeting potential criteria for coverage.
3. The perceived value of certain pharmacosurveillance evidence varies according to the roles and responsibilities of the decision-maker.

12 Lessons on Pharmacosurveillance Evidence for Formulary Decision-Making

1. Plan input

It is possible for teams of researchers in 2 provinces to work closely with their respective drug plan managers, to agree on priority areas, and to undertake research with common methods. However, getting plan input can be challenging.

Regular meetings between researchers and plan staff, such as exist in BC, can improve the use of pharmacosurveillance evidence. Similar meetings are now occurring in Ontario.

2. Sharing of methods and data

Interprovincial research, in which ideas and methods are shared, rather than data, can build local research capacity and improve efficiency. Data transfer raises privacy and logistical issues. Local researchers have established relationships with drug plan staff, better access to provincial administrative data, and know their data best. The model developed here, in which data were cut and analyzed at the local level, is preferred to interprovincial studies in which datasets are cut locally and analyzed centrally.

3. Impact of evidence

The impact of pharmacosurveillance evidence is greatest when it is designed to inform/evaluate a specific decision or policy, available at the time of decision-making, and easy to apply.

Having decision-makers involved in the generation of such evidence, from conception to write-up, will optimize its impact.^{53,54}

4. Research impact

Although the scale used to assess the impact of our research was more objective than some,⁴⁹ there were situations in which managers from the same drug plan arrived at different conclusions about the policy impact of a given study. Thus, as in other settings, the roles and responsibilities of drug plan decision-makers can influence their perception of the importance of research in policy-making.⁵⁴

5. Value of Level I studies

Feedback from drug plan managers suggests that, depending on a plan's perspective, simple interprovincial drug use studies (Level I) can be of some value when defending more restrictive policies or considering a more or less restrictive approach. In general, however, such analyses tend to raise more questions than are answered, such as:

- Who is being treated?
- What are the outcomes?
- What factors, other than drug plan policy, could contribute to different patterns of drug use?

For example, the marked interprovincial difference in the use of statins is surprising, given that they are covered without restriction in both provinces. A similar tendency to prescribe less medication in BC was noted after risperidone and quetiapine were made General Benefits in BC.

Potential reasons for lower rates of drug use in BC include:

- Greater overall skepticism about the effectiveness of drugs among patients and/or physicians;
- More concern about adverse effects of drugs among patients and/or physicians;
- Greater interest in alternative or complementary medicine;

- A healthier population, which may naturally require less medication; and,
- Differences in marketing strategies or less aggressive marketing by drug manufacturers.

A Statistics Canada Survey of pharmaceutical manufacturers suggests that Ontario had more than 3 times as many non-manufacturing (sales/marketing, administration) employees per capita compared to BC at the time coxibs were released.⁵⁵

The relative importance of these factors is not known, and, given the magnitude of the differences observed, represents an important area for future research.

6. Value of linked health administrative databases

Most of Canada's public drug plans have ready access to, and routinely use, basic drug claims data to assess budget impact. However, these data have limited value in answering questions of greatest interest to plan managers, such as whether patients using a certain drug meet criteria for coverage, or whether its use is producing promised improvements in patient or population health.

Working with local health services researchers and linked administrative databases can add such value.

7. Identifying targets for pharmacoepidemiological research

For various reasons, moving drug products from less to more restrictive formulary status can be challenging.

More work is needed to identify situations in which granting less restrictive drug coverage could be problematic, and how pharmacosurveillance evidence could be used to systematically re-evaluate listings.

8. Efforts to combine provincial drug claims data

The Canadian Institute for Health Information (CIHI) and the Patented Medicines Prices Review Board have embarked on a plan to develop a National Prescription Drug Information Service (NPDUIS).⁵⁶ While the goals of NPDUIS are important, this research has provided important lessons about working with interprovincial drug claims data.

- Provincial drug plans differ in coverage options and cost-sharing policies, and make different decisions about whether and when to fund certain products. The formulary status of products also changes over time. Ensuring that such differences are documented and tracked at the product level across jurisdictions, and that analyses are interpreted with these differences in mind, can be challenging. Studies of non-senior populations are particularly difficult, as benefit recipients typically are not continuously eligible for coverage, and limited data are available with which to estimate program denominators.
- Without the capacity to characterize drug users, prescribers, and outcomes, plan managers may find limited value in NPDUIS.
- Restrictive drug coverage policies can lead to significant costs to private insurers and patients, as demonstrated by this study's coxib analysis, which incorporated BC PharmaNet data. Thus, restricting analyses to public drug plan beneficiaries can undermine the ability to assess the impact of drugs on population health. Understanding such effects is critical.

Where possible, governments and NPDUIS should strive to capture data on all prescriptions at the point of dispensing, not just those financed by public plans.

9. Timeliness of data

Important interprovincial outcome (Level III) studies have not yet been completed. For example, there has been an increase in admissions for upper gastrointestinal hemorrhage since the introduction of coxibs in

Ontario.¹⁰ Although the close temporal relationship between the two events makes it likely they are related, evidence for causality would be greater if the smaller increase in coxib use in BC were similarly associated with a smaller increase in gastrointestinal (GI) hemorrhage.

Further, given the striking differences in statin use between the provinces, it is important to know whether relatively fewer high-risk patients, such as those with known heart disease, are being treated in BC or whether more lower-risk patients are being treated in Ontario.

Information timeliness is critical for effective policy-making, and although these studies are in progress, dedicated resources and mechanisms are needed to ensure rapid access to data in each province, while ensuring privacy, confidentiality, and appropriate use.

10. Primary data collection

Existing health administrative databases can provide useful information, but they cannot answer all of the important questions related to drug use, such as whether:

- Greater pain relief is derived from coxibs;
- Neuroleptics are effectively used to treat behavioural disturbances associated with dementia or improve caregiver quality of life; or,
- Anti-cholinergic side effects of neuroleptics represent a net loss in patients' quality of life.

In these circumstances, judicious use of chart reviews and patient surveys is necessary. In future, clinical registries and electronic medical records also may help fill these information gaps. Presently, no ideal mechanisms exist to fund such studies, which demand timely access to data and experts in health services research. One model, being tested in Australia⁵⁷ and Alberta, Canada⁵⁸ with high-cost biologic therapies, makes primary data collection and evidence of adequate response to treatment a condition for ongoing coverage by the public drug plan. This approach generates data for ongoing safety, effectiveness, and cost-effectiveness assessment, while at the same time ensuring that patients who do not meet pre-specified response criteria are withdrawn from costly treatment. These unique programs demonstrate what can be achieved through stakeholder collaboration.

More work and creativity are needed to develop ways and means to permit such research.

11. Roles and responsibilities of provincial drug plans

Consistent with previous research,^{22,41,43,59} the views expressed by interview participants reflect uncertainty about the roles and responsibilities of provincial drug plans, particularly in the areas of drug safety and effectiveness assessment. This may be partially due to tensions between availability of local data and expertise, and short supply of time and money to conduct such research. Differences in how product risk, benefit, efficiency, and affordability issues are assessed and weighed contribute to variation in the composition of provincial drug benefit formularies.²¹ Evidence from recent decisions made in BC and Ontario, on, for example, coxibs and cholinesterase inhibitors, illustrate the point that individual drug plans can use similar information yet reach different conclusions. The capacity to undertake pharmacosurveillance research and the weight placed on that work are factors that could influence which and how drugs are listed on provincial formularies in future.

The jobs of drug plan managers, advisors, and health services researchers could be made easier if governments identified and published clear, explicit goals and objectives for their drug plans.

12. Feasibility of A Canadian Network of Centres of Excellence in Pharmacosurveillance

While questions remain about the role and feasibility of a Canadian Network of Centres of Excellence in Pharmacosurveillance, will exists among stakeholders to explore the idea and seek broader input. Models exist for cooperative, applied research between regulatory decision-makers and teams of specialists in pharmacoepidemiology. For example, in the US, the Food and Drug Administration's Drug Safety Office now has five years' experience with its Cooperative Agreement Program.⁶⁰ Based on comments made by

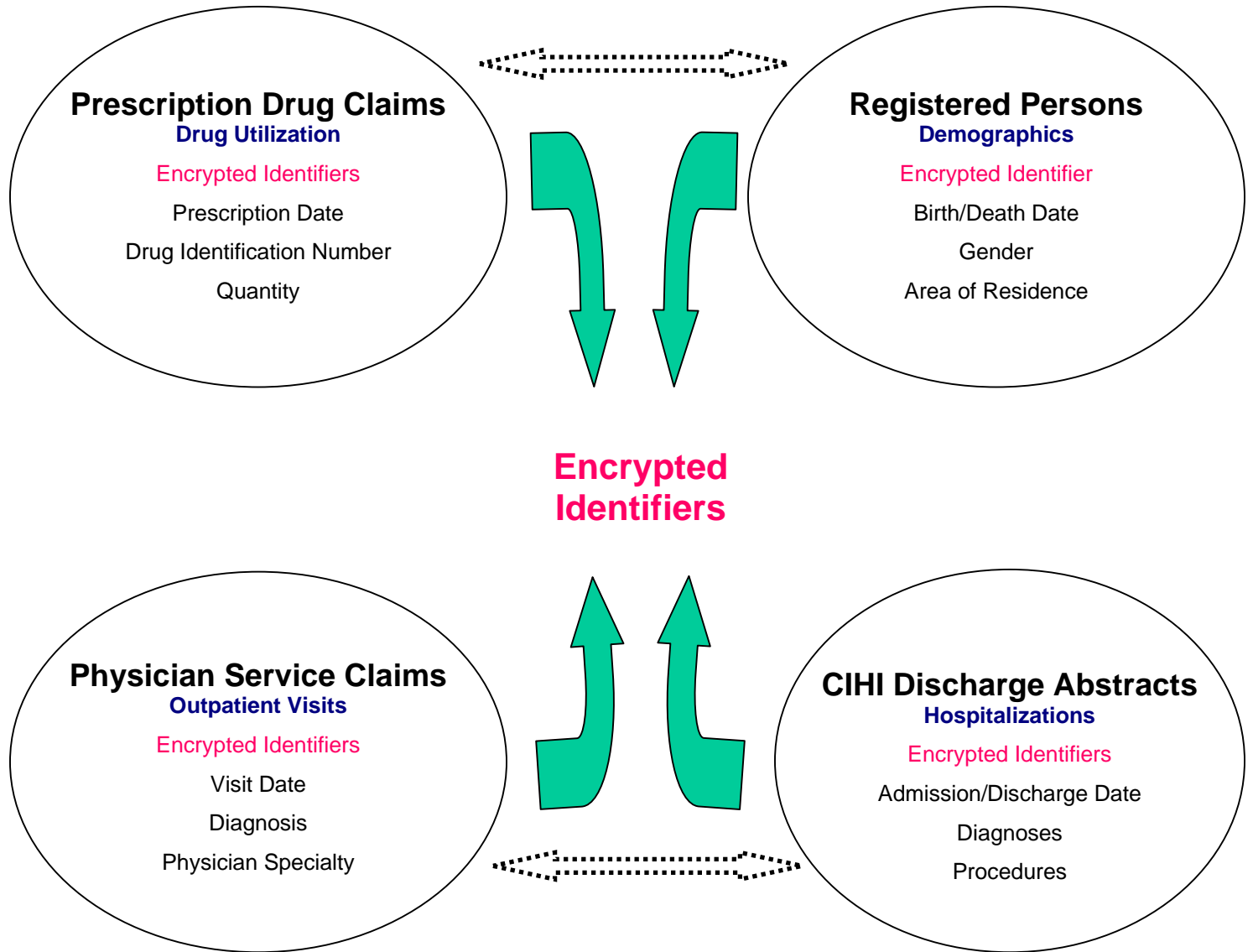
the program's coordinator and network members regarding the quality and usefulness of their research, and the BC-Ontario Pharmacosurveillance for Decision-Making Collaborative's review of studies supported by program agreements, the program is an unqualified success.

Further work is needed to develop an effective and sustainable Canadian model that can be generalized to multiple research settings with access to provincial administrative data.

List of Exhibits

- Exhibit 1.** Core provincial health administrative databases in Canada, 2004
- Exhibit 2a.** Post-market research designs and studies using health administrative data
- Exhibit 2b.** Hypothetical post-market research questions that could be addressed using health administrative data
- Exhibit 3.** Current coverage options on the provincial drug benefit formularies in Ontario and British Columbia, 2004
- Exhibit 4.** Historical provincial drug benefit coverage in British Columbia and Ontario, 1946–2004
- Exhibit 5.** Quarterly oral nonsteroidal anti-inflammatory drug prescriptions per person aged 65 years and older, by province and payer, 1997–2002
- Exhibit 6.** Quarterly cost of oral nonsteroidal anti-inflammatory drugs per person aged 65 years and older, paid by the provincial drug plans in Ontario and British Columbia, 1997–2002
- Exhibit 7.** Quarterly neuroleptic prescriptions per 100 population aged 65 years and older, and cost per person to the provincial drug plans in Ontario and British Columbia, 1997–2002
- Exhibit 8.** Monthly etanercept and infliximab prescriptions per 100,000 population, paid by the provincial drug plans in Ontario and British Columbia, 2001–2002
- Exhibit 9.** Quarterly statin prescriptions per 100 population aged 65 years and older, and cost per person to the provincial drug plans in Ontario and British Columbia, 1997–2002
- Exhibit 10.** Monthly prescriptions for proton pump inhibitors per 100 population aged 65 years and older, paid by the provincial drug plans in Ontario and British Columbia, 1996–2003
- Exhibit 11.** Monthly costs for proton pump inhibitors per person aged 65 years and older, paid by the provincial drug plans in Ontario and British Columbia, 1996–2003
- Exhibit 12a.** Ontario Drug Benefit program decision-makers' assessment of research done for the provincial drug plan, 2001–2003
- Exhibit 12b.** British Columbia PharmaCare decision-makers' assessment of research done for the provincial drug plan, 2001–2004
- Exhibit 13.** Rate of hospital admission for upper gastrointestinal hemorrhage per 10,000 population aged 66 years and older before and after the introduction of coxibs, in Ontario, 1994–2002
- Exhibit 14.** Rates of prescription refill within 1 year of index prescription among NSAID-naïve persons aged 66 years and older initiated on NSAID or coxib therapy, in Ontario, 2000–2002

Exhibit 1. Core provincial health administrative databases in Canada, 2004



Source: BC-Ontario Pharmacosurveillance for Decision-Making Collaborative

Exhibit 2a. Post-market research designs and studies using health administrative data

Post-Market Research Design*		Research Focus and Examples— Questions About the Safety, Effectiveness, Efficiency/Cost- Effectiveness of:		
		Drug or Drug Class	Prescription Practice; Drug Utilization	Drug Coverage Policy
Observational Studies (No control over exposure)	Descriptive Simple time series, single cohort, or ecological studies	<ul style="list-style-type: none"> NSAID/Coxib GI bleed and RALES cross-sectional time series (ecological) studies (Mamdani et al.¹⁰ Juurlink et al.¹¹) 	<ul style="list-style-type: none"> Coxib uptake (Mamdani et al.⁷) Statin uptake and adherence studies (Jackevicius et al.^{5,6}) Statin treatment-risk paradox (Ko et al.³²) Neuroleptic use in LTC [long term care?] (Bronskill et al.³³) 	<ul style="list-style-type: none"> Interprovincial formulary policy studies (Marshall et al.³⁴)
	Comparative Multi-group cohort, case-control, nested case-control, case-crossover, pre-post studies with concurrent or historical controls, quasi-experimental longitudinal designs	<ul style="list-style-type: none"> NSAID/Coxib cohort studies (Mamdani et al. on GI bleeds, acute myocardial infarction, congestive heart failure^{8,9,35}) Nested case-control drug-drug interaction studies (Juurlink et al.¹¹) 		<ul style="list-style-type: none"> Interprovincial formulary policy studies (Marshall et al.³⁴) BC reference pricing studies (Schneeweiss et al.^{23,24} Grootendorst et al.²⁵) Quebec and BC cost-sharing studies (Tamblyn et al.²⁷ Schneeweiss et al.: in progress)
Experiments (Control over exposure)	Crossover, N-of-1	<ul style="list-style-type: none"> Cholinesterase inhibitor (N-of-1) trial (Carleton et al.: in progress) 	<ul style="list-style-type: none"> Multi-province academic detailing initiative (Maclure et al.: in progress) 	
	Real World Randomized Controlled Trials		<ul style="list-style-type: none"> Prescriber feedback studies (Hux et al.,³⁶ Pimlott et al.,³⁷ Doupe et al.³⁸) MOXXI trial (Tamblyn et al.³⁹) 	<ul style="list-style-type: none"> Randomized temporary exemption (nebulizer) trial (Schneeweiss et al.⁴⁰)

*These studies rely upon core population-based health administrative databases, but primary (e.g., survey, audit) and secondary (e.g., registry, electronic medical record) data sources can be used to supplement the administrative data where available and appropriate.

Source: BC-Ontario Pharmacosurveillance for Decision-Making Collaborative

Exhibit 2b. Hypothetical post-market research questions that could be addressed using health administrative data

Study Hierarchy*	Potential Post-Market Research Questions to Address Questions About the Safety, Effectiveness, Efficiency/Cost-Effectiveness of:		
	Drug or Drug Class	Prescription Practice	Drug Coverage Policy
(Level I) Studies using drug claims data only	How many prescriptions were there for coxibs and other NSAIDs in Canada in 2003?	Does coxib prescription vary among small geographic areas in Ontario?	How did the utilization of coxibs and NSAID differ under the different coverage policies in Ontario and BC?
(Level II) Studies using drug claims linked to other data collected prior to drug use	What proportion of coxib prescriptions were for people who had a previous history of rheumatoid arthritis (RA)?	Were specialists more likely than family doctors to prescribe coxibs versus NSAIDs for patients with a prior history of GI bleeds?	Did the Ontario Limited Use (LU) policy succeed in limiting use of coxibs to those who either had a history of GI bleeds or had been tried on other NSAIDs?
(Level III) Studies using drug claims linked to data collected prior to and after drug use	Compared to NSAIDs, are coxibs more or less likely to cause admissions for congestive heart failure or acute myocardial infarction?	Are younger physicians more likely than older physicians to co-prescribe gastroprotective agents with coxibs for patients with RA?	What happened to the overall admission rate for GI bleeds in Ontario (with its LU policy for coxibs) versus in BC (with its more restrictive policy)?

*These studies rely upon core population-based health administrative databases, but primary (e.g., survey, audit) and secondary (e.g., registry, electronic medical record) data sources can be used to supplement the administrative data where available and appropriate.

Source: BC-Ontario Pharmacosurveillance for Decision-Making Collaborative

Exhibit 3. Current coverage options on the provincial drug benefit formularies in Ontario and British Columbia, 2004

Option*	Availability and Example	
	British Columbia	Ontario
<p>No Restriction: General Benefit (GB)</p> <ul style="list-style-type: none"> Products in this category are generally available to all plan beneficiaries through the presentation of a regular, valid prescription. 	✓	✓
<p>Minimal Restriction: Limited Use (LU)**</p> <ul style="list-style-type: none"> Products in this category are available only to beneficiaries who meet pre-specified clinical criteria for coverage. Prescribers must use a specially designed prescription pad, and enter a code corresponding to the appropriate pre-approved indication/criterion for coverage. Approval is valid for 1 year. 	x	✓ <i>Criteria for coxibs:</i> Trial of acetaminophen; plus failure/intolerance to ≥ 3 non-selective NSAIDs or history of documented, clinically significant ulcer or GI bleed
<p>Moderate Restriction: Special Authority (SA)</p> <ul style="list-style-type: none"> Products in this category are available only to beneficiaries who meet pre-specified clinical criteria for coverage. (Note: Some products are available only through specialists; and some specialties are exempt from the SA process for certain products.) Prescribers must complete and fax a structured form that provides information about the patient's medical and medication history, and confirmation that pre-specified criteria have been met. Applications are reviewed by a plan pharmacist (which takes 1–10 days depending on the level of priority) and must be approved prior to dispensation. Approval is valid for various time periods, depending on the product and indication. 	✓ <i>Criteria for coxibs:</i> Trial of acetaminophen; plus failure/intolerance to ≥ 1 of enteric-coated acetylsalicylic acid (ECASA), ibuprofen, or naproxen; plus failure/intolerance to ≥ 3 NSAIDs, including meloxicam	x
<p>Maximal Restriction: Individual Clinical Review (Section 8)</p> <ul style="list-style-type: none"> Products in this category are available only to beneficiaries who meet pre-specified clinical criteria for coverage, although the criteria are not routinely published. For each request, prescribers must write and fax a detailed letter to the Director, Ontario Drug Benefit program. Applications are reviewed by an external consultant (which takes an average of 15 days, 33% over 21 days) and must be approved prior to dispensation. Approval is typically valid for 1 year. 	x	✓

* Province-specific deductible and co-payment policies apply throughout.

** Prior to December 1998, LU-type products were typically classified as Non-Formulary Benefits and were accessed through a process similar to BC's current SA mechanism.

Sources: BC PharmaCare; Ontario Drug Benefit Program

Exhibit 4. Historical provincial drug benefit coverage in British Columbia and Ontario, 1946–2004*

Province	Beneficiary Subgroup	Dates	Deductible (Annual, unless indicated otherwise)	Co-Payment (Applies to total prescription cost, unless otherwise indicated)	Maximum Beneficiary Contribution
BC**	Seniors (aged ≥ 65 years)	Apr 1987–Mar 1994 Apr 1994–Jan 2002 Feb 2002–Apr 2003 May 2003–Jun 2004	None Income-based	75% of dispensing fee 100% of dispensing fee Up to \$25 per prescription (\$10 for those on premium assist) None	\$125 \$200 \$275 Income-based
	Social Assistance Recipients	Circa 1946–Jun 2004	None	None	
	General Population • Lower income [†] • Others	Jan 1991–Mar 1994 Apr 1994–Apr 2003 May 2003–Jun 2004 Apr 1994–Mar 1998 Apr 1998–Apr 2003 May 2003–Jun 2004	Increased from \$325 to \$500 over period \$600 Income-based \$600 \$800 Income-based	20% 30% None 30% 30% None	\$2,000/family \$600/family Income-based \$2,000/family \$2,000/family Income-based
Ontario	Seniors (aged ≥ 65 years) • Lower income [‡] • Others	Aug 1975–Jul 1996 Aug 1996–Jun 2004 Aug 1996–Jun 2004	None None \$100	None \$2/prescription \$6.11/prescription	None None None
	Social Assistance Recipients (Ontario Disability Support Program or Ontario Works)	Sep 1974–Jul 1996 Aug 1996–Jun 2004	None None	None \$2/prescription	None
	General Population (Trillium Drug Program)	Apr 1995–Mar 1996 Apr 1996–Jul 1999 Aug 1999–Jun 2004	Based on family size and income Based on family size and income Same as above, but paid in quarterly instalments	None \$2/prescription \$2/prescription	None None None

* Adapted from Grootendorst 2002⁵⁰

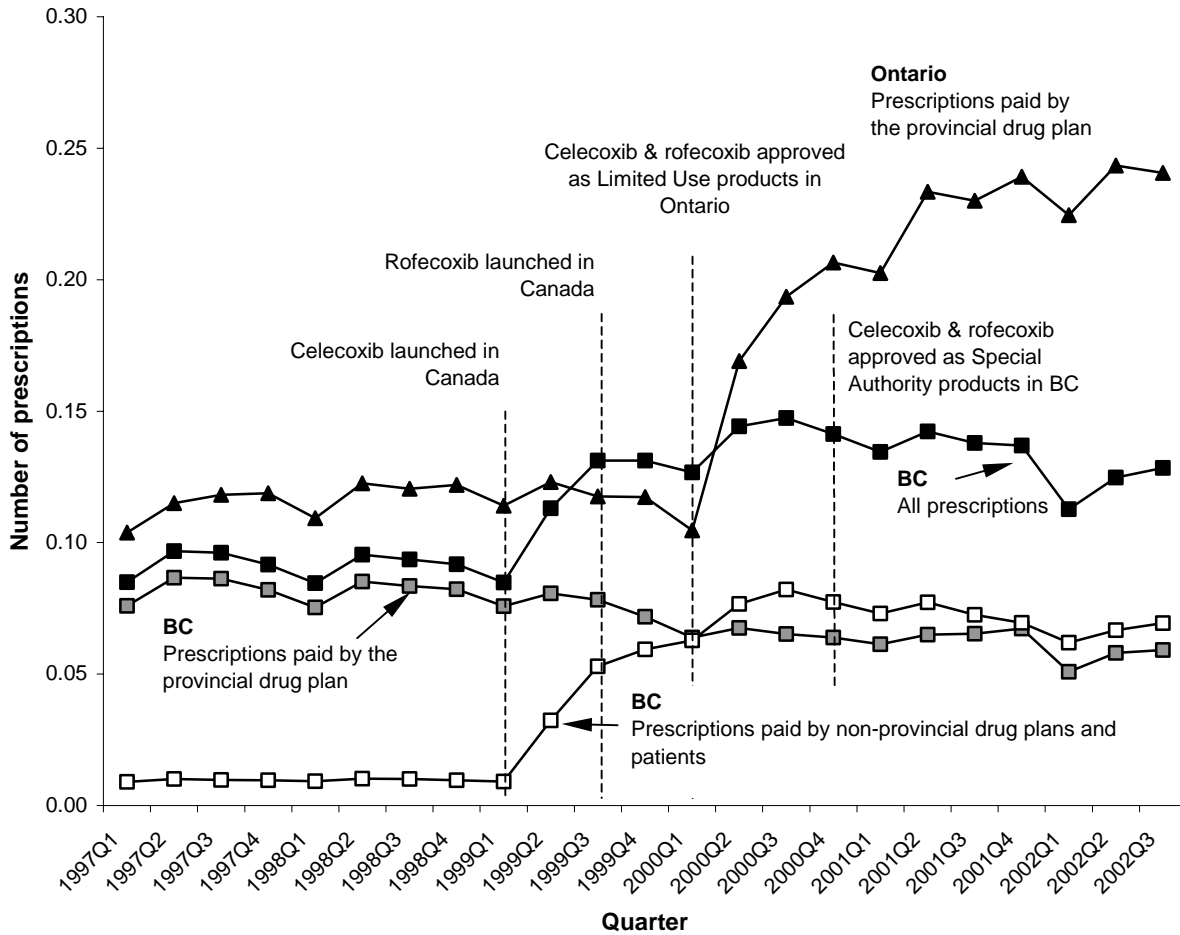
** Reference pricing for histamine-2 receptor antagonists, nitrates, nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, and dihydropyridine calcium channel blockers in effect since 1995.

† Households on Plan E in which at least one member receives a rebate on premiums charged by the Medical Services (health insurance) Plan

‡ Singles with a net annual income < \$16,018, or couples with a net annual income < \$24,175

Source: Adapted from Grootendorst⁵⁰

Exhibit 5. Quarterly oral nonsteroidal anti-inflammatory drug prescriptions per person aged 65 years and older, by province and payer, 1997–2002

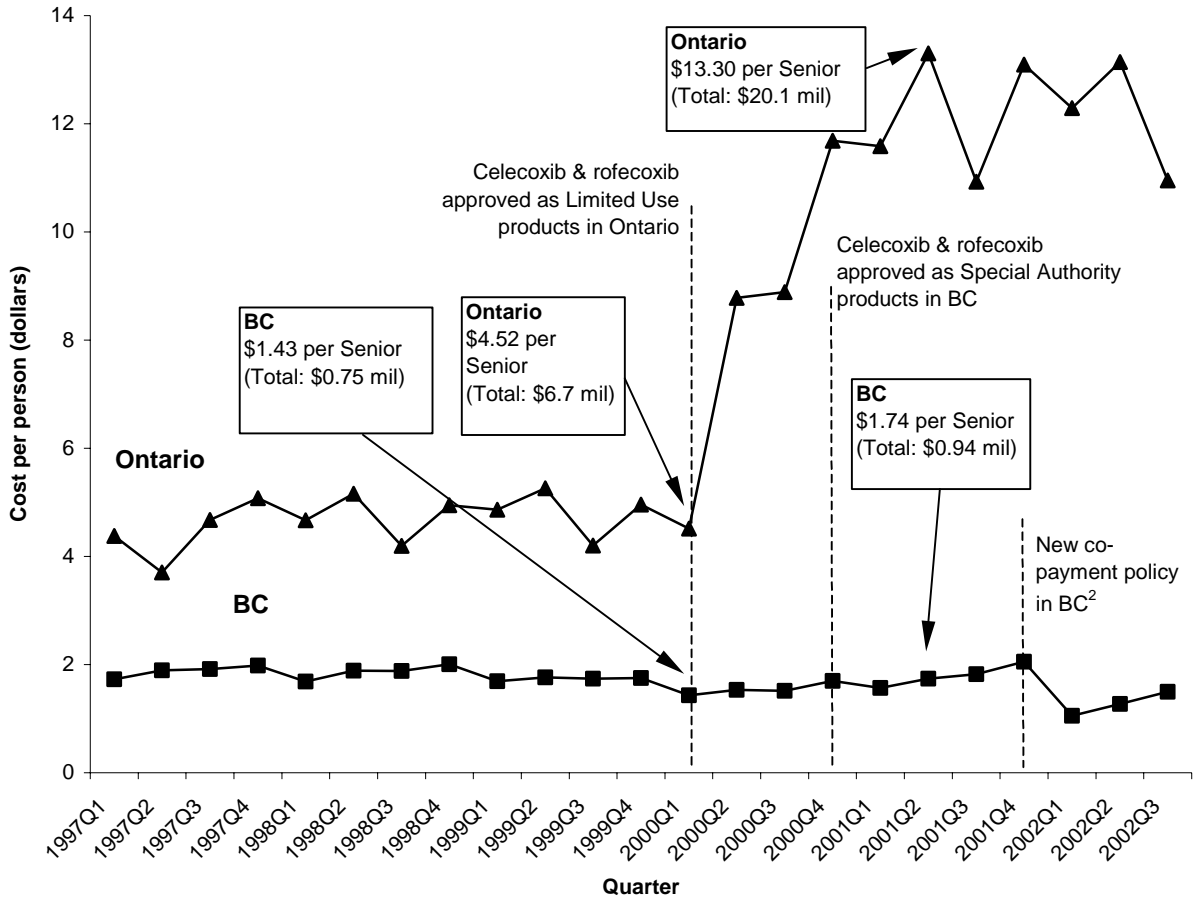


Note:

This analysis includes prescriptions for agents for which PharmaNet data were available at the time of study: celecoxib, diclofenac, diclofenac-misoprostol, etodolac, ibuprofen, meloxicam, nabumetone, naproxen, and rofecoxib. These represent 85% of prescriptions for oral NSAIDs during the study period. All oral NSAID prescriptions were included in the analysis of costs to BC PharmaCare and the Ontario Drug Benefit Plan (Exhibit 6).

Data sources: Ontario Drug Benefit Program; BC PharmaCare; BC PharmaNet

Exhibit 6. Quarterly cost of oral nonsteroidal anti-inflammatory drugs per person aged 65 years and older, paid by the provincial drug plans in Ontario and British Columbia, 1997–2002

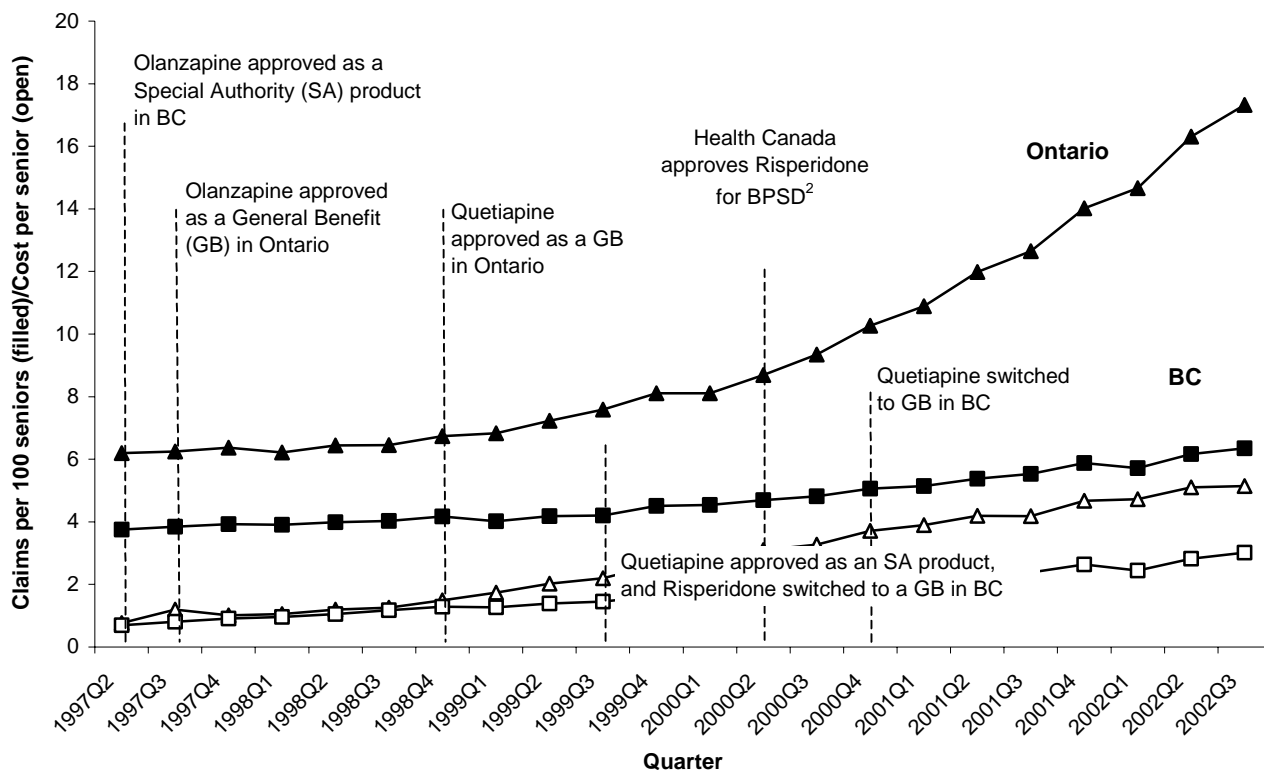


Notes:

1. Reference-based pricing for NSAIDs was in effect in BC throughout the study period.
2. January 2002, the per prescription co-payment was increased in BC from the dispensing fee (and an annual maximum of \$200) to a per prescription maximum of \$25 (and an annual maximum of \$275) (Exhibit 4).

Data sources: Ontario Drug Benefit Program; BC PharmaCare

Exhibit 7. Quarterly neuroleptic prescriptions per 100 population aged 65 years and older, and cost per person to the provincial drug plans in Ontario and British Columbia, 1997–2002

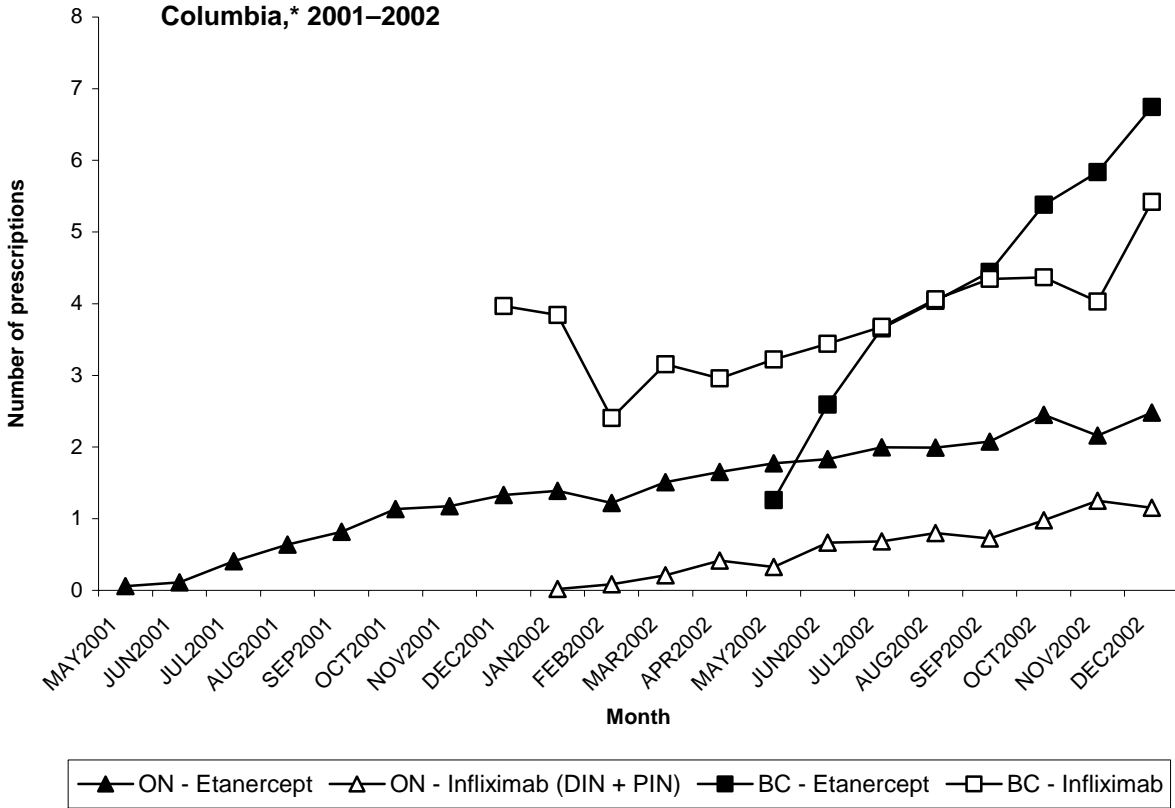


Notes:

1. Risperidone was approved as an SA product in BC and a GB in Ontario in 1994.
2. BPSD = behavioural and psychological symptoms of dementia.

Data sources: Ontario Drug Benefit Program; BC PharmaCare

Exhibit 8. Monthly etanercept and infliximab prescriptions per 100,000 population, paid by the provincial drug plans in Ontario and British Columbia,* 2001–2002



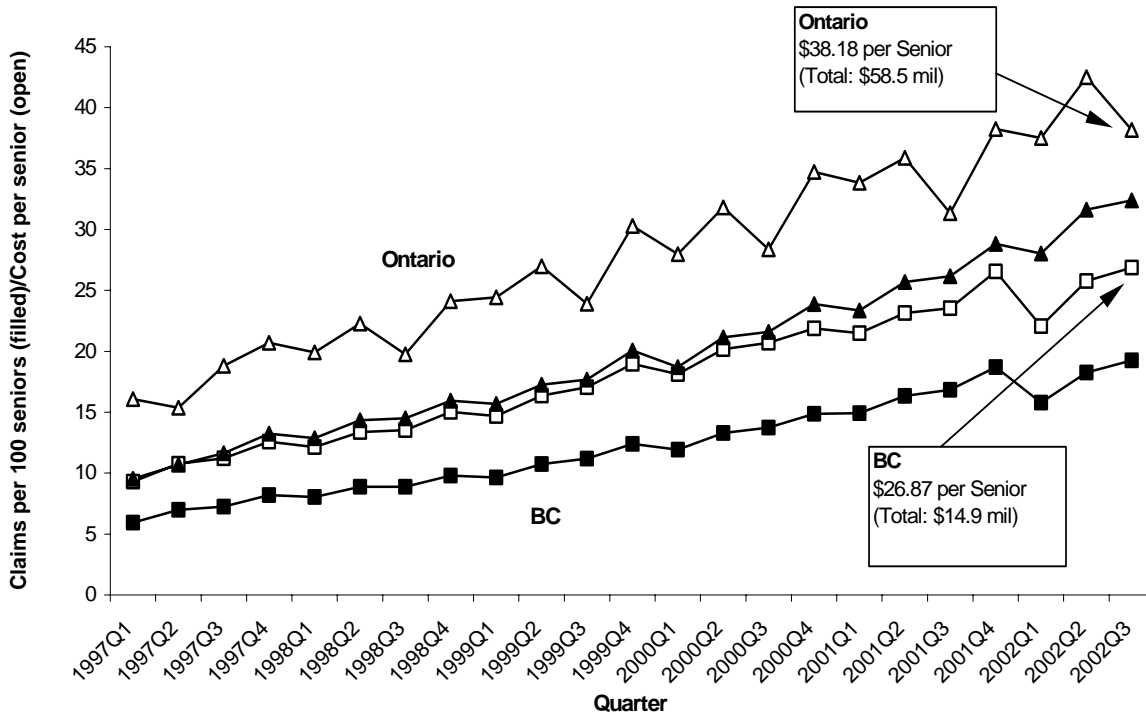
*excluding infliximab billed as an extemporaneous preparation

Notes:

DIN = Drug Identification Number; PIN = Product Information Number
Cytokine inhibitors have Section 8 status in Ontario and SA status in BC.

Data sources: Ontario Drug Benefit Program; BC PharmaCare

Exhibit 9. Quarterly statin prescriptions per 100 population aged 65 years and older, and costs per person to the provincial drug plans in Ontario and British Columbia, 1997–2002

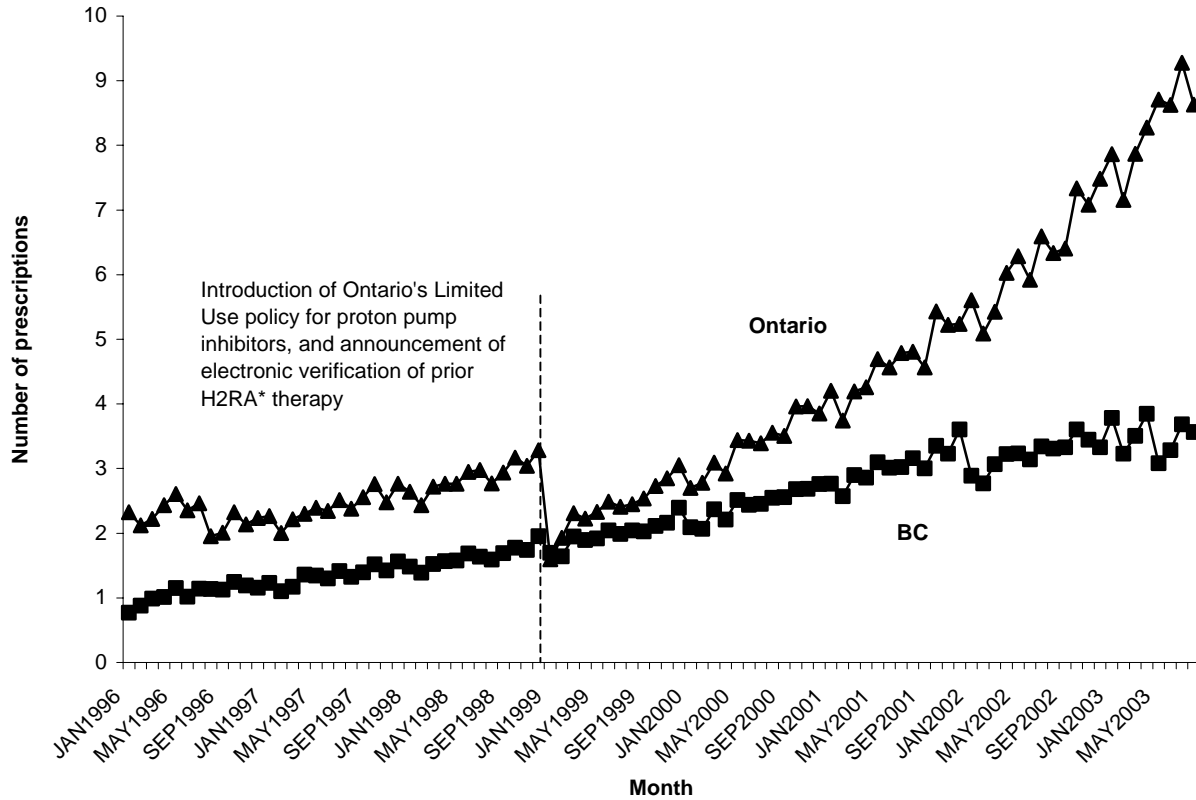


Note:

Statins have General Benefit status in both provinces.

Data sources: Ontario Drug Benefit Program; BC PharmaCare

Exhibit 10. Monthly prescriptions for proton pump inhibitors per 100 population aged 65 years and older, paid by the provincial drug plans in Ontario and British Columbia, 1996–2003



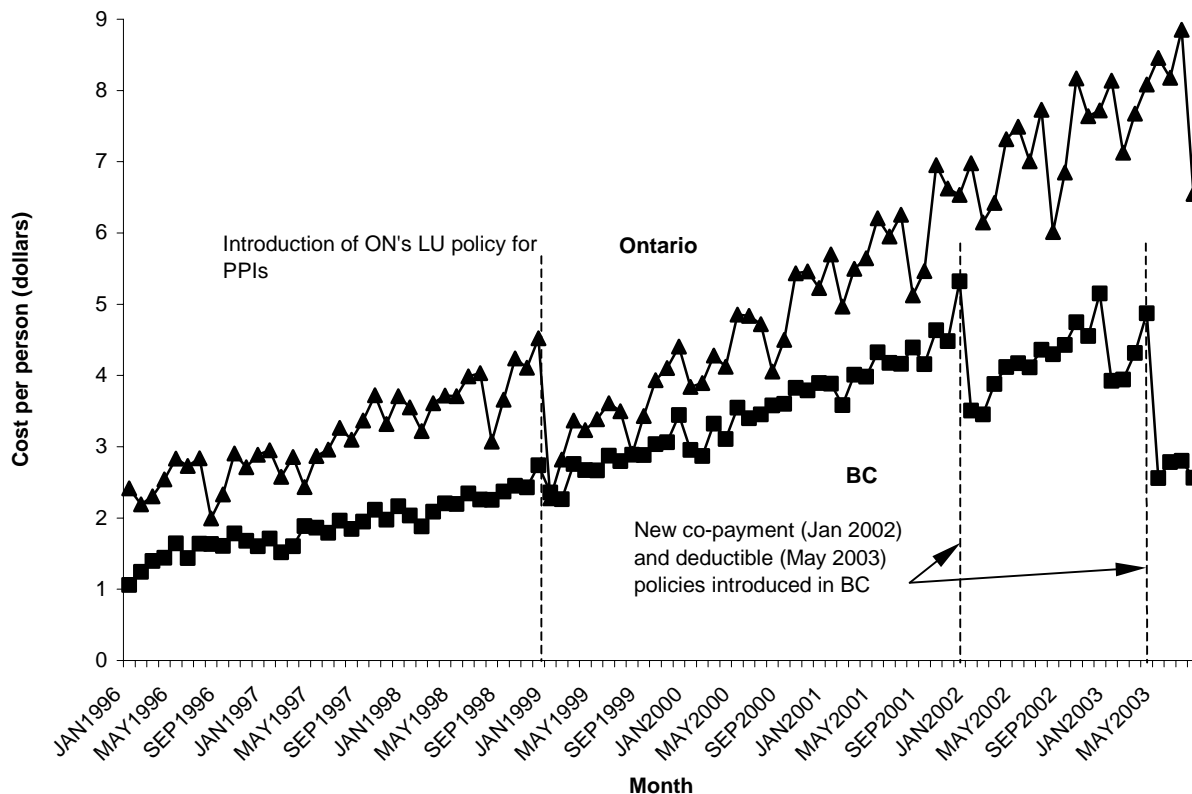
*histamine 2 receptor antagonists

Notes:

1. BC – Special Authority (SA) for proton pump inhibitors (PPIs) introduced October 1995.
2. Ontario – PPIs were a non-formulary benefit (similar to BC's SA) until December 1998, when they were reclassified as Limited Use. Rabeprazole was introduced as a General Benefit in July 2002.

Data sources: Ontario Drug Benefit Program; BC PharmaCare

Exhibit 11. Monthly costs for proton pump inhibitors per person aged 65 years and older, paid by the provincial drug plans in Ontario and British Columbia, 1996-2003



Notes:

BC – Special Authority for proton pump inhibitors (PPIs) introduced in October 1995.

Ontario – PPIs were a non-formulary benefit (similar to BC's Special Authority) until December 1998, when they were reclassified as Limited Use. Rabeprazole was introduced as a General Benefit in July 2002.

Data sources: Ontario Drug Benefit Program; BC PharmaCare

Exhibit 12a. Ontario Drug Benefit program decision-makers' assessment of research done for the plan, 2001–2003

Project Number	Project Title	Date	Design and Objective or Main Message	Ontario Drug Benefit Program Assessment (See page 34 for rating scale.)	
				Subject No. 1 Rating	Subject No. 2 Rating
1	Formulary decision-making (Health Canada) project: Effects of a differential listing for Pariet* on drug plan utilization and costs for upper GI medication in BC and Ontario (suppresses gastric acid secretion)	Oct 2003	<p>Design</p> <p>Monthly time series analysis of Ontario Drug Benefit (ODB) program and BC PharmaCare claims for seniors for Apr 1993–Feb 2004</p> <p>Messages (from Ontario data)</p> <ul style="list-style-type: none"> Between Jan 1999 and Jul 2003, ODB claims and costs for proton pump inhibitors (PPI) grew at rates of roughly 2,200 claims and \$175K per month, respectively. The introduction of Pariet in Ontario led to an estimated \$3.4 million (95% CI: \$2.0–\$4.9 million) savings in total PPI cost for new PPI users for the year ending Aug 2003. BC results to follow. 	NR	3
2	Clopidogrel utilization following a change in listing status (heart attack and stroke prevention)	Jul 2003	<p>Design</p> <p>Research protocol for a retrospective cohort study (to be conducted in 2005)</p> <p>Objectives</p> <ul style="list-style-type: none"> To determine the proportion of patients dispensed clopidogrel that met pre-specified criteria for use. To examine clopidogrel utilization before vs. after a change in formulary listing status (from Section 8 to Limited Use – [LU]). 	1	1
3	Spiriva (tiotropium) evaluation (chronic obstructive pulmonary disease [COPD] treatment)	Jul 2003	<p>Design</p> <p>Research protocol for a retrospective cohort study with repeated measures (to be conducted in 2005)</p> <p>Objective</p> <p>To compare rates of COPD-related hospitalization before vs. during tiotropium therapy.</p>	1	1
4	Conditional coverage of pharmaceuticals on the ODB formulary: guidelines for the evaluation of pharmaceutical outcomes (for the Ontario Drug Strategy Review)	Jun 2003	<p>Design</p> <p>Qualitative review with recommendations</p> <p>Objective</p> <p>To discuss the role of conditional coverage as a listing option in the drug approval process.</p>	2	1

Project Number	Project Title	Date	Design and Objective or Main Message	Ontario Drug Benefit Program Assessment (See page 34 for rating scale.)	
				Subject No. 1 Rating	Subject No. 2 Rating
5	The COX-2 paradox: less (bleeding) is more (anti-inflammatory; cyclooxygenase-2)	Jun 2003	<p>Design</p> <p>Population-based time series analysis of ODB claims and hospitalizations for upper gastrointestinal hemorrhage (UGIH) among Ontario seniors</p> <p>Message</p> <p>A 100% increase in monthly (nonsteroidal anti-inflammatory drug) NSAID utilization upon the release of COX-2 inhibitors was temporally associated with an estimated 15% increase in the rate of hospital admission for UGIH.</p>	2	2
6	Formulary decision-making (Health Canada) project: development and evaluation of a framework for incorporating pharmacosurveillance in provincial formulary decision-making— NSAIDs and neuroleptics	May 2003	<p>Design</p> <p>Quarterly time series analysis of ODB and BC PharmaCare and PharmaNet claims for seniors for 1997Q1–2002Q3</p> <p>Messages</p> <ul style="list-style-type: none"> • Different coverage policies for COX-2 inhibitors and atypical neuroleptics (anti-psychotics) in Ontario and BC have led to markedly different patterns of overall use of and cost to the provincial drug plans. • More restrictive policies shift costs to private insurers and consumers. • Do higher utilization rates translate to superior health outcomes? 	3	1
7	Formulary decision-making (Health Canada) project: drug and health services utilization among users of cytokine system inhibitors (CSIs) (arthritis treatment)	May 2003	<p>Design</p> <p>Monthly time series analysis of ODB and BC PharmaCare claims for Apr 1997–Dec 2002</p> <p>Message</p> <p>Rates of use and growth for Enbrel[®] and Remicade[®] appear greater in BC than in Ontario, although an unknown number of Ontario's Remicade prescriptions are lost to analysis due to billings for extemporaneous preparations.</p>	NR	NR

Project Number	Project Title	Date	Design and Objective or Main Message	Ontario Drug Benefit Program Assessment (See page 34 for rating scale.)	
				Subject No. 1 Rating	Subject No. 2 Rating
8	Potential utilization and acquisition costs of clopidogrel following hospital admission for acute myocardial infarction (AMI), unstable angina or percutaneous coronary interventions	Feb 2003	<p>Design</p> <p>Population-based retrospective cohort study of Ontario seniors, and an economic modeling exercise</p> <p>Message</p> <p>Given the number of seniors potentially eligible for clopidogrel therapy (based on rates of hospitalization for AMI, unstable angina, and percutaneous coronary intervention), the ODB could pay between \$5 million and \$20 million per year depending on the duration of therapy permitted for each approved indication (for LU).</p>	1	1
9	Clopidogrel utilization following stent insertion	Oct 2002	<p>Design</p> <p>Population-based retrospective cohort study of Ontario seniors, Jan 1999–Dec 2001</p> <p>Message</p> <p>Post-stent ODB claims for clopidogrel were infrequent during the study (about 4%), but are growing in prevalence and are expected to exceed 60% by the end of 2003. Related cost projections range from \$350,000 to \$600,000 for 2003.</p>	1	1
10	COX-2 inhibitor studies: outcomes associated with COX-2 inhibitors and non-selective NSAIDs in the ODB population—AMI and UGIH	Aug 2002	<p>Design</p> <p>Population-based retrospective cohort studies of seniors</p> <p>Messages</p> <ul style="list-style-type: none"> • Relative to seniors not exposed to NSAIDs, new users of non-selective NSAIDs, Arthrotec[®], or rofecoxib were at increased short-term risk UGIH, with adjusted rate ratios of 4.0, 3.0, and 1.9, respectively. Users of celecoxib were not at such risk (aRR = 1.0). • A similar study revealed no significant differences in short-term AMI risk for new users of celecoxib, rofecoxib, naproxen, or non-naproxen non-selective NSAIDs. 	1	3

Project Number	Project Title	Date	Design and Objective or Main Message	Ontario Drug Benefit Program Assessment (See page 34 for rating scale.)	
				Subject No. 1 Rating	Subject No. 2 Rating
11	Effect of similar new products on existing pharmaceuticals	Aug 2002	<p>Design</p> <p>Quarterly time series analysis of ODB claims and claimants for 1991Q3–2002Q2</p> <p>Message</p> <p>Based on analyses for 5 categories of drugs: Angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), acid suppressants, cholesterol-lowering agents, neuroleptics, and NSAIDs), uptake of new medicines appears to be a function of at least 5 factors:</p> <ul style="list-style-type: none"> • Order of appearance in class; • Possession or perception of clinical or economic advantage; • Manufacturer promotion; • Opportunity for off-label use; and • Coverage by insurers. 	3	2
12	Cost and prescription patterns associated with ACEIs and ARBs (blood pressure)	Aug 2002	<p>Design</p> <p>Monthly time series analysis of ODB claims for seniors for Apr 1997–Feb 2002</p> <p>Messages</p> <ul style="list-style-type: none"> • Over 1 in 4 seniors were dispensed an ACEI or ARB during the study period. • Although there are trends toward the prescription of higher doses of ACEI, average cost per day for ACEI has remained relatively stable and is significantly lower than that for ARB. • Dosing trends and costs for ACEI and ARB should be monitored closely for changes in prescribing practice. 	1	3

Project Number	Project Title	Date	Design and Objective or Main Message	Ontario Drug Benefit Program Assessment (See page 34 for rating scale.)	
				Subject No. 1 Rating	Subject No. 2 Rating
13	Patterns of nasal steroid use among young children covered by the ODB, April 1997–March 2002	Jul 2002	<p>Design</p> <p>Monthly time series analysis of ODB claims and retrospective cohort study of ODB claimants aged 3–12 years</p> <p>Messages</p> <ul style="list-style-type: none"> Over the study period, the ODB paid about 60,000 claims for nasal steroids at a total cost of about \$1.1 million or \$19 per prescription. Among new users followed for 2 years, 90% had 5 or fewer claims. <p>The findings suggest there is a need for a balanced approach to cost projection, based on a combination of unit cost for most (intermittent) nasal steroid users, and daily cost for the small proportion of patients that requires continuous therapy.</p>	3	NR
14	Using drug claims data to improve prescribing quality: how well do we know the prescriber?	Jun 2002	<p>Design</p> <p>Cross-sectional analysis of ODB claims for Jan 1998–Jan 2002</p> <p>Messages</p> <ul style="list-style-type: none"> An inability to link drug claims to individual prescribers hinders efforts to improve prescribing quality. Over 4 years, 23.1 million drug claims (12%) paid by the ODB were missing prescriber ID. <p>The prevalence of unidentified prescriptions varies substantially according to the characteristics of the medication, patient, dispensary, and drug plan; in some groups reaching as high as 25%.</p>	4	3

Project Number	Project Title	Date	Design and Objective or Main Message	Ontario Drug Benefit Program Assessment (See page 34 for rating scale.)	
				Subject No. 1 Rating	Subject No. 2 Rating
15	Proton pump inhibitor use among the ODB population (Apr 1997–Feb 2002): trends and considerations	Apr 2002	<p>Design</p> <p>Monthly time series analysis of ODB claims for seniors for Apr 1997–Feb 2002, and a modeling exercise</p> <p>Messages from Study</p> <ul style="list-style-type: none"> • Prevalence of use of acid suppression therapy is high (about 16%) and rising, as is the prevalence of twice daily PPI dosing. • Omeprazole is losing market share to cheaper PPIs, but still represents over half of all PPI prescriptions. • Consideration should be given to a reference pricing strategy for PPIs. <p>Message from Modeling Exercise</p> <p>An interactive Budget Impact Analysis demonstrates varying levels of cost savings and/or expenses depending on how key variables are altered.</p>	1	1
16	How have the utilization and costs of newer antiplatelet drugs changed since the introduction of clopidogrel?	Mar 2002	<p>Design</p> <p>Monthly time series analysis of ODB claims and claimants for Jan 1999–Dec 2001</p> <p>Messages</p> <ul style="list-style-type: none"> • Monthly claims for ticlopidine have remained relatively stable since the introduction of clopidogrel, although patients new to ticlopidine represent a small and shrinking fraction of antiplatelet users. • In contrast, claims for clopidogrel grew at a constant rate of about 10% per month. • Reclassifying Aggrenox[®] from Section 8 to LU was associated with a marked increase in its utilization. 	1	NR
17	Adherence with statins in elderly patients with vs. without acute coronary syndromes: use without benefit?	Dec 2001	<p>Design</p> <p>Population-based retrospective cohort study of Ontario seniors with at least 1 statin prescription</p> <p>Messages</p> <ul style="list-style-type: none"> • Patients with and without recent acute coronary syndromes have low (2-year) rates of adherence to statins. • An estimated 50% of all drug plan expenditures on statins (about \$50 million for the cohorts studied) was wasted due to drug discontinuation. 	3	2

Project Number	Project Title	Date	Design and Objective or Main Message	Ontario Drug Benefit Program Assessment (See page 34 for rating scale.)	
				Subject No. 1 Rating	Subject No. 2 Rating
18	COX-2 inhibitor studies: COX-2 inhibitor utilization—a descriptive evaluation	Jul 2001	<p>Design</p> <p>Monthly time series analysis of ODB claims for seniors for Jan 1997–Nov 2000, and a population-based retrospective cohort study</p> <p>Messages</p> <ul style="list-style-type: none"> • The listing of COX-2 inhibitors had an immediate and substantial impact on ODB use and costs for NSAIDs. • COX-2 inhibitor use is not associated with a reduced probability of prescription for gastroprotection. 	2	NR
19	Donepezil utilization and the drug cascade (Alzheimer's disease treatment)	Jul 2001	<p>Design</p> <p>Monthly time series analysis of ODB claims for seniors for Jun 1999–Dec 2000, and a population-based retrospective cohort study</p> <p>Messages</p> <ul style="list-style-type: none"> • Over \$18 million was spent on donepezil during the study period. • Donepezil use was associated with an increased utilization of antipsychotics, antidepressants, and urinary incontinence medication relative to a random sample of non-user controls. 	3	3
<p>Rating scale for assessing research influence on/support for the Ontario Ministry of Health and Long-Term Care Drug Programs Branch (Branch) decision-making or policy</p> <p>1 = The research had considerable influence on a Branch decision or policy in a direct, instrumental way.</p> <p>2 = The research had moderate influence on a Branch decision or policy. It could have been an instrumental impact or by way of enlightenment (i.e., introduction to new concepts, insights, perspectives, etc.)</p> <p>3 = The research had limited influence in terms of instrumental impact or enlightenment, or by playing part in Branch discussion or debate.</p> <p>4 = I see no evidence of the research's influence on a Branch decision or policy, but it did/does help support a previous decision/existing policy.</p> <p>5 = I see no evidence of the research's influence on/support for a Branch decision or policy.</p> <p>NR = Not Reviewed.</p>					

Source: BC-Ontario Pharmacosurveillance for Decision-Making Collaborative

Exhibit 12b. British Columbia PharmaCare decision-makers' assessment of research done for the plan, 2001–2004

Project Number	Project Title	Date	Objective or Main Message	BC PharmaCare Assessment (See page 36 for rating scale.)	
				Subject No. 1 Rating	Subject No. 2 Rating
1	N-of-1 trial	Jan 2004	Objective To propose a way to reach a mutually agreeable solution to channelling Alzheimer's drugs to the appropriate patients	2	2
2	Production and use of evidence of drug effectiveness	Mar 2004	Message Lack of evaluation expertise at drug programs necessitates better methods to link drug programs and researchers across Canada to aid in policy evaluation and measurement of policy impacts	5	5
3	Thiazide trial	May 2004	Objective To rationalize prescribing of antihypertensives in line with the evidence of benefit of diuretics	1	1
4	Proton pump inhibitor (PPI) policy evaluation	Ongoing	Objective Evaluate the impact of the PPI policy instituted Jul 2003	1	2
5	Incentive trial	Ongoing	Objective To test a series of incentives to improve cost-effective prescribing	4	1

Project Number	Project Title	Date	Objective or Main Message	BC PharmaCare Assessment (See page 36 for rating scale.)	
				Subject No. 1 Rating	Subject No. 2 Rating
6	Plan I evaluation—2	Ongoing	<p>Objective</p> <p>To evaluate the impact of the income-tested PharmaCare program</p>	NR	2
7	Impact of differential listing for Pariet* in BC and Ontario	Oct 2003	<p>Messages</p> <p>Between Jan 1999 and Jul 2003, Ontario Drug Benefit program (ODB) claims and costs for PPIs grew at rates of roughly 2,200 claims and \$175,000 per month, respectively.</p> <ul style="list-style-type: none"> • The introduction of Pariet in Ontario led to an estimated \$3.4 million (95% confidence interval (CI): \$2.0–\$4.9 million) savings in total PPI cost for new PPI users for the year ending Aug 2003. • BC results to follow. 	NR	3
8	BC/Ontario pharmacosurveillance regarding NSAIDs	Nov 2003	<p>Messages</p> <ul style="list-style-type: none"> • More restrictive policies shift costs to private insurers and consumers. • Do higher utilization rates translate to superior health outcomes? 	2	3
9	BC/Ontario pharmacosurveillance regarding immunomodulators	Nov 2003	<p>Message</p> <p>Rates of use and growth for Enbrel® and Remicade® appear greater in BC than in Ontario, although an unknown number of Ontario's Remicade prescriptions are lost to analysis</p>	2	3

Project Number	Project Title	Date	Objective or Main Message	BC PharmaCare Assessment (See page 36 for rating scale.)	
				Subject No. 1 Rating	Subject No. 2 Rating
10	Randomized temporary exemption (nebulizer) policy trial	May 2001	<p>Message</p> <p>It is faster, cheaper, and easier to evaluate a policy by using randomized optional temporary exemption than it is to organize rigorous external retrospective evaluations supported by health research grants.</p>	4	3

Scale for assessing research influence on/support for the BC Ministry of Health Services PharmaCare (Branch) decision-making or policy

1 = The research had considerable influence on a Branch decision or policy in a direct, instrumental way.

2 = The research had moderate influence on a Branch decision or policy. It could have been an instrumental impact or by way of enlightenment (i.e., introduction to new concepts, insights, perspectives, etc.).

3 = The research had limited influence in terms of instrumental impact or enlightenment, or by playing part in Branch discussion or debate.

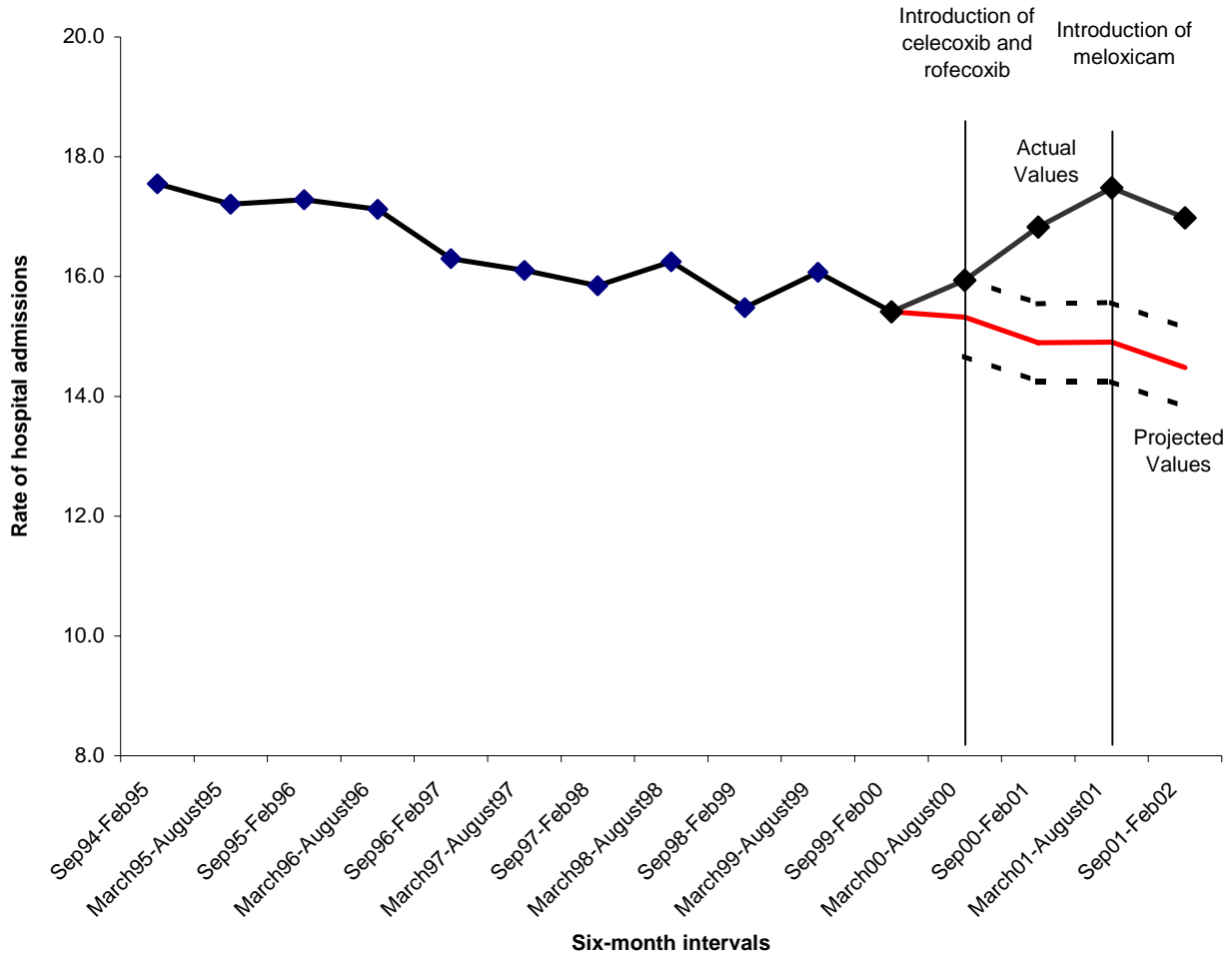
4 = I see no evidence of the research's influence on a Branch decision or policy, but it did/does help support a previous decision/existing policy.

5 = I see no evidence of the research's influence on/support for a Branch decision or policy.

NR = No Rating

Source: BC-Ontario Pharmacosurveillance for Decision-Making Collaborative

Exhibit 13. Rate of hospital admission for upper gastrointestinal hemorrhage per 10,000 population aged 66 years and older, before and after the introduction of coxibs, in Ontario, 1994–2002*



*Mamdani et al. 2004¹⁰

Data source: Canadian Institute for Health Information–Discharge Abstract Database

Exhibit 14. Rates of prescription refill within one year of index prescription among NSAID-naïve persons aged 66 years and older initiated on NSAID or coxib therapy, in Ontario, 2000–2002

Utilization during 1-year follow-up	Initial Drug			
	NSAID	Percent	Coxib	Percent
Total number of patients	34,649		33,167	
Patients according to number of prescriptions				
1	21,247	61.3	16,953	51.1
2	7,081	20.4	7,143	21.5
3	2,927	8.4	3,701	11.2
≥ 4	3,394	9.8	5,370	16.2

Data source: Ontario Drug Benefit Program

Appendix A. How the Research was Done

Analyses

Identifying decision-makers' information needs

Baseline interviews

In the fall and winter of 2002/03, 30 semi-structured interviews were conducted with drug plan executives (19) and advisors (11): British Columbia [BC] (8 executives), Alberta (1 executive), Saskatchewan (1 executive), Manitoba (1 executive), Ontario (5 executives, 7 advisors), Quebec (1 executive, 2 advisors), Nova Scotia (1 executive), Newfoundland (1 advisor), and Yukon Territories (1 executive). The main purpose of the interviews was to collect information about decision-makers' information needs: the types and use of evidence in formulary decision-making, and the drugs or drug categories of greatest concern, due to public health impact, cost, or both. Interviews were recorded, transcribed, coded, and analyzed. Similar concepts were grouped under overarching themes, which were organized according to perceived importance, based on prevalence and the emphasis participants placed on them.

Communication processes

Communication between research team members and drug plan decision-makers differed in the 2 provinces. In BC, Ken Bassett and Jim Wright are active members of 2 of PharmaCare's expert advisory committees, the Therapeutics Initiative and the Drug Benefits Committee,³ and others (Leanne Warren and Greg Carney) spend at least part of their time as data analysts for the BC Ministry of Health Services. These relationships were maintained throughout the course of the project, which meant team members were in close proximity to, and communicating with, drug plan staff on a daily basis.

In contrast, in Ontario, Gary Naglie and Andreas Laupacis are former members of the Ontario Drug Benefit program's (ODB) Drug Quality and Therapeutics Committee^{2,44} and Muhammad Mamdani and Michael Paterson did research for the Ontario Ministry of Health and Long-Term Care Drug Programs Branch during the course of the project. Project-specific communication between the research team and the ODB was infrequent, with the exception of Dr. Mamdani, who met with drug plan staff on an ad hoc basis. Excluding interviews, the team had only 1 face-to-face meeting with senior ODB staff to share findings from the first 3 interprovincial analyses, and to seek direction regarding a further 2.

Drugs of interest

At the outset, the research teams and drug plan directors jointly identified 2 drug categories as suitable candidates for analysis:

1. Celecoxib, rofecoxib, and meloxicam, together known as selective cyclooxygenase-2 inhibitors or coxibs; and,
2. Newer neuroleptic drugs (risperidone, olanzapine, and quetiapine), collectively known as atypical neuroleptics.

These categories were of interest due to high cost, rapid uptake, broad use, and, importantly, were listed differently on the 2 provincial formularies. This provided an opportunity to compare utilization under different coverage policies.

Three additional categories were identified using a similar process over the subsequent 12 months, again based largely on population health impact or cost:

Cytokine inhibitors; proton pump inhibitors (PPIs); and, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins. Among these categories, cytokine inhibitors represented the only case in which both senior and non-senior beneficiaries were studied, and the only case in which coverage was relatively more restrictive in Ontario. Statins were the only group with full coverage or General Benefit status in both provinces.

Exhibit 3 lists the coverage options currently available to the provincial drug plans in BC and Ontario, and gives the clinical criteria for coverage of coxibs as an example of conditions that must be met under the more restrictive options. Exhibit 7 provides a history of provincial drug benefit and cost-sharing policies in the two provinces.

Developing and sharing methods to produce pharmacosurveillance evidence

To streamline communication within and across the project teams and with decision-makers, a hierarchical classification scheme for the research was developed.

- *Level I* studies examine temporal trends in drug utilization, claimants, and costs, and can be used to compare patterns of use across jurisdictions.
- *Level II* studies examine prior medical history and concurrent drug use for individuals exposed to specific drugs. These provide information about appropriateness of use and can be used to test the validity of assumptions made in cost-effectiveness or budget impact analyses.
- *Level III* studies consider outcomes associated with drug exposures, and can be used to test hypotheses about specific drug safety or effectiveness issues.

Exhibit 2b provides sample research questions that correspond with each level of the hierarchy.

Computer macros for use with Statistical Analysis System (SAS; Cary, NC) software were developed for use at the Institute for Clinical Evaluative Sciences with Ontario's health administrative data platforms and variables. Throughout the project, the macros were transferred to the BC team for adaptation to BC data. Level I and Level II macros are now fully functional in both provinces. The Level III macros are being adapted for use in BC. Consequently, interprovincial outcome studies of the type described in the proposal have not been achieved, but are underway. Building on the work of Mamdani et al.,¹⁰ an ecological study of admissions for UGIH in relation to coxib use, as well as Level II studies in which new statin users and new neuroleptic users are characterized, are in progress.

Exhibits 4–6 and 8–11 are representative of the Level I interprovincial analyses shared with the drug plan managers in Ontario and BC. Ontario data are provided in Exhibits 13 and 14 as illustration of the types of studies in progress. The Level I analyses plot prescription drug claims and costs on a monthly or quarterly basis, using Statistics Canada population estimates to express results in terms of the number of residents eligible for coverage.⁵¹ For the coxib study, the BC PharmaNet database was used to add information about the number of prescriptions financed by sources other than the provincial drug plan. No such data exist for Ontario. Total costs to the provincial drug plans were recorded in the ODB Database and BC PharmaCare Database:

(Total cost = dispensing fee + ingredient cost + mark-up + compounding fee (if applicable) – patient's share).

Assessing the impact of pharmacosurveillance evidence on formulary decision-making

Closing interviews

The main objective of the closing interviews was to seek input from the drug plans regarding the usefulness and application of our research, to better understand and optimize its use in decision-making. In the spring of 2004, following 1 week to preview the questionnaire, 2 senior staff from different administrative areas of each plan were interviewed (for example, in Ontario, 1 person was responsible for coordinating the review of drug submissions, and the other negotiated agreements with manufacturers).

The questionnaire had 3 main sections. Section 1 confirmed the subject's roles and responsibilities

within the drug programs Branch during the period of study, and requested a description of the kinds of decisions that typically can be/are informed by pharmacosurveillance research of the type described above. Section 2 listed reports and presentations team members prepared for the drug plans over the previous 3 years, including interprovincial analyses. Each record identified the author, date of presentation, study design, key study objectives and/or messages, and whether the Branch commissioned the work. For each entry, subjects were asked to reflect upon the research and assess the extent to which it influenced Branch decision-making or policy.

Scale for assessing research influence on/support for Drug Programs Branch (Branch) decision-making/policy

1. The research had considerable influence on a Branch decision or policy in a direct, instrumental way.
2. The research had moderate influence on a Branch decision or policy. This could have been an instrumental impact or by way of enlightenment (i.e., introduction to new concepts, insights, perspectives, etc.).
3. The research had limited influence in terms of instrumental impact or enlightenment, or by playing a part in Branch discussion or debate.
4. I see no evidence of the research's influence on a Branch decision or policy, but it does help support a previous decision/existing policy.
5. I see no evidence of the research's influence on/support for a Branch decision or policy.

Once completed, subjects were asked to identify the 3 most and least influential studies and to elaborate. The final section of the questionnaire helped define the research-based information considered most useful for formulary decision-making and why. Questions included:

- Are reports or analyses done by/for the Branch on a routine basis? If yes, please describe.
- How important to the usefulness of pharmacosurveillance research are factors such as: quality; relevance; ease of access; timeliness; format/presentation; level of financial risk involved in the decision informed by the research, etc.?

Appendix B. Canadian Network of Centres of Excellence in Pharmacosurveillance

Stakeholder queries regarding feasibility

Given strong support in Ontario and BC (on the part of both plan managers and researchers) for having local pharmacosurveillance expertise, preliminary feedback was sought from other drug plans, researchers, and Health Canada officials regarding the need for and feasibility of a potential network of centres of excellence in pharmacosurveillance.⁵² Written and verbal comments made during 2 national meetings (a Health Canada Meeting: Drug Effectiveness in the Real World in Ottawa, Ontario, March 2004; and a symposium on Evidence-based Drug Policy at the annual meeting of the Canadian Association for Population Therapeutics in Winnipeg, Manitoba, June 2004) were collected and analyzed for themes.

General questions related to: the generalizability of the Ontario-BC model to other, particularly smaller provinces; the mechanics of how research questions would be identified, agreed upon, and assigned, and how disagreement would be resolved; and, the kinds of research the network would undertake.

Specific questions included:

- Do we have sufficient human resources at the local level to be responsive to decision-makers' needs? Can we get long-term, sustainable funding to recruit and retain such staff?
- Do researchers and plan staff have sufficient time to do research to support individual listing decisions? Should we focus our research efforts on more innovative projects, such as conditional coverage agreements with manufacturers?
- Procedures for, and players involved in, drug policy/formulary decision-making vary among provinces and territories. Is the Institute for Clinical Evaluative Sciences (ICES) model⁵² sufficiently flexible to incorporate regional decision-makers outside the drug plan?
- How do we optimize use of available clinical databases and registries?
- What can be learned from other successful/less successful applied research networks, particularly in terms of policies and procedures for handling issues such as leadership, communication, authorship, dispute resolution, etc.?
- What are the best mechanisms to ensure those who could, would, in fact, benefit from the network's research?

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