Research Study on the Prophylaxis of Gastrointestinal Side Effects of Non-Steroidal Anti-Inflammatory Drugs in Nova Scotia senior population

by

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Acknowledgement and Endorsement

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Bogdan Superceanu
Executive Summary

This internship was performed as part of Drug Use Management and Policy Research Residency Program at the College of Pharmacy and involved developing a research project under the supervision of Dr. Sander van Zanten from the Gastroenterology research unit, Centre for Clinical Research.

The main objective was to assist decision makers in examining the appropriateness of prescribing gastroprotective agents especially as it relates to advanced age that is considered a risk factor for people taking non-steroidal anti-inflammatory drugs (NSAIDs).

The main responsibilities were to do a retrospective database analysis of seniors who are participants in the Nova Scotia Pharmacare drug program, to supplement it with a literature review to and to attend the biweekly knowledge development and skills building workshops provided through the Drug Use Management and Policy Research Residency Program.

This project is relevant for Health Informatics because it addresses real life health care problems using the tools and skills from computer science. Analyzing the huge amounts of data from health care databases of various institutions is one of the areas where Health Informatics students can find jobs.

Data was extracted from Population Health Research Unit (PHRU) and imported into an Access database. A cohort was created and data was analyzed using Structured Query Language (SQL) and Visual Basic. A statistical analysis was performed to see how coprescribing varies with age.

The most important finding is that the likelihood of being coprescribed GPAs with NSAIDs does not appear to be associated with increasing age even though the literature shows age to be an independent risk factor for serious GI complications. The results suggest an inadequate prevention of gastrointestinal side effects related to advanced age and NSAID use in Nova Scotia elderly population.
1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used classes of drugs, being commonly prescribed for the treatment of acute and chronic pain and inflammatory syndromes and in the case of ASA (aspirin is the generic name in the USA, but brand name in Canada) for cardiovascular protection. NSAIDs can cause serious gastrointestinal (GI) side effects, especially bleeding from duodenal or gastric ulcers [1,2].

According to the dual-injury hypothesis of Schoen and Vender [3], NSAIDs have direct toxic effects on the gastro-duodenal mucosa and indirect effects through their active hepatic metabolites and by decreasing mucosal prostaglandins which have a protective role for the gastro-duodenal mucosa.

![Figure 1. Mechanisms of nonsteroidal anti-inflammatory drug-induced gastro-duodenal damage (by Schoen and Vender)](image)

In patients who are at increased risk of gastrointestinal complications from NSAIDs it is recommended that a new class of NSAIDs, the cyclooxygenase-2 (COX-2) selective inhibitors or a traditional NSAID plus gastroprotective agents (GPAs) be prescribed. Both approaches have shown a similar risk reduction [6,7]. In patients who do
require NSAIDs and who are at an increased risk of GI complications due to NSAID use, it has been recommended that they receive prophylaxis with either a proton pump inhibitor (PPI), high dose H2-Blocker or Misoprostol [14]. These three medications have all proven to be efficacious in NSAID prophylaxis by decreasing the risk of serious upper GI side effects especially when started at the same time as the NSAIDs are prescribed. However, it is recognized that often such prophylaxis does not take place when it is indicated [4,5].

1.1 Study Rationale/Objectives

With the introduction of COX-2 inhibitors on the Canadian market, the prevalence of NSAID use among the elderly in one Canadian province increased 41% from 1999 to 2002. This increased use has been correlated with an increase in the rate of hospitalizations for upper GI bleeding [8]. Serious gastro-intestinal complications (bleeding, perforation, obstruction) among NSAID users account for an estimated 100,000 hospitalizations and more than 16,500 deaths/year in USA. The prevalence has been estimated to be similar in other developed nations [10,11,12]. The use of classical NSAIDs is associated with a three to four fold increase in the risk of upper gastrointestinal ulcer complications, such as bleeding and perforation [9]. Underprescription of gastroprotective agents (GPAs), especially in older patients using NSAIDs can cause clinical problems [5,13].

The main reasons for performing this study are:

- The high rates of gastrointestinal complications seen by the gastroenterology department in older patients using NSAIDs.
- To assist decision makers in examining the appropriateness of prescribing GPAs especially as it relates to advanced age that is considered a risk factor for people taking NSAIDs.
- The study can identify an area where educational programs are needed for health care providers to improve their prescribing practices.
- The study can help form drug policy around age related access to proton pump inhibitors.
1.2 Overview

This study consisted of a retrospective database analysis of seniors who are participants in the Nova Scotia Pharmacare drug program for the fiscal years 1998-2002. The database analysis was supplemented by a literature review on the coprescribing of NSAIDs and GPAs and another literature review to examine the evidence that age is an independent risk factor for GI complications and how the odds ratio or risk of GI complications increases with advanced age. In addition to the practical experience gained by performing the project, the author’s learning experience was supplemented by the biweekly knowledge development and skills building workshops provided through the Drug Use Management and Policy Research Residency Program and by other specific learning objectives as specified in the learning agreement signed after the beginning of the residency.

The author, Bogdan Superceanu, received support from Canadian Health Services Research Foundation/Canadian Institute of Health Research while participating in the Drug Use Management and Policy Research Residency Program. The project was presented at the 4th Dalhousie Computer Science In-House Conference, September 29, 2005.

2. Description of the Organization

In July 2000, Dr. Ingrid Sketris of the College of Pharmacy received a Chair in health services research. The Chair is funded by the Canadian Health Services Research Foundation (CHSRF) and the Canadian Institutes of Health Research (CIHR) and is cosponsored by the Nova Scotia Health Research Foundation. Through their research Dr. Sketris and her IMPART team (Initiative for Medication Management, Policy Analysis, Research & Training) examines issues related to drug use management and policy. She has established a Drug Use Management and Policy Residency which has had 4-6 residents each year [15].

The Drug Use Management and Policy Research Residency enables Dalhousie University graduate students from a variety of disciplines to spend four month working on research projects to inform health policy decision-making in regards to drug therapies. This program is a vehicle to facilitate interaction among decision-makers, researchers and
graduate students in relation to the development and use of applied health services research in decision-making about drug therapies. During the Residency, graduate students are placed in a host organization like Nova Scotia Department of Health, District Health Authorities, acute care facilities and other public or private sector organizations. Residents are matched with a host organization on the basis of mutual research interests. In addition to practical experience gained by working closely with preceptors from host organizations, other important learning objectives for the residents are:

- To understand the knowledge needs of decision makers and current health policy issues
- To understand how drug policy is developed
- To understand how drug use is managed
- To learn how the research is best disseminated to decision makers [16]

I worked on my project with my preceptor and supervisor Dr. Sander van Zanten at the Gastroenterology Research Unit, Centre for Clinical Research, Capital Health. This research unit is mainly involved in clinical trials and systematic reviews. The research conducted here is peer reviewed by other doctors in the Gastroenterology department and is funded by pharmaceutical companies and by various granting agencies. This unit has strong links with the College of Pharmacy and Population Health Research Unit (PHRU) of Dalhousie University. Dr. Sander van Zanten has a Howard Webster Research Chair and his main areas of research are prescribing of acid suppressor therapies, dyspepsia, helicobacter pylori and health outcomes.

3. Work Performed for the internship

3.1 Job description

The job required:

1. Attending the biweekly knowledge development and skills building workshops provided through the Drug Use Management and Policy Research Residency Program. A more detailed description of these seminars is provided below in the section 3.2 “Other learning experiences”.
2. Analysis of the Nova Scotia Pharmacare administrative database. As it was agreed in the project proposal developed after the start of the residency this job involves analysis of the Nova Scotia Pharmacare administrative database for health research to address the following objectives:
   • To document the overall use rate of NSAIDs, COX-2 and GPAs.
   • To determine simultaneous use of NSAIDs and GPAs.
   • To determine the rate in which GPAs are started at the same time as NSAIDs.
   • To document how the coprescribing of GPAs changes with age.

3. Determining an appropriate methodology for data analysis

4. Doing two literature reviews:
   • To document the coprescribing rates of NSAIDs and GPAs in similar studies
   • To see if age is an independent risk factor for GI complications and how the odds ratio or risk of GI complications increases with advanced age.

5. Statistical data analysis

6. Interpreting the results and writing a report that is suitable as a publication in a peer-reviewed journal.

3.2 Other Learning experiences

• I attended about 12 hours/month of seminars, workshops and meetings on topics relevant for drug use management, research and policy analysis. In these seminars I learned about:
  ➢ Making briefing notes and the Department of Health (DOH) briefing notes format
  ➢ Drug Evaluation Alliance of Nova Scotia (DEANS) by attending DEANS meetings
  ➢ Nova Scotia legislative process (DOH meeting)
  ➢ Health Planning Policy and Policy Analysis (DOH meeting)
  ➢ Health Care financing
  ➢ How to conduct a systematic review
  ➢ Ethics review process
  ➢ Knowledge translation from researchers to decision makers
- Pharmaceutical Policy Strategy (factors affecting drug expenditures, drug reimbursement, cost sharing mechanisms like premiums, deductibles, co-payments)
- How to deal with Media (Media Training)
- Ethics and Resource allocation in health care

- I had to read documentation and to learn about the Nova Scotia Pharmacare dataset.
- I learned about specific drug policies in relation to my project (The Nova Scotia Pharmacare formulary reimbursement policy for the drugs used in my project).
- I learned about the Anatomical Therapeutic Chemical (ATC) drug classification system, Drug Identification Number (DIN) and Defined Daily Dose (DDD) which are all used in drug utilization studies.
- I have got the DIN numbers and ATC codes for all drugs used in my project. These codes were used to extract data from the Population Health Research Unit (PHRU) databases.
- I worked to do my first ethics proposal document and I learned what it takes to go through the ethics approval process. My project was approved by the Dalhousie Health Sciences Human Research Ethics Board.
- I wrote and submitted for the first time a short paper summary for the Dalhousie Computer Science In-house Conference (DCSI).
- I learned a lot of tips about working with Pubmed when building my queries for the literature review.
- With the help of the College of Pharmacy’s librarian I learned how to use Mesh terms in my search queries.

4. The Relationship with Health Informatics

This project is relevant for Health Informatics because it addresses real life health care problems using the tools and skills from computer science. This is similar with the motto: “Health is the focus, technology the enabler”. The project attempts to provide support for better understanding of problems in the health care system (like inappropriate
prescribing of doctors) and it is also a support for health services because it brings more insight that can shape the policy of the Nova Scotia Pharmacare program. Analyzing the huge amounts of data from health care databases of various institutions is one of the important areas where Health Informatics students can find jobs.

The Pharmacare dataset contains Anatomical Therapeutic Chemical (ATC) codes and Drug Identification Number (DIN) numbers. At the beginning of my summer internship I had to find the DIN numbers and ATC codes of all drugs used in my project. These codes were used to extract data from the Population Health Research Unit. As a result I learned about the ATC drug classification system and DIN numbers which are used very often in drug utilization studies. This learning is related to the coding schemes and vocabulary domains learned in HINF 6100X/Y: Health Information: Its Flow and Use course and HINF 6220 Networks and the Web course.

By doing my literature review and searching for articles I gained practical experience and learned a lot of tips for using online databases and building search queries. I learned to build sophisticated queries combining Mesh terms and keywords. These are useful skills for a health informatician.

A major learning for me was related to ethics in health research and came from the need to submit an ethics proposal for my project. By developing a document like this I learned many aspects related to privacy, confidentiality of data and ethical standards. On this occasion I also learned about the Population Health Research Unit (PHRU) Data Access Guidelines and Procedures (www.phru.dal.ca/data_access/guidelines.cfm). One of the seminars attended during my residency was also about ethics and resource allocation in health care. In our health informatics program we also talked about ethical aspects related to health information, privacy and security.

My work was very much related with HINF 6020, Research Methods course because this class explores the logic and principles of research design and discusses methodological issues related to research. What I learned in this class helped me especially for the literature review when I had to do a critical appraisal of various studies based on study design. It also helped me with the methodology for data analysis.

The database analysis task required some of the skills learned in HINF 6220 course: database design, connecting to databases, manipulating data using SQL. Also this
project required programming skills, which are very useful skills to have for a health informatician.

Another skill that a health informatician must have is a good understanding of the healthcare system. My summer experience helped me a lot here. I learned more by attending the Health Care financing and Health Planning and Policy Analysis seminars. I learned how health policy (drug policy) is made by attending DEANS meetings, by understanding the Nova Scotia Pharmacare formulary reimbursement policy and learned about policy instruments used for drug use management. In addition I worked in a health setting understanding the needs and process inside the organization. All these real-life experiences supplemented what I learned about the health system in HINF 6100X/Y, Health Information, Its Flow and Use course.

The HINF 6030, Statistics for Health Informatics helped me to learn quickly about the logistic regression which was used in my project but we didn’t learn in class. I used Minitab statistical package to make graphs for my results. It would have been more useful for me if we learned SAS statistical package which was the ideal approach for the data analysis that I had to do.

General skills that would be required in health informatics should include not only the ability to analyse medical information but to be able to communicate that information as medical knowledge. This requires a good understanding of medical problems, ability to articulate the results into meaningful conclusions that can have an impact on health care policy.

Communication skills and management skills are important as health informaticians tend to act as a bridge between clinicians and non clinicians or technical people. This project exposed me to constant feedback from the supervisor, co-supervisor, residency director and residency coordinator. I learned to coordinate different messages especially when things changed and to plan ahead for the time when no feedback or help was available because of the summer holiday.

Even though I didn’t take yet the data mining course I believe that the data analyzed in my summer internship is suited for applying data mining algorithms on it. The techniques to link data mining applications with databases will be very useful to learn for me.
5. Critical analysis of a task and its health informatics solution

5.1 Task description and the information needs of host organization

The most important task I had to do for my internship was the analysis of the Nova Scotia Pharmacare administrative database to answer clinically relevant questions of interest for the Gastroenterology department at Queen Elizabeth II Health Sciences Centre.

They have seen high rates of gastrointestinal complications in older patients using NSAIDs. Knowing that non-steroidal anti-inflammatory drugs (NSAIDs) can have harmful effects on gastro-duodenal mucosa, their information needs/knowledge gaps were directed towards exploring the appropriateness of prescribing gastroprotective agents (GPAs) especially as it relates to advanced age that is considered a risk factor for gastrointestinal (GI) complications in people taking NSAIDs.

The study consisted of a retrospective database analysis of seniors (age more than 65 years) who are participants in the Nova Scotia Pharmacare drug program for the period 1998-2002. We agreed in the project proposal to approach this problem by dividing it into four objectives:

1. To document the overall use rate of NSAIDs, COX-2 and GPAs.
2. To determine simultaneous use of NSAIDs and GPAs.
3. To determine the rate in which GPAs are started at the same time as NSAIDs.
4. To document how the coprescribing of gastroprotectives changes with age.

5.2 The solution

5.2.1. Introduction and data description

The data we wanted to analyze resides on secure research computing facilities at the Dalhousie University Population Health Research Unit (PHRU). I did not have direct access to the original dataset. The study population and data was extracted from the database by Chris Skedgel who was an analyst at PHRU for eight years prior to his current position with the Dalhousie Department of Medicine. To ensure patient confidentiality I received encrypted unique identifiers and aggregated data. The MSI
number was encrypted at PHRU using their encryption algorithm. To identify the drugs studied before data extraction I had learn about the Anatomical Therapeutic Chemical (ATC) drug classification system and Drug Identification Number (DIN) and submit these codes for data extraction. Data was extracted using the SAS system, exported as a text file and given to me for analysis. I imported the data received from PHRU in an Access database using the import wizard which helps you determine the exact format of data received.

The dataset imported had 6,442,642 records. At this size some people estimated that I won’t be able to import it because it will exceed the maximum size that an Access database can handle. I didn’t expect to receive such a big dataset.

An example of how the data looks like is provided in Figure 2. The studyid is the encrypted MSI number, month is the calendar month where 0 is the month starting at April 1st 1998. Agegrp column has the value of 14 for patients in the age group 65-69 years and increments with one for each five year age interval. The columns representing drug use have the value of 0 for a non-user of a particular drug or 1 for users. The ID is the unique identifier for each row and was included automatically by Access when data was imported. It is the primary key for the table. Even though we have 60 month of data not all individuals have 60 records because they may not be eligible in the Pharmacare program for the entire period.
5.2.2. Objective 1

For this objective the calculations were done on all eligible Pharmacare population and only simple SQL queries were used. I calculated the use rates of drugs using two methods. The overall use rates of a particular drug were calculated taking into consideration any patient who had at least one drug prescription during the fiscal year divided by total number of people eligible for Pharmacare in the same year. With the other method I calculated the yearly use rates as an average of monthly use rates which were calculated as the number of people using a particular medication in a month divided by total number of people eligible for Pharmacare in the same month. Here I had my first exposure to methodology issues related to data analysis. The two methods yielded different results so I had to consider which method is more realistic and gives more...
meaningful results. A screenshot of the queries used for these calculations can be seen in Figure 3.

![Queries used for calculating drug use rates (Objective 1)](image)

Figure 3. Queries used for calculating drug use rates (Objective 1)

The use rates of COX-2 rise from 0 when they were launched on the Canadian market to almost 12% in 2001. At the same time there was a decrease in the use of classical NSAIDs. NSAID and COX trends are similar with trends from other administrative databases (Ontario) and can be seen in Figure 4. The results for gastroprotectives class of drugs show that histamine-2 receptor antagonists (H2RA) are the most widely prescribed far more than proton-pump inhibitors (PPI). PPI rates are low because there are restrictions on the reimbursement for this drug. However the use rates for PPI almost doubled in this 5 year interval – Figure 5.
Figure 4. Use rates of NSAIDs

Figure 5. Use rates of gastroprotectives (GPA)
5.2.3 Objectives 2, 3 and 4

For the last three objectives I created a cohort of incident NSAID and GPA users. After successfully finishing the first objective I thought that I can do the entire data analysis using just SQL but the methodology used for creating the cohort required the design of specific algorithms for data processing. As a result I had to use a programming language. Visual Basic was my natural choice because I am a Microsoft Certified Professional in Visual Basic 6.0.

As inclusion criteria for the cohort the patients had to be:

a) non-NSAIDs users in the 12 months prior to their index prescription, which is the relative month (not calendar month) of their first NSAID prescription.
b) non-gastroprotective users in the 2 months prior to their index NSAID prescription
c) eligible for Pharmacare program at least 13 months (12 months before index month plus at least the index month). After using the criteria only 12906 people remained in the cohort.

The reasons for creating a cohort in this way are:

a) The old NSAID users may already have GI problems due to NSAIDs and take GPA for it. We wanted to see the preventive coprescribing so we needed new NSAID users.
b) People who used any GPA in the 2 month before starting NSAIDs are more likely to use GPA for various gastrointestinal diseases not related to the prophylaxis of NSAIDs side effects.

To create the cohort and facilitate calculations I had to create two new columns in the database, then to insert the appropriate values in each column according to an algorithm. The eligibility column was needed to take into account the fact that people may become eligible or lose their eligibility at any point in time. The inserted value was one when they became eligible then the value was incremented until the end of their eligibility. To find the relative month when each patient in the cohort started to use NSAIDs, the column named NSAIDstart was created. I inserted the value of one when patient started to use NSAIDs then incremented the value until the end of eligibility. To insert these values I connected to the Access database using Microsoft Visual Basic ADO (ActiveX Data Objects) technology then manipulated the recordset using the Visual Basic
programming language. Because the dataset was big I witnessed slow execution times when inserting new values into database and for nested queries.

After creating the columns again SQL queries were used to calculate the co-prescribing rate (Figure 6)

![Database Screenshot](image)

Figure 6. Queries used for objectives 2, 3 and 4

The coprescribing rates were calculated by drug and by age. In Figure 7 we can see that most of the coprescribing is done with histamine-2 receptor antagonists (H2RA) which was expected given their high use rates compared with proton-pump inhibitors (PPI). We can also see an increase in coprescribing rates as people were using NSAIDs more.
The results in figure 8 show an increase in coprescribing as patients were more month on NSAIDs. The relationship between coprescribing rate and age is not so clear from the results so we performed a statistical analysis of the data using logistic regression.
The statistical analysis was performed on 12906 people and compared all age groups with the age group 65-69 years. Even though we normally expect to see higher coprescribing as the age increases the odds ratio of being coprescribed were lower than 1 (one) in two groups with higher age than the group 65-69. However the confidence intervals show that the p values for these comparisons are higher than 0.05.

**Odds Ratio Estimates**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Point Estimate</th>
<th>95% Wald Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>agegrp 70-74 vs 65-69</td>
<td>0.779</td>
<td>0.605 1.003</td>
</tr>
<tr>
<td>agegrp 75-79 vs 65-69</td>
<td>0.849</td>
<td>0.649 1.112</td>
</tr>
<tr>
<td>agegrp 80-84 vs 65-69</td>
<td>1.098</td>
<td>0.826 1.459</td>
</tr>
<tr>
<td>agegrp 85+ vs 65-69</td>
<td>1.285</td>
<td>0.959 1.722</td>
</tr>
</tbody>
</table>

**6. Conclusions**

Based on the use rates we can see that the H2RA are used a lot more than PPI even though PPI are very effective in prevention and healing of GI complications related to NSAIDs. This low use rate for PPI is explained by the restriction criteria on the Nova Scotia formulary for the reimbursement of this class of drugs. These drugs are approved to be used only for a short period of time and only for people considered at high risk of developing GI complications due to NSAIDs.

The coprescribing rates are lower than in other similar studies that investigated coprescribing rates and most of the coprescribing is done with H2RA.

The most important finding is that the likelihood of being coprescribed GPAs with NSAIDs does not appear to be associated with increasing age even though the literature shows age to be an independent risk factor for serious GI complications.

The results suggest an inadequate prevention of gastrointestinal side effects related to advanced age and NSAID use in Nova Scotia elderly population.

The gastroenterology department might consider developing an educational program related to the increasing need for coprescribing in elderly patients requiring NSAIDs.
7. Recommendations

There are other interesting research questions on the same topic that could be investigated as a possible future work:

- How long were patients on NSAIDs before taking GPA
- Rates in which GPA are continued after NSAIDs are stopped
- Rates in which GPA are started after NSAID prescription started (>1 month)
- Classifying the NSAID prescriptions by length and look at the coprescribing rates of short term incident NSAID users

Advanced age is one of the important risk factors for GI complications in older people taking NSAIDs but currently age by itself as a single risk factor is not sufficient to qualify for reimbursement of proton pump inhibitors on the Nova Scotia formulary and there is no clear cutoff age in the criteria for coverage of this class of drugs (Appendix 1).

Future research can bring additional evidence to convince decision makers to include age as standalone criteria for reimbursement of PPI and can also clarify what age represents an important enough risk for GI complications to qualify PPI as a benefit for people covered by the Nova Scotia Pharmacare program.
References


Appendix 1
Criteria for coverage of Proton Pump Inhibitors for Peptic Ulcer Disease, January 2005
(from http://www.gov.ns.ca/health/pharmacare/)

**NSAID induced Ulcers**
- for the treatment of NSAID induced complicated peptic ulcer (bleeding ulcer, perforation, etc.) when the NSAID is discontinued
  Coverage Duration: up to 8-12 weeks
- for the treatment and prophylaxis of NSAID induced complications in patients who have had previous NSAID related ulcer or ulcer complications and NSAID therapy cannot be discontinued
  Coverage Duration: while on NSAID or a maximum of 1 year with reassessment
- for the prophylaxis of NSAID induced complications in patients who are at high risk (i.e., NSAID therapy plus two other risk factors including advanced age, concomitant anticoagulant or oral corticosteroid therapy)
  Coverage Duration: while on NSAID or a maximum of 1 year