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Use of Fibrates in the United States and Canada

Cynthia A. Jackevicius, BScPhm, PharmD, MSc[1,2,3,4,5], **Jack V. Tu, MD, PhD**[2,3,6], **Joseph S. Ross, MD, MHS**[7,9], **Dennis T. Ko, MD, MSc**[2,6], **Daniel Carreon, PharmD**[1], and **Harlan M. Krumholz, MD, SM**[8,9,10,11]

[1]Department of Pharmacy Practice and Administration, College of Pharmacy, Western University of Health Sciences, Pomona, CA

[2]Institute for Clinical Evaluative Sciences, Toronto, Canada

[3]Department of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto, Toronto, Canada

[4]Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA

[5]University Health Network, Toronto, Canada

[6]Division of Cardiology, Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

[7]Department of Medicine, Section of General Internal Medicine, Toronto, Canada

[8]Section of Cardiovascular Medicine, Center for Outcomes Research and Evaluation, Yale New Haven Hospital, New Haven, CT

[9]Yale University School of Medicine, Center for Outcomes Research and Evaluation, Yale New Haven Hospital, New Haven, CT

[10]Department of Epidemiology and Public Health, Section of Health Policy and Administration, New Haven, CT

[11]Robert Wood Johnson Clinical Scholars Program, New Haven, CT

Abstract

Context—Interest in the role of fibrates has intensified with the publication of the negative ACCORD trial with fenofibrate, especially since the evidence for clinical outcomes benefit for fibrates is heavily weighted on older fibrates, gemfibrozil and clofibrate.

Corresponding and reprint author: Cynthia Jackevicius, BScPhm, PharmD, MSc, BCPS, FCSHP, Western University of Health Sciences, College of Pharmacy, 309 E. Second St., Pomona CA, 91766 Phone: 909-469-5527 Fax: 909-469-5539, cjackevicius@westernu.edu.

Disclosures

Dr. Krumholz is a member of an advisory board for UnitedHealthCare and is under contract to develop performance measures for the Centers for Medicare and Medicaid Services. The remaining authors have no disclosures to report.

Author access to data: Dr. Jackevicius had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Authors' Contributions:

Study concept and design: Jackevicius, Krumholz, Tu, Ko, Ross
Acquisition of data: Jackevicius, Krumholz
Analysis and interpretation of data: Jackevicius, Krumholz, Carreon, Tu, Ko, Ross
Drafting of the manuscript: Jackevicius
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Objective—This study seeks to examine trends in the current use of fibrates, and for fenofibrate, to illuminate the relationship between differences in the availability of proprietary versus generic formulations and use and economic implications in the United States (US) compared with Canada.

Design/Setting/Patients—Population-level, cohort study using IMS Health data in the United States and Canada of patients prescribed fibrates between 2002 and 2009.

Main Outcome Measure(s)—Fibrate prescribing and expenditures.

Results—From 2002–2009, fibrate prescriptions increased 117.1% in the US, by 12,000/month to 2.1 million prescriptions/month, yet only increased by 18.1% in Canada. ($p<0.001$) Fenofibrate use was relatively constant in Canada, while in the US, it increased by 159.3%, comprising 47.9% of total fibrate prescriptions in 2002 and 65.2% in 2009. The annual ratio of generic:brand fenofibrate use in the US from 2002 to 2008 ranged from 0:1 to 0.09:1, while the ratio in Canada steadily increased from 2005 to 2008 from 0.51:1 to 1.89:1. In the US, crude fenofibrate expenditures rose from $33.2 million/month in 2002 to $129.6 million/month in 2009, while those in Canada declined from $5.6 million/month to $5.1 million/month. Fibrate expenditures per 100,000 population were 3-fold higher in the US compared with Canada in 2009.

Conclusions—During the past decade, prescriptions for fibrates, particularly, fenofibrate, increased in the United States, while prescriptions for fibrates in Canada remained stable.

Introduction

Health care reform has generated interest in identifying strategies to decrease healthcare costs, without depriving patients of health benefits such as, greater use of evidence-based therapies, including generics.[1–3] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial recently showed that fenofibrate plus statins in patients with type 2 diabetes, did not reduce cardiovascular events more than statins alone.[4] The only other fenofibrate study, Fenofibrate Intervention and Event Lowering in Diabetes (FIELD), also failed to show reduced cardiovascular morbidity and mortality.[5] These negative studies raise questions about a medication with more than $1 billion in sales in the United States (US).[6]

Evidence that fibrates have clinical benefit is mixed, with most studies focusing on lipid effects.[7,8] Fibrates primarily reduce triglycerides with only modest effects on low- and high-density lipoprotein.[7,8] The main evidence for clinical outcomes benefit are placebo-controlled trials with the older fibrates, gemfibrozil, for which some safety concerns were raised, primarily when used with cerivastatin, and clofibrate, which is no longer available due to safety concerns.[9–13] These trials exert substantial influence in the meta-analyses that show in aggregate, fibrates significantly reduce cardiac events, but not overall mortality.[7,8] The relevance of this older evidence to contemporary practice is uncertain, particularly given that the only trial to assess fibrates in a population taking statins was negative.[4] A post-ACCORD meta-analysis subgroup analysis found that individually, fenofibrate did not reduce coronary events versus placebo.[8]

Little is known about how fibrates are used in practice. Gemfibrozil and fenofibrate are available in the US and Canada, with bezafibrate only available in Canada, and Trilipix® (fenofibric acid), available only in the US.[9,10] While generic fenofibrate has long been available in Canada, it has lagged behind in the US, creating market differences.[14–15] (e-Figure 1) This study seeks to examine trends in the current use of fibrates, and for fenofibrate, to examine the association between differences in generic product availability and use and economic implications in the United States compared with Canada.

Methods

We conducted a population-level, observational cohort study using IMS Health US and Canada data from 2002 to 2009. This study was approved by the Institutional Review Board of Western University of Health Sciences. The source of prescription data was IMS Health's CompuScript Audit® in Canada and the National Prescription Audit in the US, which measures through pharmacy audits the number of dispensed prescriptions, and their actual cost to the consumer (which includes product cost, mark-ups and pharmacist fees) in retail pharmacies in Canada and retail, mail order and long-term care pharmacies in the US.[16] We had data on numbers and costs of prescriptions but we did not have information on patient or prescriber characteristics. The pharmacy outlet population is stratified by region, type (independent, chain, outlet, etc.) and size of outlet. Sample stores are selected from the reporting stores by applying criteria such as, prescription type and volume, consistency of reporting, and payment type and include approximately two-thirds of pharmacies. Data are collected electronically from the sample comprising drugstores and pharmacy outlets distributed proportionally within each stratum. After passing through various quality control checks and stability processes specific to the audits to ensure consistency and accuracy of the estimates, the collected data are projected to the population in each region and region totals are summed to provide a national estimate (US data rounded to the nearest 1,000 prescriptions nationally).[17,18]

The monthly number of prescriptions and expenditures for fibrate products in the US and Canada were the primary variables for analysis. We used descriptive statistics to characterize the number of prescriptions and costs of those prescriptions for single-entity and combination product fibrates. We standardized medication use and expenditures per 100,000 population using US and Canada 2001 census estimates.[19,20] All expenditures are expressed in US dollars. In order to achieve comparable price differences between countries, Canadian dollar costs were converted to US dollar costs using yearly purchasing power parity values from 2002–2009.[21]

We calculated rates of use of fibrate prescriptions overall and for each individual fibrate (bezafibrate, fenofibrate, gemfibrozil, fenofibric acid [the active metabolite of fenofibrate]) by country and compared the rates of change from January 2002 through December 2009. Rates of use of fibrates were estimated and compared over time and by country by constructing an ordinary least squares linear regression model using monthly utilization data and time variables by country (R^2=0.97 US; 0.09 Canada). The slopes for the rates of change were compared using t-tests. For comparison purposes, the rate of change in overall statin use over the same time period was calculated and compared in the same manner. In addition, using the same methods, the rate of change in fibrate use was compared with statin use within each country as a reference standard. The proportion of each individual fibrate prescription volume and cost compared with the total for the entire fibrate class in each country was calculated annually to determine the market share accounted for by each individual fibrate. The ratios of use of generic to brand fibrate products were compared by country overall, using Wilcoxon W, and by year, using Chi-square statistics. All analyses were performed using SPSS software, version 18.0.3 for Mac. A 2-sided p-value < 0.05 was considered statistically significant. The study was designed and written by the authors.

Results

Overall Fibrate Utilization

Fibrates accounted for 8.9% of all lipid lowering prescriptions in 2002 and 9.4% in 2009 in the United States, while in Canada, fibrate market share declined from 10.9% in 2002 to 5.3% in 2009. Between 2002 and 2009, fibrate use in the US increased by a mean of 12,000

prescriptions/month to reach 2,102,000 prescriptions in December 2009, an increase of 117.1%. In comparison, statin use increased 71.9% during this period (from 9,762,000 prescriptions per month in January 2002 to 16,781,000 prescriptions per month in December 2009). (p-value) In Canada, between 2002 and 2009, fibrate use increased to a lesser extent by a mean of 240 prescriptions/month to reach 148,849 prescriptions in December 2009, an increase of only 18.1%. (Figure 1) In comparison, statin use increased 164.1% during this period in Canada. (p-value) Fibrate prescriptions increased in both countries over the seven-year period, however, the rate of increase was substantially higher in the US compared with Canada. ($p<0.001$) Fibrate use overall was similar until 2006, when use in the US began to exceed that in Canada. (Figure 2) In 2002, there were 422 fibrate prescriptions/month/100,000 population dispensed in Canada and 356 in the US, and in December 2009, this increased to 474 and 730 prescriptions, respectively. In 2009, population-adjusted fibrate use in the US exceeded that in Canada by 50.4%. (Figure 2) Conversely, the rate of increase in population-adjusted statin use in the US was less than half that in Canada. ($p<0.001$)

Individual Fibrate Product Utilization

During the study period, fenofibrate use in the US increased by a mean of 9,000 prescriptions/month to reach 1,268,000 prescriptions in December 2009, while gemfibrozil use slowly declined with only 524,000 prescriptions dispensed in December 2009. The relative use of individual fibrates in Canada changed minimally over the study period. Since Trilipix® was introduced in the US in December 2008, its use increased by a mean of 26,000 prescriptions/month to 310,000 prescriptions in December 2009. (Figure 1) Population-adjusted fenofibrate use increased in the US between 2002 and 2009. At baseline, there were 343 fenofibrate prescriptions/month/100,000 population dispensed in Canada and only 170 in the US, yet by December 2009, there were 429 and 440 prescriptions/month/100,000 population, respectively, making fenofibrate the predominant fibrate in both countries. The rate of gemfibrozil prescriptions/month/100,000 population dispensed in Canada and the US declined from 46 and 185, respectively at baseline, to 24 and 182 in December 2009, representing minimal decline in the US and greater in Canada. Figure 2 summarizes yearly prescription rates.

Individual Fibrate Product Marketshare

In Canada, fenofibrate use was relatively constant between 2002 and 2009, while in the US, fenofibrate use increased by 159.3%, comprising 47.9% of total fibrate prescriptions in 2002 and 65.2% in 2009. (Table 1; Figure 1) In 2009, fenofibrate and fenofibric acid products combined comprised 73.9% of the market share of fibrates in the US (fenofibric acid unavailable in Canada). While gemfibrozil comprised only 10.9% and 5.2% of fibrate use in Canada in 2002 and 2009, respectively, it comprised 52.1% and 26.1% of the US fibrate market. Bezafibrate (only in Canada), comprised 7.8% of the fibrate market in 2002, decreasing to 4.6% in 2009. The annual ratio of generic:brand fenofibrate in the US from 2002 to 2008 ranging from 0:1 to 0.09:1, demonstrated lower use of generic fenofibrate each year and overall than in Canada where the ratio steadily increased from 2005 to 2008 from 0.51:1 to 1.89:1 ($p<0.001$ each year; $p=0.009$ overall). (Figure 3)

Overall and Individual Fibrate Expenditures

Between 2002 and 2009, the crude costs associated with fibrate use in the US increased from $51,541,000/month in 2002 to $164,728,000/month in 2009, with a notable rise in 2005, while costs in Canada decreased from $6,943,603/month to $5,819,921/month, most notably after 2006. An increase in fenofibrate costs in the US from $33,235,000/month in 2002 to $129,584,000/month in 2009 mirrored its increase in use, while stable use in Canada led to a slight decline from $5,551,247/month to $5,054,869/month, respectively. The decline in gemfibrozil use was paralleled by a decrease in costs to a low of $16,431,000/

month in December 2009 in the US, and $321,698 in December 2009 in Canada. (Figure 4) The proportion of total fibrate costs accounted for by fenofibrate rose from 64.5% in 2002 to 78.7% in 2009, while in Canada, the proportion rose from 79.9% to 86.9%. (Table 1) Although fenofibrate accounts for only 65.2% of use in the US, it accounts for a disproportionate 78.7% of expenditures ($p<0.001$).

Adjusted fibrate expenditures/100,000 population in 2009 were approximately three-fold higher in the US compared with Canada, despite only 50.4% more prescriptions. Despite similar numbers of population-standardized fenofibrate prescriptions, expenditures associated with this use was 2.5-fold higher in the US, with expenditures continuing to diverge through 2009. (Figure 4) For 2009, per-capita expenditure for fibrates was $6.86 in the US and $2.23 in Canada, for fenofibrate/fenofibric acid $6.20 and $1.93, and for gemfibrozil $0.66 and $0.12, respectively.

Discussion

Our study found that the use of fibrates steadily increased in the US in the last decade, but not in Canada, even as evidence emerged to question the benefit of newer fibrates in the contemporary statin era. Increased fibrate use in the US appears to be largely driven by a steady rise in fenofibrate use of nearly 200% over the study period, while in Canada, fenofibrate use remained stable. These rapidly rising rates are over double the increase in statin use in the US over the same period. This pattern is paradoxical to declines that might have been expected, since the only clinical outcomes evidence for fenofibrate during our study period was the FIELD trial, which failed to find a significant reduction in the primary endpoint of coronary events in a diabetes population.[6] In fact, more robust outcomes evidence in reducing cardiac death and non-fatal MI supports the preferential use of gemfibrozil, though these studies preceded the statin era and enrolled patients with slightly worse lipid profiles.[8,13,22] Prior reports have noted an increasing use of fenofibrate since 1999, over five years before publication of FIELD.[23] Our study shows that the use of fenofibrate was increasing both before and after the FIELD study was published, suggesting that other factors besides clinical trial evidence are influencing fibrate prescribing.

While fenofibrate use rose in the US, gemfibrozil use declined. The increased use of fenofibrate in favor of gemfibrozil may be due to its greater perceived safety relative to gemfibrozil.[11,12,24] However, fenofibrate use has been steadily increasing since 1999, preceding 2000, when the first pharmacokinetic study signaled a potential statin-gemfibrozil drug interaction, and certainly prior to 2001, when the gemfibrozil-cerivastatin drug interaction became apparent.[25,26] Therefore, while this reasoning may account for some to switch or preferentially use fenofibrate over gemfibrozil, the rise in brand name fenofibrate use far exceeded declines in gemfibrozil use. Additionally, subsequent research has demonstrated that gemfibrozil could be used safely in patients receiving statins, such as the Veterans Affairs study that found a rhabdomyolysis rate with combined use was only 0.16%, well within expected rates.[11,12,27]

Our second major finding was that there was a strong preference observed for prescribing brand over generic fenofibrate products in the US, but not in Canada. The US pattern is unusual in that brand name formulations typically comprise only ~25–30% of product marketshare for medications 12 years post-product launch.[28] Instead, brand name fenofibrate (mainly Tricor®) was the predominant fenofibrate used in the US, accounting for 90% of the fenofibrate market share until recently, while in Canada, the comparable Lipidil® brand declined from 66% to 35% of fenofibrate marketshare during the study. To illustrate this disparate pattern between countries, for every 100 brand name fenofibrate prescriptions

dispensed in 2008, 166 generic fenofibrate prescriptions were dispensed in Canada, while in the US, only 9 generic fenofibrate prescriptions were dispensed.

Access differences to generic fenofibrate between the US and Canada likely contributed to vastly different patterns of fenofibrate use, and are associated with a great economic burden for US consumers and third-party payers.[9] Although both countries had similar rates of population-adjusted fenofibrate use between 2007–2009, US fenofibrate expenditures exceeded those in Canada by nearly three-fold. Using 2008 rates of fenofibrate use, had the US market had open access to generic fenofibrate formulations, and prescribed with a generic:brand ratio similar to that in Canada where access was not limited, we would expect $364 million/year to be saved.

While Canada has benefited from access to generic fenofibrate for over a decade, creative patent protection actions with brand name fenofibrate products in the US appear to have instead allowed brand name fenofibrate products to dominate the market, potentially contributing to escalating fibrate drug costs.[29,30] The preferential use of brand name fibrates continues with the latest product, Trilipix®, the active metabolite of fenofibrate, showing a rate of increase in utilization that far exceeds that even for fenofibrate, even though this specific formulation has yet to be evaluated in clinical outcomes studies.[6] Trilipix's® advantageous unique indication approves it for use with statins, while all other fibrates have warnings against combined use with statins.[9] Given that this distinctive indication simplifies concomitant fibrate-statin therapy and may therefore facilitate the use of Trilipix® for clinicians, prompt evaluation of its efficacy in reducing cardiovascular morbidity and mortality when added to the current standard of lipid therapy, statins, along with evaluation of its safety is warranted.

During our study, new clinical outcomes evidence should have steered usage away from fenofibrate during the period where there was escalating use of fibrates, particularly fenofibrate. While clinicians may have been reluctant to initially accept the negative findings from the FIELD study in 2004, now in 2010, ACCORD, the only fibrate study to use a statin-treated comparison group, likewise found no clinical outcome benefit with fenofibrate plus a statin compared with a statin alone, reiterating the negative findings from FIELD.[4] At a time when a "less-is-more" approach is being embraced by the medical community, this ever-increasing pattern of brand name medication use without evidence of clinical outcomes benefit warrants attention and close scrutiny in order to ensure medication use is optimized for clinical outcomes benefit, while avoiding unwarranted costs.[2,31] Current US guidelines recommend that fibrates, without regard to type, should only be considered for reducing very high TG to prevent pancreatitis, for treatment of dysbetalipoproteinemia, and as supplemental therapy to statins for non-HDL cholesterol in diabetics.[32,33] The Canadian guidelines, 2006 revision, now more cautiously reserves fibrates primarily for severe hypertriglyceridemia. Continued caution is warranted in guideline recommendations for fibrates as we await evidence of clinical outcomes benefits with fibrates.

Our study has some limitations. IMS Health uses data collected from audits of prescriptions dispensed to describe general trends in drug utilization. These data do not provide exact drug utilization by individual patients or providers to determine the appropriateness of drug use. We did not have access to state-level data, patient or prescriber characteristics or clinical data, such as medical conditions, or lipid profile to determine whether fibrate prescribing was clinically appropriate. Although increased fibrate use was demonstrated, its relationship to patient outcomes could not be evaluated.

Conclusion

Fibrates are used commonly in the US and Canada, with use rising steadily in the US over the last decade, despite negative fibrate trials in patients with diabetes published in the statin era, while use in Canada remained stable. Fenofibrate dominates the market, despite it having the least supportive clinical outcomes evidence. While this growth, in the setting of a strong preference for brand over generic fenofibrate in the US has been associated with escalating medication costs, improvement in clinical outcomes is uncertain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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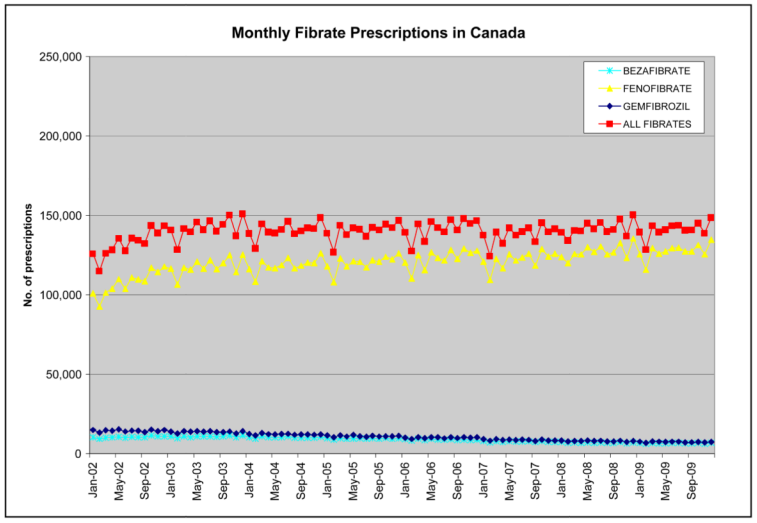

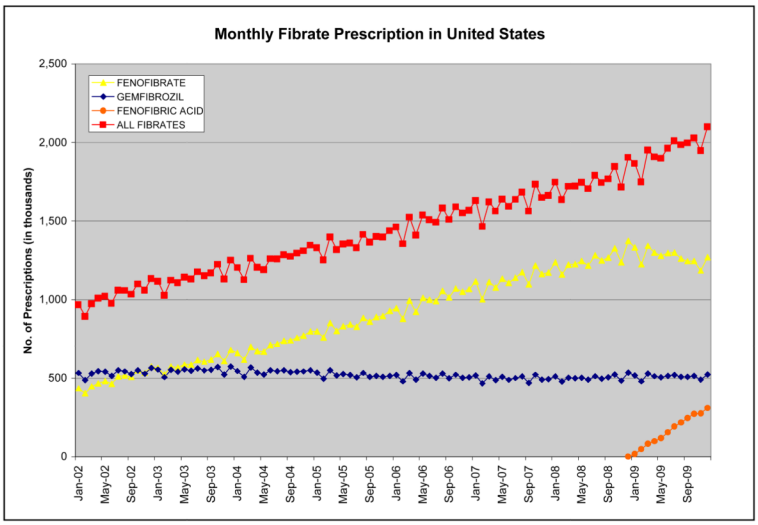

Figure 1.

Figures 1A and 1B. Crude Number of Fibrate Prescriptions in the US and Canada per Month
NOTE: Y-axis for the United States is 10-fold greater than Canada, reflecting the approximate population differences between countries.
Source: IMS Health-US National Prescription Audit and IMS Health-Canada, Canadian CompuScript Audit®.

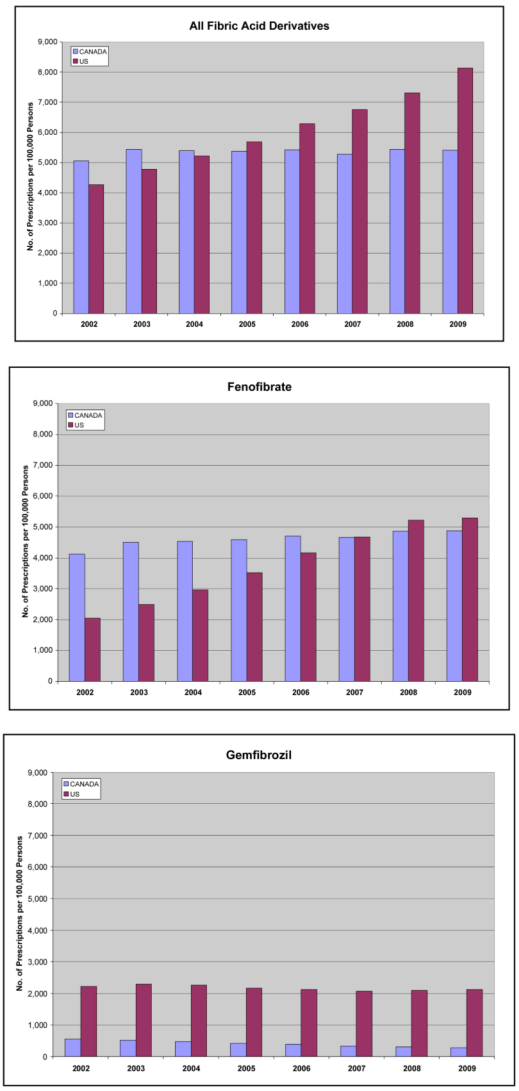

Figure 2.

Figures 2A, 2B, 2C. Standardized Annual Fibrate Prescriptions per 100,000 Population by Country

Source: IMS Health-US National Prescription Audit and IMS Health-Canada, Canadian CompuScript Audit®.

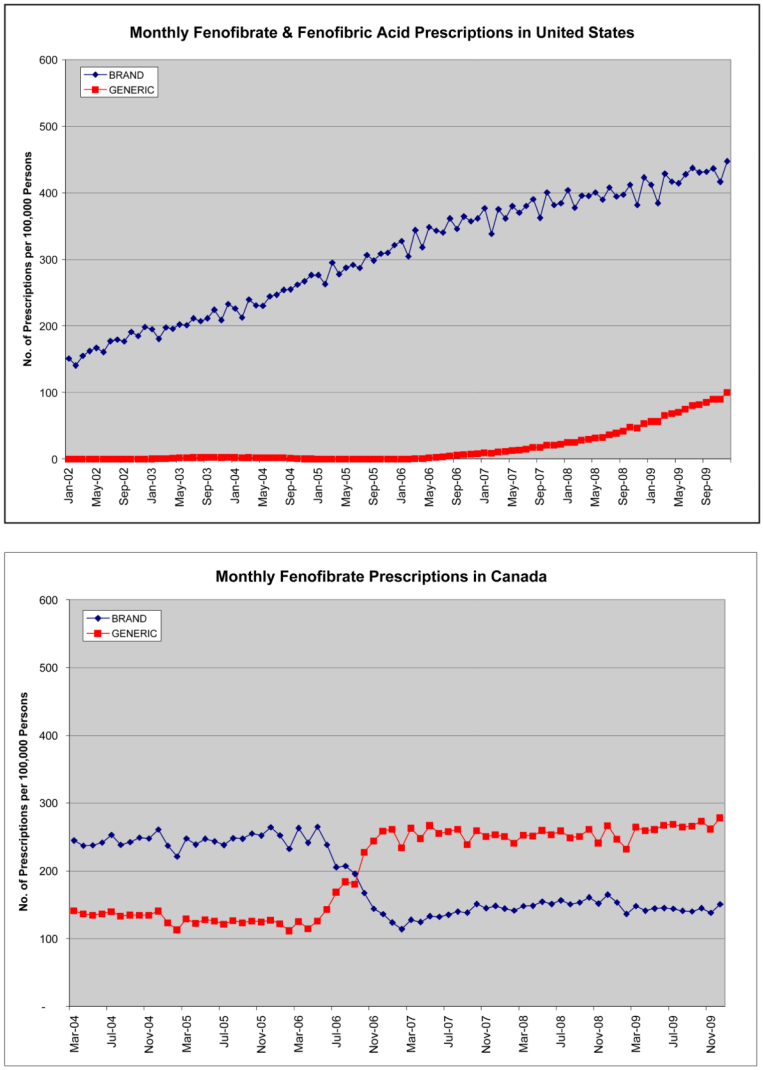

Figure 3.

Figures 3A and 3B. Number of Brand and Generic Fibrate Prescriptions in the US and Canada per Month

Source: IMS Health-US National Prescription Audit and IMS Health-Canada, Canadian CompuScript Audit®.

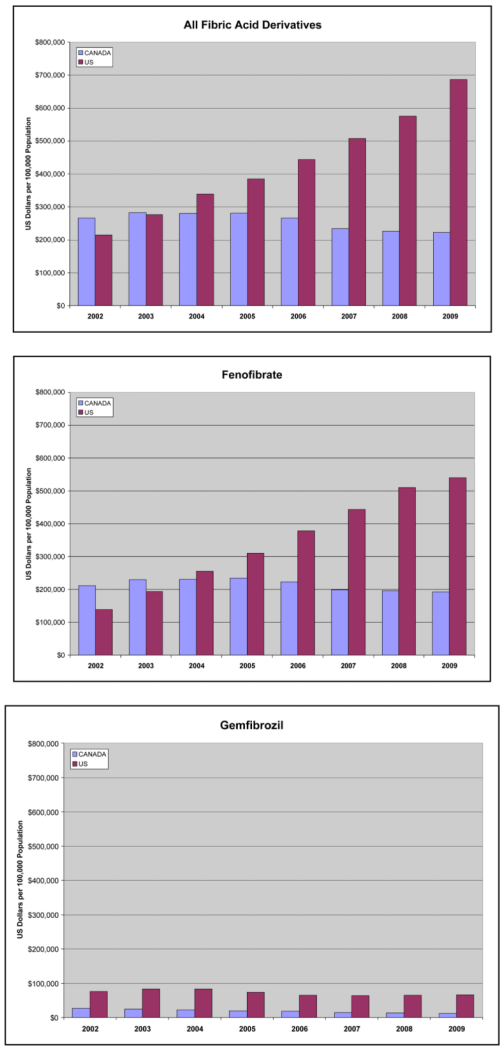

Figure 4.

Figures 4A, 4B, 4C. Standardized Annual Fibrate Prescription Expenditures per 100,000 Population by Country

Source: IMS Health-US National Prescription Audit and IMS Health-Canada, Canadian CompuScript Audit®.

Table 1

Annual Prescription Volume and Expenditures of Fibrates Overall and by Individual Fibrate

	2002		2003		2004		2005		2006		2007		2008		2009	
	thousands	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)
Volume of Prescriptions																
Canada																
Bezafibrate	125	7.8%	129	7.5%	123	7.3%	114	6.8%	106	6.2%	91	5.5%	84	4.9%	78	4.6%
Fenofibrate	1,291	81.2%	1,416	82.9%	1,423	84.1%	1,441	85.4%	1,477	86.7%	1,464	88.3%	1,526	89.5%	1,529	90.2%
Gemfibrozil	173	10.9%	164	9.6%	146	8.6%	132	7.8%	120	7.1%	103	6.2%	95	5.6%	88	5.2%
Total	1,589		1,709		1,692		1,687		1,703		1,657		1,705		1,695	
United States																
Fenofibrate	5889	47.9%	7,175	52.1%	8,539	56.8%	10,147	62.0%	11,985	66.2%	13,497	69.4%	15,033	71.4%	15,271	65.2%
Gemfibrozil	6407	52.1%	6,586	47.9%	6,494	43.2%	6,225	38.0%	6,120	33.8%	5,960	30.6%	6,034	28.6%	6,121	26.1%
Fenofibric acid	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2,031	8.7%
Total	12,296		13,761		15,033		16,372		18,105		19,457		21,067		23,423	
Expenditures																
Canada																
Bezafibrate	$8,474	10.2%	$8,901	10.0%	$8,649	9.8%	$8,189	9.3%	$7,459	9.0%	$6,304	8.6%	$5,620	7.9%	$5,358	7.7%
Fenofibrate	$66,615	79.9%	$71,881	81.1%	$72,400	82.3%	$73,706	83.6%	$70,226	84.3%	$62,520	85.0%	$61,495	86.4%	$60,658	86.9%
Gemfibrozil	$8,230	9.9%	$7,893	8.9%	$6,916	7.9%	$6,232	7.1%	$5,620	6.7%	$4,767	6.5%	$4,097	5.8%	$3,822	5.5%
Total	$83,323		$88,675		$87,966		$88,127		$83,306		$73,590		$71,212		$69,839	
United States																
Fenofibrate	$398,815	64.5%	$557,866	70.0%	$735,817	75.5%	$894,477	80.8%	$1,088,418	85.2%	$1,279,653	87.4%	$1,471,662	88.8%	$1,555,005	78.7%

	2002		2003		2004		2005		2006		2007		2008		2009	
	thousands	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)	*thousands*	Proportion of Total (%)
Gemfibrozil	$219,670	35.5%	$239,526	30.0%	$239,193	24.5%	$212,776	19.2%	$188,818	14.8%	$184,348	12.6%	$186,456	11.2%	$190,989	9.7%
Fenofibric acid											$0	0.0%	$1	0.0%	$230,740	11.7%
Total	$618,493		$797,392		$975,010		$1,107,253		$1,277,236		$1,464,001		$1,658,119		$1,976,734	

Source: IMS Health-US National Prescription Audit and IS Health-Canada, Canadian CompuScript Audit®.