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ORIGINAL RESEARCH

Trends in prescription claims following the withdrawal of rofecoxib from the Canadian market

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ABSTRACT

Objective: Rofecoxib (Vioxx, MK996) was voluntarily removed from the Canadian market by Merck in September 2004. No studies have examined the impact of its removal on utilization of other NSAIDs. We examined the utilization (i.e., numbers of claims) of NSAIDs, proton pump inhibitors (PPIs) and salicylic acid derivatives (SADs) in Ontario and Québec one year prior to and after rofecoxib's withdrawal from the Canadian market. **Methods:** Monthly claims of coxibs occurring between October 2003 and November 2005 were obtained from Brogan Inc. NSAIDs were analyzed as a group and by chemical class. Interrupted time series (segmented regression) was used to examine changes in utilization of other coxibs, COX-1 NSAIDs, PPIs and SADs after rofecoxib's removal. **Results:** Segmented regression analysis revealed that the monthly number of claims for all NSAIDs (including coxibs) decreased by 19%, from 622,347 to 500,397 between October 2003 and November 2005. We also identified a marked reduction for all NSAIDs between September 2004 and January 2005 (-141,524 claims/month; 95%CI -188,889 to -94,159; P <0.001). Monthly coxibs claims decreased after rofecoxib's withdrawal (-156,883 claims/month; 95%CI= -184,393 to -129,373; P <0.001). Non-selective COX-1 inhibitors exhibited the opposite trend; monthly claims increased 32% to 414,813 at study end. No shift in utilization of PPIs or SADs was observed. **Conclusions:** The removal of rofecoxib from the Ontario and Québec markets resulted in an immediate decrease followed by a slow increase in all NSAID claims.

Key words

Claims analysis; Drug utilization; Linear models; Non-steroidal anti-inflammatory agents; Regression analysis

RÉSUMÉ

Objectif: Le rofecoxib (Vioxx, MK 996) a été volontairement retiré par Merck du marché canadien en septembre 2004. Comme il n'y avait pas d'étude sur l'impact de l'utilisation des autres AINS, nous avons examiné l'utilisation (nombres de demandes) des AINS, des inhibiteurs de la pompe à proton (IPP) et des dérivés de l'acide acétylsalicylique (AAS) dans l'Ontario et le Québec l'année précédant et celle suivant le retrait du rofecoxib du marché canadien. **Méthodes:** La demande mensuelle des coxibs entre octobre 2003 et novembre 2005 a été obtenue de Brogan Inc. Les AINS ont été analysés en tant que groupe et d'après leur classe chimique. Les changements de l'utilisation des autres coxibs, des inhibiteurs de la COX-1, des IPPs et des dérivés de l'AAS ont été analysés au moyen de séries interrompues dans le temps (analyse de régression segmentée). **Résultats:** L'analyse de régression segmentée a montré que le nombre mensuel de demandes des AINS (incluant les coxibs) a diminué de 19 %, de 622,347 à 500,397, entre octobre 2003 et novembre 2005. La demande de tous les AINS a également diminué significativement entre septembre 2004 et janvier 2005 (-141,524 demandes/mois; 95% CI -188,889 – -94,159; P <0,001). La demande mensuelle des coxibs a diminué après retrait du marché du rofecoxib (-156,883 demandes/mois; 95% CI -184,393 – -129,373; P <0,001). Les inhibiteurs non-sélectifs de la COX-1 ont montré une tendance en sens opposé: les

demandes mensuelles ont augmenté de 32 %, atteignant 414,813 à la fin de l'étude. Nous n'avons pas identifié de changement dans l'utilisation des IPPs ou des AAS. **Conclusions:** Le retrait du rofecoxib des marchés ontarien et québécois a entraîné une diminution immédiate suivie par une lente augmentation des demandes des AINS.

Mots clés

Analyses de demandes; Utilisation des médicaments; Modèles linaires; Anti-inflammatoires non-stéroïdiens; Analyses de régression

RESUMEN

Objetivo: Rofecoxib (Vioxx, MK 996) fue retirado voluntariamente del mercado canadiense por Merck en septiembre del 2004. Sin embargo, no existen estudios que examinen el impacto de su retiro en la utilización de otros AINES. En este estudio examinamos la utilización (i.e. número de solicitudes) de los AINES, de los inhibidores de la bomba de protones (IBP) y de los derivados del ácido salicílico (ASA) en Ontario y Quebec el año antes y después del retiro de rofecoxib del mercado canadiense. **Métodos:** Las solicitudes de estos medicamentos generadas entre octubre del 2003 y noviembre del 2005, fueron obtenidas de Brogan Inc. Los AINES fueron analizados como grupo y como clase de acuerdo a su estructura química. Los cambios en la utilización de otros coxibs, COX-1, AINES, IBP, y derivados del ASA después del retiro del rofecoxib se analizaron mediante series temporales interrumpidas (regresión segmentaria). **Resultados:** El análisis de regresión segmentaria reveló que el número mensual de solicitudes de todos los AINES (incluyendo coxibs) disminuyó 19%, de 622,347 a 500,397, entre octubre del 2003 y noviembre del 2005. Entre septiembre del 2004 y enero del 2005, se observó una marcada reducción en la solicitud de todos los AINES (-141,524 solicitudes/mes; 95%CI -188,889 a -94,159; P <0.001). Los inhibidores COX-1 no selectivos mostraron la tendencia opuesta; las solicitudes mensuales incrementaron 32% a 414,813 al final del estudio. No se observaron cambios en la utilización de los IBP o de los derivados del ASA. **Conclusiones:** El retiro del rofecoxib de los mercados de Ontario y Quebec resultó en una inmediata disminución, seguida de un lento incremento, en las solicitudes de AINES.

Palabras clave

Análisis de solicitudes; Utilización de medicamentos; Modelos lineales; Agentes anti-inflamatorios no esteroideos; Análisis de regresión;

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are comprised of non-selective cyclo-oxygenase (COX) inhibitors, selective COX-2 inhibitors and acetylsalicylic acid (ASA). They are commonly indicated for the treatment of inflammation, arthritis, and musculoskeletal problems [1]. In addition, they are among the most frequently prescribed medications worldwide [2].

Non-selective NSAIDs have been associated with adverse gastrointestinal (GI) event complications including dyspepsia, ulcers, bleedings, and perforations [3]. These complications are secondary to COX-1 inhibition resulting in a reduction of protective GI mucosal prostaglandins. Approximately 2-4% of NSAID users will have a serious adverse GI event each year [4]. Selective COX-2 inhibitors exert the beneficial effects of non-selective NSAIDs but are associated with lower rates of GI complications [5].

COX-2 inhibitors were first listed on the Ontario Drug Benefit formulary in April 2000. Mamdani et al. [6] reported a 68% increase in the total number of claims for NSAIDs (both COX-2 and non-selective) seen between March and November 2000.

Rofecoxib (Vioxx) is a selective COX-2 inhibitor indicated for the treatment of osteoarthritis, rheumatoid arthritis, acute pain, and menstrual symptoms [7]. Rofecoxib was initially introduced in the market as a novel drug because it was associated with fewer gastrointestinal symptoms than traditional NSAIDs [8] [9] [10]. In September 2004, rofecoxib was voluntarily removed from the Canadian market by its manufacturer, Merck & Co., Inc. following preliminary analysis of data from the Adenomatous Polyp Prevention On Vioxx (APPROVe) study [11]. The preliminary results suggested an association between cardiovascular events and rofecoxib use.

The sudden withdrawal of rofecoxib from the market resulted in two consequences: first, rofecoxib users were left to find alternative treatments, and second, other drugs in the COX-2 family including valdecoxib and celecoxib were closely scrutinized for similar cardiovascular events [12].

To our knowledge, there have not been any published studies examining the impact of rofecoxib removal on the utilization of other medications. Therefore, the objective of this study was to examine the Ontario and Québec utilization (i.e., numbers of claims) of NSAIDs, salicylic acid derivatives (SADs) and proton pump inhibitors (PPIs) in the year prior to and after the withdrawal of rofecoxib from the Canadian market. Specifically, we explored the association of the

removal of rofecoxib from the market with the utilization of other coxibs, as well as on COX-1 inhibitor NSAIDs [acetic acid derivatives (AADs), propionic acid derivatives (PADs), and oxicams], SADs, and PPIs.

METHODS

Data sources

Monthly claims were collected electronically from the PharmaStat database, provided by Brogan Inc [13]. The PharmaStat database included information on the number of claims, units and cost of prescribed medications for all of the publicly funded federal and provincial drug benefit programs with the exceptions of Prince Edward Island and Alberta, as well as over 65% of private drug plans.

The study time horizon was chosen to include at least one year prior to and at least one year after market withdrawal of rofecoxib. Monthly data were available starting from January 2003; however, the period from January 2003 to September 2003 was excluded from analysis since only Ontario data were available.

Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) system [14]. Monthly numbers of claims for NSAIDs, SADs, and PPIs for Ontario and Québec were retrieved for the period between October 2003 (13 months before market withdrawal of rofecoxib) and November 2005 (14 months after).

Analysis

Data grouping

NSAIDs were first analyzed as a group and after stratifying them by individual chemical classes in order to identify changes in resource utilization for the different NSAIDs. The SADs dataset included only acetylsalicylic acid products, while the PPI dataset obtained was a subclass of the ATC group 'drugs for peptic ulcer and gastro-esophageal reflux disease'.

Interrupted time-series model and data transformation

An interrupted time-series design by segmented regression was used to study the effects of rofecoxib withdrawal from the market on the utilization of other coxibs, as well as on COX-1 inhibitor NSAIDs, SADs, and PPIs [15] [16]. Series were plotted (utilization versus time) and were visually inspected to identify apparent trends or cycles. Descriptive statistics were computed. Different models (e.g., ARIMA, log linear trends with or without seasonal effects) were fitted to each independent series in order to account for autocorrelation. Autocorrelation was tested using the AUTOREG procedure from SAS and first order autocorrelations were tested with a Durbin-Watson test [17]. In addition, residuals were plotted and tested for normality, using a Shapiro-Wilks test.

Segmented regression of interrupted time series

The trend of the outcome variables, (i.e., number of claims) was observed over time. Where appropriate (i.e., allowing for a transition period and market stabilization), an intervention (break point) was introduced into the time-series as an explanatory variable. This regression was then tested to determine if there had been a change in intercept and/or slope, using a segmented regression test [15].

We first tested for a shift in the time-series occurring in October 2004 (i.e., the month following rofecoxib withdrawal from the market). Series were analyzed using a regression model. We used dichotomous dummy variables in the model to differentiate between the period before rofecoxib withdrawal (including September 2004) and the period after rofecoxib withdrawal. If necessary, a transition period was also taken into consideration, when time-series showed a delayed response after the removal of rofecoxib from the market. The full regression model is presented in the following equation:

$$y_t = b_0 + b_1(time) + b_2(dummy) + b_3(time * dummy)$$

where y_t is the total number of claims at time t, b_0 is the baseline level of the outcome variable y_t, b_1 is the slope of the trend before the intervention, b_2 is the magnitude of the intervention, and b_3 is the difference in slope of the trend post intervention. The variable dummy represents the dichotomous dummy variable inserted in the regression model to discriminate between the two periods. Differences between intercepts and slopes for each trend were assessed using regressions as part of the AUTOREG procedure in SAS. All descriptive and statistical analyses were performed using SAS version 9.1 [17].

RESULTS

Model fit

All time-series could be fitted with either an ARIMA or a log linear trend. In most cases, a seasonal component was present, although the series did

not show strong cycles. The R^2 values were relatively high, ranging from 0.79 to 0.98, indicating a good fit in each case. No first-order autocorrelation was observed, as identified by the Durbin-Watson test. Detailed results are presented in Table 1.

Monthly number of claims

Between October 2003 and November 2005, the monthly number of claims for all NSAIDs (including coxibs) decreased by 19%, from 622,347 to 500,397 (Figure 1). The reduction rate for the period prior to rofecoxib withdrawal was not significantly different than zero (m= -691.0; 95%CI= -2,492 to 1,110; P =0.407). In addition, the monthly number of claims for the period between January and November 2005 (between 4 and 14 months after rofecoxib market withdrawal) did not show a significant change (Δm= 1,815; 95%CI= -1,017 to 4,647; P =0.169). Thus, this reduction can be attributed for the most part to the decrease in the monthly number of claims observed during the three months following the removal of rofecoxib from the market (a decrease of 18% in January 2005, compared to September 2004). Regression parameter estimates are presented in Table 2.

A marked reduction in the monthly claims of coxibs was observed after September 2004 (Figure 1). This reduction coincides with the withdrawal of rofecoxib from the market [11]. For the post-rofecoxib period, the reduction compared to baseline was significant (Δl= -156,883; 95%CI= -184,393 to -129,373; P <0.001). Furthermore, a significantly decreasing month-to-month trend was found after January 2005 (Δm = -2,319; 95%CI= -3,933 to -704.9; P <0.001).

While the month-to-month number of claims for all NSAIDs decreased during the study period, monthly claims for non-selective COX-1 inhibitors increased by 32% to 414,813 per month in November 2005 (Figure 1). The monthly trend during the baseline period (before rofecoxib withdrawal) and the post-rofecoxib period was found to remain constant (Table 2).

A closer examination of the different subclasses of COX-1 inhibitors revealed different trends for the post-rofecoxib period. Only PADs and AADs experienced a significant increase in monthly claims after the withdrawal of rofecoxib (Table 2). Furthermore, while the number of claims for PADs increased immediately after the removal of rofecoxib, this increase was more gradual for AADs, following a transition period similar to the one observed with coxibs, but in the opposite direction (Figure 2).

The month-to-month trend of COX-1 claims for the baseline period was constant except for oxicams, where there was an increase over time (m= 136.5; 95%CI= 2.795 to 270.1; P =0.039). This trend did not change during the post-rofecoxib period. This was not the case for PADs and AADs, as both classes showed a significant increase in the monthly number of claims in comparison to the trend observed during the baseline period (Table 2). For all other COX-1 inhibitors, there was no significant change identified by the segmented regression analysis.

With the decreased use of coxibs and increased use of COX-1 inhibitors, it was postulated that PPIs use would increase accordingly to counteract the GI events associated to non-selective NSAIDs [18]. We therefore investigated the post-rofecoxib impact on PPI use, in comparison with the baseline period. No increase was observed after rofecoxib withdrawal from the market, as depicted in Figure 1 and Table 2. Similar results were found in the resource utilization of SADs where no change was observed during the post-rofecoxib period (Figure 1).

Table 1 Fitted model and resulting first order autocorrelation for each medication class series

Medication Class Name (ATC class number)	Model	R^2	Autocorrelation		
			Durbin-Watson Test	P < DW (Positive AC)	P > DW (Negative AC)
Coxibs (M01AH)	ARIMA (0,1,0) (1,0,1)s	0.98	2.106	0.314	0.686
ASA derivatives (M01AB)	ARIMA (2,0,0) (0,0,1)s	0.95	1.794	0.105	0.895
Oxicams (M01AC)	ARIMA (2,0,0) (1,0,0)s	0.85	1.843	0.131	0.869
Propionic Acid Derivatives (M01AE)	ARIMA (3,0,0) (1,0,0)s	0.95	2.030	0.269	0.731
Other NSAIDs*	Log-linear with seasonal dummies	0.87	2.017	0.292	0.708
All NSAIDs	ARIMA (2,0,0) (1,0,0)s	0.93	2.454	0.653	0.347
NSAIDs (without coxibs)	ARIMA (2,1,0) (1,0,0)s	0.88	1.764	0.095	0.905
PPIs (A02BC)	Log-linear with seasonal dummies	0.98	2.047	0.263	0.737
SADs (N02BA)**	ARIMA (2,1,0) (1,0,1)s	0.79	2.002	0.244	0.756

AC = autocorrelation, DW = Durbin-Watson; see the text for other abbreviations.*Other NSAIDs include the following classes: M01AA (Butylpyrazolidines), M01AG (Fenamates) and M01AX (Other antiinflammatory and antirheumatic agents, non-steroids). **Salicylic acid derivatives include only acetylsalicylic acid (N02BA01)

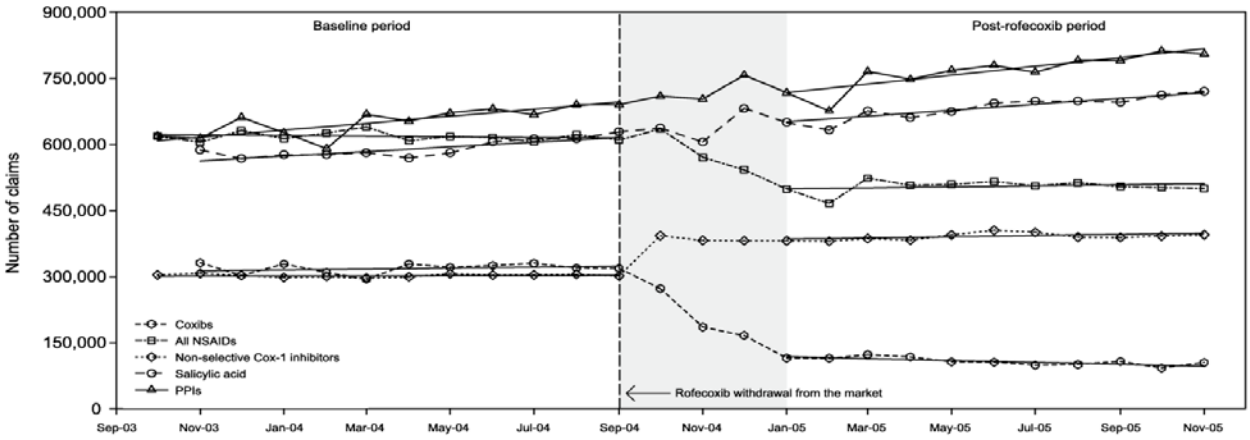

Figure 1 Graphical representation of the monthly number of claims in Ontario and Québec for non-steroid anti-inflammatory drugs (all, without coxibs and coxibs only), proton-pump inhibitors and salicylic acid derivatives. Abbreviations: NSAIDs= non-steroid anti-inflammatory drugs, PPIs = proton-pump inhibitors.

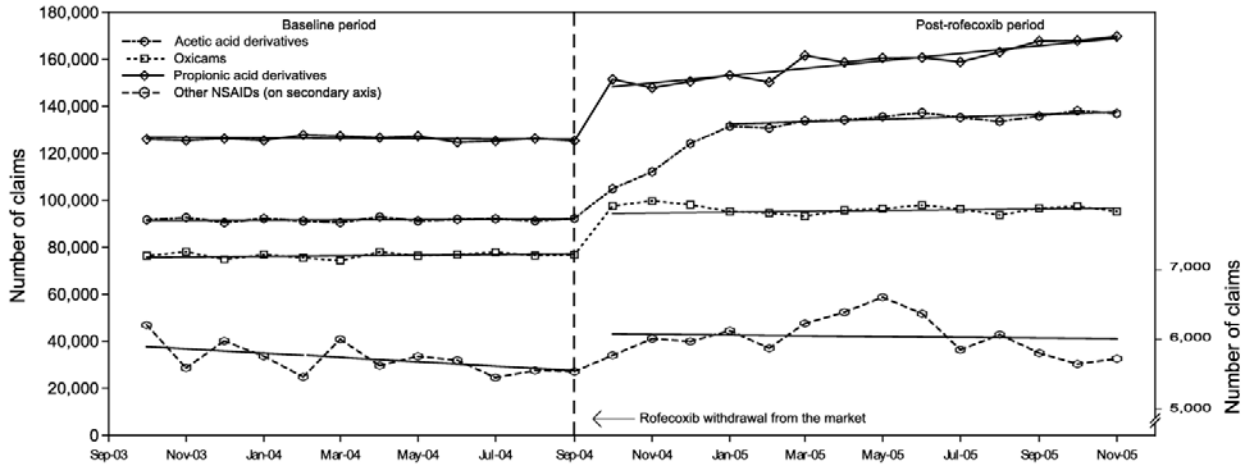

Figure 2 Graphical representation of the monthly number of claims in Ontario and Québec for different medication classes of non-steroid anti-inflammatory drugs. Note: Other NSAIDs are plotted against the secondary y-axis Abbreviations: NSAIDs= non-steroid anti-inflammatory drugs.

Table 2 **Parameter estimates, standard errors and p-values from the regression models predicting monthly number of claims for each class of medication for the periods prior and post rofecoxib withdrawal**

		Baseline					Post-Intervention			
Medication Class Name (Regression pooled R^2)	**Period (2003-2004)**	**b_0 (SE)**	**P value***	**b_1 (SE)**	**P value**	**Period**	**b_2 (SE)**	**P value**	**b_3 (SE)**	**P value**
Coxibs (0.997)	**Nov – Sep**	**310,534 (3,995)**	**<0.001**	**1,069 (537.1)**	**0.066**	**Jan–Nov 2005**	**-156,883 (12,161)**	**<0.001**	**-3,272 (781.1)**	**0.001**
ASA derivatives (0.999)	**Oct –Sep**	**91,245 (398.1)**	**<0.001**	**62.21 (56.86)**	**0.292**	**Jan–Nov 2005**	**33,077 (1,521)**	**<0.001**	**447.3 (92.64)**	**<0.001**
Oxicams (0.991)	**Oct – Sep**	**75,632 (421.9)**	**<0.001**	**136.5 (59.99)**	**0.039**	**Oct 2004 – Nov 2005**	**16,521 (1,584)**	**<0.001**	**34.69 (95.82)**	**0.723**
Propionic Acid Derivatives (0.995)	**Oct – Sep**	**126,861 (513.9)**	**<0.001**	**-76.90 (71.12)**	**0.295**	**Oct 2004 – Nov 2005**	**763.0 (1,062)**	**0.482**	**1,665 (78.10)**	**<0.001**
Other NSAIDS (0.564)**	**Oct – Sep**	**5,897 (179.8)**	**<0.001**	**-30.45 (24.67)**	**0.234**	**Oct 2004 – Nov 2005**	**211.6 (416.1)**	**0.618**	**25.45 (31.02)**	**0.423**
All NSAIDs (0.972)	**Oct – Sep**	**623,038 (5,718)**	**<0.001**	**-691.0 (808.3)**	**0.407**	**Jan 2005 – Nov 2005**	**-141,524 (20,938)**	**<0.001**	**1,815 (1,252)**	**0.169**
NSAIDs (without coxibs) (0.995)	**Oct – Sep**	**300,740 (2,756)**	**<0.001**	**172.1 (388.5)**	**0.665**	**Jan–Nov 2005**	**62,313 (10,078)**	**<0.001**	**1,190 (603.3)**	**0.069**
PPI (0.949)	**Oct – Sep**	**600,577 (6,037)**	**<0.001**	**7,941 (863.7)**	**<0.001**	**Jan–Nov 2005**	**-43,942 (22,942)**	**0.076**	**2,082 (1,386)**	**0.155**
SADs (0.943)	**Oct – Sep**	**552,257 (8,253)**	**<0.001**	**5,251 (1,102)**	**<0.001**	**Oct 2004 – Nov 2005**	**-7,257 (14,975)**	**0.635**	**1,387 (1,185)**	**0.259**

***For b_0 and b_1, the regression tested if the slope (b_0) or the intercept (b_1) was significantly different than 0. For all other parameters, the regression tested for $b_i = b_i\text{-}2$. **Other NSAIDs include the following classes: M01AA (Butylpyrazolidines), M01AG (Fenamates) and M01AX (Other antiinflammatory and antirheumatic agents, non-steroids)**

DISCUSSION

A decrease in all NSAID claims was observed following rofecoxib withdrawal. Further extrapolation of the data illustrates that this reduction may be accounted for by a significant decrease in claims of coxibs. This decrease in coxib claims could be a result of safety concerns provoked by the removal of rofecoxib [11]. Physicians may have been cautious about prescribing other COX-2 inhibitors.

Incidentally, valdecoxib was eventually removed from the market in April 2005 [6] [19]. In addition, Health Canada released new restrictions on celecoxib use [19]. Although there was a slight increase of celecoxib claims immediately after the removal of rofecoxib, this increase lasted only one month. This finding reaffirms the possible concerns of the coxib family as a whole.

The significant decrease in coxib claims was stabilized three months after the removal of rofecoxib. This time delayed stabilization could be explained by several factors. First, frequent visits by pharmaceutical representatives providing samples of rofecoxib may have enabled physicians to continue distributing samples to patients who previously benefited from the drug [20]. Second, patients in Ontario are able to fill prescriptions for up to a 100 day supply [21], and may have been finishing their supply during the three month-transition period.

When NSAID claims were observed after excluding COX-2 inhibitors, different trends were noted within the other classes. These trends could be due to patients' switching to alternative NSAIDs such as AADs (i.e., diclofenac), PADs (i.e., naproxen and ibuprofen), and SADs (e.g., Aspirin). Diclofenac, naproxen, and ibuprofen were commonly utilized as controls in initial clinical trials of rofecoxib [22] [23] [24] [25] [26] [27] [28] [29] [30]. As such, physicians may have switched their patients to these standard therapies, therefore suggesting an explanation for the significant increase in claims of AADs and PADs after the removal of rofecoxib. No significant changes were observed with SADs perhaps due to the fact that SADs have several indications other than those shared with rofecoxib. For example, ASA is an analgesic, anti-inflammatory, antipyretic, anti-rheumatic, and anti-thrombotic drug [31]. Therefore, the multiple indications of SADs may have masked the overall effect of rofecoxib's removal.

With the potential increased use of non-selective COX-1 inhibitor NSAIDs due to the decreased use of COX-2 inhibitors, we postulated that there would be a higher demand for PPIs as they are commonly prescribed to patients using non-specific NSAIDs to decrease the chances of adverse GI events [18].

However, no significant changes in PPI claims were observed. Since PPIs have many indications, it is not possible to make a definitive association with the removal of rofecoxib from the market. For example, the PPI omeprazole is used not only for NSAID-associated gastric and duodenal ulcers, but also for eradication of H. pylori, reflux esophagitis, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome [31].

LIMITATIONS OF THE STUDY

The nature of the design of the study precludes the establishment of causality, thus, it is only possible to infer that the steady increase of NSAID claims were due to the removal of rofecoxib. Another limitation is that only NSAIDs were examined as the alternative therapy for COX-2 inhibitors. Therefore, changes in over-the-counter, other prescriptions (disease modifying anti-rheumatic drugs, biological response modifiers), and natural health products, may have experienced significant changes in sales. Moreover, the data we collected was solely based on claims, and therefore it was not possible to account for alternative therapies that were not covered by this method. Similarly, use of combination therapy (COX-1 NSAIDs and PPIs) could not be identified. Therefore, we were not able to identify the magnitude of the change, if any, in the proportion of patient using combination therapy after rofecoxib was withdrawn. Furthermore, we were unable to ascertain the indications for the claims. This is pertinent information for medications with multiple indications, as seen with rofecoxib, SADs and PPIs.

In conclusion, the removal of rofecoxib from the Ontario and Québec market was associated with an immediate decrease followed by a slow increase in NSAID claims. The marked increase of COX-1 after September 2004 suggests that a portion of traditional coxibs users switched to these non-selective NSAIDs. No apparent association could be observed between rofecoxib withdrawal and the monthly number of SADs and PPIs claims. It would be beneficial to investigate the claims from a Canada-wide perspective to observe if the associations observed in this study are representative of Canada.

AUTHORS' PARTICIPATION

OD performed the analyses and contributed to the text of the results and discussion. JM, NN, and YIG performed the review of the literature and contributed to the text of the introduction and discussion. RS contributed to the results and discussion sections. TRE significantly contributed to all parts of this manuscript.

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CONFLICT OF INTERESTS/DISCLAIMERS

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