

COMMENTARY

Opioid promotion in Canada: A narrative review

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Abstract

Studies based on the United States Open Payment database have demonstrated an association between the promotion and prescribing of opioids. An equivalent database does not exist in Canada; therefore, I undertook a narrative review of the literature. In 2015, Purdue spent over CAN\$4 million promoting a single product and generated over 160 pages of journal advertising. In the current review, I describe each of the six different forms of promotion that companies used to try and influence prescribing behaviour: messages from sales representatives, journal advertisements, company involvement in undergraduate medical education, key opinion leaders, clinical practice guidelines, and the funding of patient groups. Recent regulatory changes have decreased the volume of opioid promotion, but it would be incorrect to assume that it does not continue to influence the prescribing of this class of drugs.

Keywords: Canada, doctors, drug promotion, opioids, pharmaceutical industry

Introduction

There is compelling evidence of an association between exposure to information from pharmaceutical companies and prescribing quality. A systematic review by Spurling et al investigated the impact of drug promotion on prescribing quality, volume, and cost [1]. Despite including 58 studies, this review did not find evidence of a net improvement in prescribing following interactions between prescribers and pharmaceutical companies in terms of the appropriateness of the prescriptions written, the cost of the drugs prescribed, or the number of prescriptions. The findings varied, with some studies showing an increase in prescribing quantity and costs, a decrease in quality, or no association, except for one US econometric study that reported both greater prescribing frequency and greater price sensitivity following sales visits.

More recent systematic reviews, which focus on a subset of prescribers and non-trainee physicians [2], or which are restricted to a narrative synthesis of results [3], align with the study by Spurling et al. These collective results support the hypothesis that promotion is associated with increased prescribing costs and volumes as well as aligning with companies' interests in terms of increased sales and market share.

Specifically, regarding opioid promotion, studies conducted in the United States (US) using the Open Payments database have demonstrated an association between promotion and interactions with the pharmaceutical industry and the quality of prescribing of opioids. Physicians who received any opioid-related payments from the industry in 2014 were associated with generating 9.3% more opioid claims in 2015 compared with physicians who received no such payments [4]. A second study linked the marketing of opioid products with increased opioid prescribing and subsequently an elevated mortality from overdoses [5]. A third study [6] demonstrated that opioid-related payments to physicians from pharmaceutical manufacturers were associated with a greater likelihood that Medicare beneficiaries would be prescribed opioids at dosages exceeding those recommended by the Centers for Disease Control and Prevention despite having no hospice care claims or diagnoses of cancer that could have justified those higher doses [7].

It is highly unlikely that promotion has a significantly different impact on prescribing in Canada when compared to the US. However, due to the lack of a database similar to Open Payments in Canada, replication of the research is not feasible. While the promotion of opioids is not the sole cause of the epidemic of overdoses and deaths [8], it is widely acknowledged that it played a major role, particularly in its early stages [9].

An analysis of the nature and extent of promotion is necessary to understand its role in the misprescribing of prescription drugs overall, and within specific drug classes in particular. Understanding the role of promotion can not only shed light on past occurrences but also helps policymakers take steps to safeguard against similar occurrences in the future. Ultimately, it contributes to bringing a measure of justice to individuals and health systems affected by the promotion of opioids in Canada. The government of British Columbia is pursuing a class action lawsuit against the global consulting company, McKinsey & Co, over its alleged

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role in boosting opioid sales [10]. Simultaneously, another class action lawsuit has been undertaken by the firm Koskie Minsky on behalf of Canadians who were prescribed and subsequently developed an addiction to opioids [11]. In both instances, a crucial part of the evidence hinges on the extent and effect of the promotion of opioids on the prescribing behaviour of doctors.

This narrative review draws on a wide range of material, including a search of the US National Library of Medicine using the terms (opioids) and ((promotion) or (advertising)) and (Canada). There were no restrictions on the language or date of the research identified. The search was supplemented by reports from the Intercontinental Marketing Statistics (IMS) Brogan (now IQVIA) on the volume of promotion between 2013 and 2016, newspaper articles and other media reports, the author's extensive experience in analysing drug promotion in Canada, and discussions with other Canadian and international experts who have examined the extent of opioid promotion in Canada.

This comprehensive review begins by presenting evidence on how the Health Canada approved wording in the product monograph (PM) for Purdue Pharma's OxyContin (controlled-release oxycodone), facilitated the dissemination of misleading promotion of the drug. (In the US, the equivalent of the PM is the Label, and in the United Kingdom and Europe, it is the Summary of Product Characteristics.) The review then presents data about promotional spending on opioids and continues by examining different forms of promotion — first presenting a summary of key international literature on the topic and then discussing Canadian evidence on each form of promotion, specifically of opioids. Finally, it examines recent efforts by Health Canada to control and limit the promotion of opioids.

Misleading information in OxyContin's product monograph

Companies are required to only use material from the PM in their promotional activities. However, this requirement means that if the information within the PM is inaccurate or incomplete, it may be reflected in the promotional material. Similarly, any information that is absent in the PM, such as safety details, is not mandated to appear in advertisements or company-sponsored talks.

Bavli has detailed the initial wording in the PM and how it enabled Purdue to misleadingly promote OxyContin. The following description is drawn from his work [12]. When OxyContin first received approval from Health Canada in 1996, the PM included the sentence: "Drug abuse is not a problem in patients with pain in whom oxycodone [OxyContin] is appropriately indicated." This statement appears to be based on a letter to the *New England Journal of Medicine*, which provided no evidence to back its assertion regarding the lack of abuse potential [13]. Subsequently, this sentence appeared in Purdue's Canadian promotional material. Additionally, Health Canada also did not require the inclusion of a

statement regarding the risk of addiction to OxyContin, although 5 of the 24 studies that were referenced in Purdue's submission to the agency discussed the addictive potential of opioid-based products. Finally, no recommended maximum dose was specified, allowing the drug to be marketed with no upper-dose threshold.

It took Health Canada until 2006 to revise OxyContin's PM and strengthen the warning on how to take the pill, state the danger of breaking, chewing, or crushing the pills, and minimally change the misleading sentence regarding the abuse liability of the drug, adding the word "usually" in the sentence: "Drug abuse is usually not a problem...". Many of these changes had been made by the US Food and Drug Administration (FDA) five years earlier, and its action was known to Health Canada, although not emulated.

Spending on opioid promotion

Table 1 provides a summary of data extracted from annual Canadian Pharmaceutical Industry Reports from IMS/Brogan regarding Purdue's spending between 2013 and 2016 on the promotion of three opioid products: Butrans (transdermal buprenorphine), OxyNeo (controlled-release oxycodone), and Targin (oxycodone/naloxone). Although the data is incomplete, it indicates that in a single year, Purdue spent over CAN\$4 million promoting a single product (Butrans). Additionally, in another year, it placed advertisements in more than 160 pages of journals for Targin [14–17].

Purdue disclosed that between 2016 and 2020, it distributed more than CAN\$10 million to healthcare professionals, healthcare organisations, and for international travel to healthcare professionals [18]. Since no further details are provided, it is unclear if all that money was for promotional purposes.

In addition to the data in Table 1, IMS reports that in 2016, sales representatives made more than 6,000 visits to promote Kadian (morphine) — a drug made by BGP Pharma [17].

Messages delivered by sales representatives

Sales representatives, the individuals from pharmaceutical companies who visit doctors in their offices and clinics, are seen by about 65% of Canadian physicians [19]. An international study involving primary-care physicians in Canada, France, and the US examined the messages that sales representatives supplied to primary-care physicians about the effectiveness and safety of the medications they were promoting. The results suggested a serious lack of information sharing on the harmful effects of the promoted medicines. Sales representatives generally failed to provide "minimally adequate safety information" [20]. Information on health benefits was provided twice as often as information on harm, with not a single harmful effect mentioned in over half the promotions in the three sites in Canada and the US [20].

Table 1: Promotion spending by Purdue on opioids, 2013-2016

Drug	2013					
	Total expenditures (details and ads) (000)	Journal ad expenditures (\$000)	Number of details (000)	Number of detail minutes (000)	Number of ad pages	Number of samples (000)
Butrans		528	15			
OxyNeo	2014	551	17	81	143	1
Targin	3718	611	20	127	161	2
2014						
Butrans		275	14			
OxyNeo		428	13			
Targin			10			
2015						
Butrans	4171	329	26	148	61	5
OxyNeo		0	12			
Targin		263	16			
2016						
Butrans		181	12			
OxyNeo		20	5			
Targin		261	7			
Source: References 14-17						

That same study had primary-care physicians report what sales representatives had told them about the opioid products they were promoting. Table 2 summarises the results from Canada, all of which emphasise the benefits of opioids and downplay the harms [21].

In 2014, there were discussions between McKinsey and Purdue Pharma on how McKinsey could “help Purdue determine whether there are opportunities to ‘better target and reach high-potential prescribers’ and increase the motivation of Purdue’s pharmaceutical sales representatives by analyzing ‘what opportunities exist to change incentive compensation to better align the sales force goals to company objectives’” [10]. There is no information available on what, if any, promotional activities came of these discussions.

Journal advertising

A systematic review of the quality of pharmaceutical

Table 2: Comments of sales representatives to Canadian primary care doctors about opioids

Theme	Comment	Product
Effectiveness	effective and safe	tramadol
Safety	Tramacet is well-tolerated and safe	tramadol
Convenience	longer 24-hour effect	tramadol
	ease of dose adjustments	morphine
Substitution	of interest when stopping NSAIDs in patients with private insurance who require treatment for chronic pain	tramadol
Low addiction/abuse	good drug if you are concerned about drug abuse, it cannot get abused	hydromorphone
	safer than codeine and other opiates and non-addictive	tramadol
Superiority	better option than Tylenol 3 [codeine + acetaminophen]	tramadol
Multiple indications	use in a new indication	tramadol + acetaminophen
Reminder	reminder of the existence of the product	hydromorphone
Source: Reference 21		

advertisements in medical journals examined 24 studies from 26 countries published between 1975 and 2006 [22]. While the majority of the ads mentioned the product’s brand and generic names, other information needed for rational prescribing, including contraindications, interactions, side effects, warnings, and precautions was less commonly provided. Moreover, when such details were provided, they were often presented in fine print. Notably, a few of the references supporting the claims were methodologically rigorous, with the majority being funded by the manufacturer [22]. Only 38% of the references pertained to clinical trials, systematic reviews, or meta-analyses. Unpublished data, listed as “data on file”, were often not supplied on request, leading to the conclusion that globally information quality is poor. By 2008, nearly half the physician-directed ads in US medical journals failed to adhere to at least one guideline from the FDA’s content regulations. In addition, ads did a poor job of conveying basic information necessary for safe prescribing — with most failing to quantify serious risks, over one-quarter failing to quantify benefits, and nearly half providing no verifiable references [23]. More recent studies continue to

confirm that claims in ads are not supported by high-quality evidence [24–26].

While the significance of medical journal advertising is decreasing, as evidenced by reduced company expenditures, it remains an important element in promotion. In Canada, journal advertising is regulated by the Pharmaceutical Advertising Advisory Board (PAAB), an independent organisation [27]. Of its board of 13 members, 5 come from organisations that potentially financially benefit from pharmaceutical advertising. A study comparing three methods of regulating advertising — direct government regulation, industry self-regulation, and regulation by the PAAB — found that direct government regulation was by far the best in terms of overall ad quality [28].

In 2014, an ad for Butrans was featured in *Canadian Family Physician*. While the ad promoted the product for “moderate” pain, it failed to provide a clear definition of the term. The “potential for abuse and diversion” and “dependence” were only mentioned among multiple other warnings in the main body of the ad and in the detailed prescribing information. However, the latter was not contiguous with the rest of the ad. In addition, the warnings in the main body of the ad were in much smaller print than the description of the benefits of the medication.

A 2016 ad for Targin in the *Canadian Medical Association Journal* was misleading in several respects. Information about the “addiction, abuse, and misuse” of Targin was buried in the fine print and not presented in the display portion of the ad. The ad prominently featured the statement, “Demonstrated reduced drug liking relative to oxycodone, when administered intranasally or intravenously.” Below this statement, in barely visible print, was the acknowledgment that the “clinical significance of these results has not yet been established.” The extent of the reduction in liking was not disclosed. Intranasal and intravenous administration were likely tested because those are the routes most commonly used by recreational drug users. Although Targin is only available in an oral formulation, there was no information in the ad about the potential of abuse by people who had legitimately been prescribed this dosage form.

While these ads were not systematically sampled and were only analysed by a single individual, they were published in two of the most widely read general Canadian medical journals and therefore probably seen by tens of thousands of doctors. The analysis of the ads was based on criteria developed to determine the accuracy and objectivity of the information provided in print advertisements [22, 28]. The findings in the two ads described above were broadly substantiated by a systematic assessment of opioid ads appearing in five North American general medical journals, including *Canadian Family Physician* and *Canadian Medical Association Journal*. Kirubarajan et al assessed the mention of serious safety issues such as addictive potential and the possibility of death [29]. Any mention of those issues was

absent in 46.6% and 74% of the ads, respectively. Collectively, the ads cited 19 studies, all of which were either funded by pharmaceutical organisations or had pharmaceutical company employees as authors. None of the ads cited high-quality evidence to substantiate their claims.

Company involvement in undergraduate medical education

A systematic review examining the extent and effect of interactions between medical students and the pharmaceutical industry revealed that between 40% to 100% of students reported that they had interacted with the industry. Eight studies identified a correlation between the frequency of contact and positive attitudes toward industry interactions. The overall conclusion of the authors was that “undergraduate medical education provides substantial contact with pharmaceutical marketing, and the extent of such contact is associated with positive attitudes about marketing and skepticism about negative implications of these interactions” [30].

Commencing in 2000, the University of Toronto has annually offered a one-week course on pain management to all its health science students. Between 2002 and 2006, the course was funded by unrestricted educational grants from four pharmaceutical companies, including Purdue, to a total of CAN\$117,000. In some years, but not others, the student manual disclosed the industry funding sources [31].

Until 2010, students were provided with a book on pain management, which was produced by Purdue. The book contained a “modified World Health Organization analgesic ladder” that listed oxycodone among weak opioids. In actuality, oxycodone is at least 1.5 times more potent than morphine and the original World Health Organization pain ladder does not mention oxycodone. Dr Roman Jovey was one of the co-authors of the book, an unpaid guest lecturer for the course, and on the speakers’ bureau for Purdue. One of Dr Jovey’s slides included an alleged direct quote from a 2006 *Canadian Medical Association Journal* article saying placebo-controlled trials showed “strong” and “consistent” evidence that opioids relieve pain and improve function for patients with chronic, non-cancer pain. However, the article in question did not contain the quote, nor did it use the words “strong” and “consistent” to describe the evidence. In addition, Dr Jovey did not disclose his conflicts of interest in his slides, although he said that they were verbally disclosed. He described the misquote as an “inadvertent error.” The controversy around Purdue’s involvement eventually led to the University of Toronto holding an informal inquiry into the management of the course [31].

Key opinion leaders

“Key opinion leaders” (KOLs) are often paid by pharmaceutical companies to give talks to groups of physicians about the management of medical diseases. In the US, a 2007 survey found that 16% of physicians (about

141,000) received payments for serving as a speaker or being part of a speakers' bureau [32]. Over a span of five months in 2013, companies seemingly disbursed speaker payments of \$400 or more to 55,000 US doctors [33]. According to an internal Merck document, doctors who attended a lecture by a KOL on Vioxx (rofecoxib) wrote an additional \$623.55 worth of prescriptions for the drug over a 12-month period compared to doctors who did not attend [34]. After factoring in the extra cost associated with hiring a doctor to speak, Merck calculated that the "return on investment" of the doctor-led discussion group was 3.66 times the investment versus 1.96 times for a meeting with a sales representative.

One of the earliest published examples of the use of KOLs in Canada to promote the use of opioids for managing chronic non-malignant pain was a Toronto-based workshop in 1993. It was sponsored by Purdue and featured Dr Russell Portenoy, the editor-in-chief of the *Journal of Pain and Symptom Management* and director of analgesic studies at Memorial Sloan Kettering Cancer Center. Dr Portenoy's talk promoted the notion that opioid-resistant pain did not exist, that the risk of addiction in patients treated for pain with opioids was probably very low, and that clinically significant adverse pharmacologic outcomes from opioid use were uncommon [35]. A second example was the invitation from Purdue to family physicians in Ontario in 2012 to attend an evening dinner and talk on responsible opioid prescribing by Dr Joel Boardman, the medical director of the Complex Pain Program of the First Step Medical Clinics (Personal communication, Dr. C. Oliver, June 13, 2012).

In 2011, 100 Canadian doctors were paid CAN\$2,000 per talk for giving lectures about products manufactured by Purdue. One of those doctors was Brian Goldman, the host of the Canadian Broadcasting Corporation (CBC) Radio's "White Coat, Black Art". According to Goldman,

In the early 1990s, I began to be paid by a pharmaceutical company to lecture health professionals at hospital rounds or at continuing medical education events, such as conferences and dinner meetings. As well, I appeared in a number of educational videos on pain management and prescription drug abuse that were supported by educational grants from drug companies. If I travelled to another city to give the talk, it was on the company's dime. I was put up in five-star hotels and taken to nice restaurants. When I travelled across the continent, I was invariably given a ticket in business class. To my knowledge, the companies that sponsored my talks had no direct input into the opinions I expressed.

As I gave these talks, I convinced myself that I was able to educate thousands of health professionals and law enforcement officers. I also got the sense that the entire world of organized medicine was blasé about growing links between Big Pharma and continuing medical education... One conference organizer told me that without sponsorship from pharmaceutical companies, the cost of conference

tuition would double, driving tens if not hundreds of physicians away [36].

Clinical practice guidelines

Clinical practice guidelines (CPGs) are essential for doctors to deliver evidence-based healthcare. However, the organisations and committees that sponsor and write CPGs often have financial conflicts of interest (FCOIs) involving pharmaceutical companies whose products are recommended in the CPGs. The existence of FCOIs is a concern as they may compromise the quality of the CPGs. For example, Cosgrove et al [37] evaluated the American Psychiatric Association's Practice Guideline for the Treatment of Patients with Major Depressive Disorder. All members of the guideline development committee disclosed financial ties to industry. Fewer than half the studies cited in support of the recommendations met the criteria for high quality, and 17.2% did not measure clinically relevant results. One-fifth of the references were not congruent with the recommendations [37].

An appraisal of 13 guidelines on opioid prescribing, produced between 2007 and 2013 (12 guidelines from the US and one from Canada), concluded that the pharmaceutical industry had a pervasive presence in the CPGs by virtue of the fact that the guidelines had an average of 3.3 "red flags", ie, items known to introduce potential bias from financial conflicts of interest [38]. Moreover, the authors felt that their estimate of the number of red flags was conservative. They reached this conclusion because the organisations that produced the guidelines failed to regularly employ mechanisms — such as appointing a methodologist in a lead role or conducting an external review to minimise bias — and the guidelines themselves had missing or incomplete information on the sponsoring organisation's funding sources and panel members' conflicts of interest. The single Canadian guideline had three red flags — committee stacking, limited involvement of a methodologist, and lack of non-physicians or patients on the guideline committee.

Funding of patient groups

A recent systematic review of the literature on industry funding of patient groups examined four studies that investigated the association between patient-group funding and the positions that these groups took. It concluded that industry-funded groups tended to take positions favourable to their sponsors [39].

Patient group funding by pharmaceutical companies is widespread in Canada. A recent study documented that 11 member companies of Innovative Medicines Canada made donations to a total of 114 patient groups. (The other 33 members did not report if they provided donations.) [40]. A 2018 report from the CBC, Canada's public broadcaster, examined the company funding of Canadian patient

advocacy groups with a focus on pain [41]. Purdue was a “founding partner” of the Canadian Pain Coalition (CPC) but had not funded the group since 2010. The Chronic Pain Association of Canada was also listed by Purdue Canada as one of its grant recipients in 2016 and 2017. In 2017, it received CAN\$18,000 from the pharmaceutical industry to arrange and hold meetings with leaders of local support groups in Toronto and Atlantic Canada. A spokeswoman for Action Ontario, a group that advocates for people suffering from neuropathic pain, said that all of its funding comes from the industry. However, she emphasised that there were no strings attached to the donations. Similarly, a spokesman for the People in Pain Network said that he happily accepts industry funding because his group is run by volunteers on a shoestring budget. “We do not allow them to dictate what we do with it,” he told CBC News, adding that Purdue has provided funds in the past.

Health Canada’s actions to reduce promotion

In June 2018, in response to escalating opioid-related harms, Dr Ginette Petitpas Taylor, the then federal health minister, issued a letter to Canadian manufacturers and distributors of opioids requesting their commitment to voluntarily cease all marketing and advertising of opioids to healthcare professionals [42]. A few days later, Purdue announced that it would stop marketing all of its opioid products in Canada [43]. (In February 2018, Purdue stopped marketing opioids in the US, but it said that the policy would not apply to Canada [44].) Nine months later, Health Canada proposed placing a series of conditions on the promotion of all opioids that were equal to or stronger than morphine. These proposals included mandating that print and electronic ads and pamphlets should only contain statements that have been authorised by Health Canada for inclusion in the PM — the official summary of the product’s characteristics — and that any statements would have to be presented verbatim as they appear in the PM and convey the benefits and risks of opioids in a balanced way [45].

The response from brand-name and generic companies to the letter about voluntarily ceasing marketing and advertising of opioids provides insight into how the companies viewed their marketing actions and their sense of responsibility for the consequences of those activities. Overall, 103 companies and organisations were contacted by Health Canada and Eisenkraft Klein et al analysed the responses of the 41 that responded [46]. Their findings highlighted companies’ continuing efforts to frame their messaging as “information” and “education” rather than “advertising” or “promotion” in ways that served their interests in being able to continue to sell opioids. The Canadian Generic Pharmaceutical Association along with a number of generic companies maintained that they were absolved from opioid-related harms because, while they distributed opioids, they did not market or advertise them [46]. This framing of promotion as “information provision was... pushed even further to position the importance, to the

public good, of industry involvement in the discourse with health professionals about the safety, efficacy, and appropriateness of opioid analgesics” [46]. In addition to attempting to reframe their activities as being non-promotional, industry responses also repeatedly attempted to emphasise that their promotional activities were sufficiently regulated by their own internal codes of conduct.

Conclusion

Focusing on the promotion of opioids in Canada may seem moot in light of recent actions by the federal government and industry. However, diverting attention from this issue would be a mistake. Despite the measures taken by Health Canada, the number of opioid prescriptions dispensed in Canada only declined marginally from 38.5 million in 2019 to 37.2 million in 2021. While the use of opioids has declined, this has been minimal, going from 12.6% of the general population in 2019 to 12.2% in 2021. Similar minor declines were seen in the number of people who received high average morphine milligram equivalent doses [47].

There is no publicly available evidence on the volume of current opioid promotion, so it is impossible to establish an association between promotion and prescribing. However, based on previous studies on the effects of promotion — summarised by the systematic review by Spurling et al [1] — it is likely that it is continuing to influence the prescribing of some physicians. As the writer and philosopher George Santayana is reported to have said, “Those who cannot remember the past are condemned to repeat it” [48]. This narrative review about how opioids were promoted in Canada is hopefully a contribution to ensuring that we do not repeat the same mistakes in the future.

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