

The danger of imperfect regulation: OxyContin use in the United States and Canada

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Abstract. Drug companies aggressively market their products to increase sales and economic rewards. Different countries have different regulatory regimes for controlling promotion. In the United States control rests directly with the Food and Drug Administration whereas Canada relies on a mixture of voluntary self-regulation and an autonomous agency. Each method has significant weaknesses. We examine these weaknesses by analyzing the promotion of OxyContin (the time release version of the opioid oxycodone) by Purdue in Canada and the United States. We then look at the association between promotion and the misuse and abuse of OxyContin in both countries. Finally, we advance specific recommendations for regulating promotion for drugs that may have a high abuse potential.

Keywords: Canada, United States, OxyContin, promotion, pharmaceutical industry, drug regulation

1. Introduction

The research-based pharmaceutical industry continues to be challenged financially by limited product pipelines and competition from generic manufacturers as patents on major products expire. As a result, pharmaceutical companies are tasked with the often times competing goals of maximizing profits and health outcomes. The drive for profit, particularly, in an intensely competitive marketplace, may foster unethical practices and even scientific misconduct unless tightly monitored. Companies may dance a very fine line between what is right and what is wrong in their interface between them and physicians. This is an area that is particularly laden with the potential for scientific misconduct partly due to the lack of regulation in this area [1, 2].

Companies rely heavily on aggressive marketing practices and global strategies to advance whatever existing products they have, particularly those that have potential to become best sellers. Marketing can make up a significant amount of a company's overall operating expenses. In 2004, companies in the United States (US) spent in excess of \$53 billion promoting their products to doctors [3]. The information asymmetry between manufacturer and physician makes physicians vulnerable to the inaccurate presentation of research on manufacturers' products. The industry may argue that physician-industry interaction is

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necessary to educate doctors about the therapeutic qualities of new drugs and advances made in disease treatment. But, a powerful motivation of corporate-sponsored events is not health education but profit maximization, which can result in exaggerated claims about a drug product or misleading information [4]. Company influence on prescribing practices happens, despite doctors' belief in their professionalism. "Doctors' belief in their own incorruptibility appears to be honestly held. It is rare to hear a doctor – even in private, off-the-record conversation admit that industry gifts have made a difference in his or her prescribing" [5]. Despite these protestations, a recent systematic review found that exposure to information that originates with the pharmaceutical industry does not positively impact on doctors' prescribing behaviour [6].

Existing legislative and regulatory frameworks governing the promotion of pharmaceuticals (both governmental and self-regulation) typically take the form of direct government control (for example the Food and Drug Administration (FDA) in the US), voluntary self-regulation as practiced in Australia, New Zealand and the United Kingdom and a mixture of voluntary self-regulation and oversight by an autonomous agency (Pharmaceutical Advertising Advisory Board (PAAB)) in Canada. However, whatever form regulation takes it is seemingly not strong enough to ensure that drug promotion does not lead to misprescribing [7]. The FDA receives 70,000 pieces of promotional material a year with just 44 people to review them. According to a report from the US Government Accounting Office "inappropriate promotion can take many forms and occur in a myriad of places. For instance, DDMAC and other FDA staff attend only a small number of the thousands of CME programs that occur each year" [8]. Furthermore, "according to FDA officials, the agency does not have sufficient authority to gather the key evidence necessary to determine whether educational activities are independent of the influence of drug companies" [8].

To back up these assertions about the inadequacy of regulation, as recently as the latter part of 2009, Pfizer paid out the largest fine in U.S. criminal fine in history – \$1.2 billion – to settle U.S. Justice Department claims that the firm had violated marketing regulations by promoting its drug Bextra, which is no longer on the market, for uses that had not been approved by the FDA [9]. Voluntary codes are not audited, enforced with meaningful penalties, or overseen by independent and objective observers [10]. In Canada, this lack of oversight is troubling given that pharmaceutical company representatives are the second most commonly used source of drug information [11]. This monopoly on informational sources can be extremely perilous to public health. "(C)ompanies employ a variety of tactics that produce publications that present their products in the best possible light" [12].

The increase in inappropriate prescribing that is the result of poor regulation is not necessarily confined to its impact on the patients who are the recipients of the prescriptions. In the case of certain classes of drugs, these medications make their way from the pharmacy to the street and contribute to misuse and illegal use. Promotion may have been one of the reasons for the widespread street use of sedatives and stimulants in the 1960s [13]. This paper makes the case that Purdue Pharma's egregious marketing practices of OxyContin (the time release version of the opioid oxycodone) has had an impact on the use of the drug in the US and Canada and puts forward the case that we need a regulatory process that is better equipped to control the promotion of drugs with a strong potential for misuse and abuse.

2. Purdue and OxyContin promotion in the United States

In 2007 Purdue Frederick, an affiliate of Purdue Pharma, pleaded guilty in the United States District Court for the Western District of Virginia to the misbranding of OxyContin, with the intent to defraud

or mislead. Purdue was found guilty of falsely misrepresenting the addictive qualities of the prescription drug. Purdue sales representatives gave false information about the drug product to some health professionals and claimed that because it was a long-acting (12 hour) opioid it would provide the patient with less of a “high” and it had less of an abuse potential, including withdrawal symptoms, than other pain medications currently on the market. Purdue paid more than \$600 million in fines and other payments, one of the largest amounts ever paid by a drug company in such a case.

The US General Accounting Office concluded that Purdue Pharma launched an extensive marketing campaign, particularly at primary care physicians, to prescribe OxyContin from 1997 through 2002. The US Drug Enforcement Agency “expressed concern” that Purdue marketed OxyContin for a wide range of conditions to physicians who were not necessarily trained in proper pain management techniques [14]. A US House Appropriations Subcommittee received testimony that the drug maker’s “aggressive marketing practices” have made the drug more readily available. The prescription of OxyContin was further encouraged by Purdue through taking doctors on expense-paid retreats [15].

A 2009 article in the American Journal of Public Health further details some of the marketing techniques engaged in by Purdue. These included a large number of pain management conferences and speaker training conferences (which were all-expense paid for those health professionals who agreed to be recruited) and a lucrative bonus system that encouraged sales representatives to increase sales of OxyContin, resulting in a large number of visits to physicians with high rates of opioid prescriptions. From 1996 to 2000, Purdue increased its internal sales force from 318 sales representatives to 671, and its total physician call list from approximately 33,400 to 44,500 to between 70,500 to 94,000 physicians. Purdue launched a patient starter coupon program for OxyContin that provided patients with a free limited-time prescription for a 7- to 30-day supply. By 2001, an estimated 34,000 coupons had been redeemed nationally that promoted the use of opioids for use in the non-malignant pain market. The Purdue-sponsored “Partners Against Pain” web site claimed that the risk of addiction from OxyContin was extremely small [16].

Purdue sponsored an article about the use of OxyContin in osteoarthritis patients that was published in the Archives of Internal Medicine on March 27, 2000 [17]. Shortly thereafter 10,000 reprints of the study were distributed to doctors. The article claimed that only one patient suffered withdrawal symptoms after stopping OxyContin, whereas a later analysis by Purdue found this actually occurred in 11 patients. Even after learning of the difference in the number of patients likely experiencing withdrawal symptoms Purdue did not change its message.

3. FDA oversight of Purdue’s promotion

The FDA has cited Purdue twice for using advertisements in medical journals that violated the Food Drug & Cosmetic Act. The first time was in May 2000, for an ad that implied that OxyContin could be used as an initial therapy for the treatment of osteoarthritis pain without substantial evidence to support this claim. The second incident was in January 2003 where an ad minimized the risks of OxyContin and overstated its efficacy. Purdue also provided two promotional videos to physicians that, according to the FDA, appear to have made unsubstantiated claims and minimized the risks of OxyContin. The first video, released at the start of the marketing campaign for OxyContin in 1998, was available for about 3 years without being submitted to FDA for review [14]. While Purdue responded appropriately to all of these FDA warnings the issue is that these ads and videos were allowed to appear in the first place and in some cases were exerting their influence for years at a time before they were finally discontinued.

4. OxyContin misuse and abuse in the United States

The areas in which OxyContin was highly available were the first to see increasing OxyContin abuse and diversion in 1999 and 2000. “With increasing diversion and abuse, opioid-related overdoses escalated. [For example], in southwest Virginia, the number of deaths related to opioid prescriptions increased 830%, from 23 in 1997 to 215 in 2003 . . . Lifetime nonmedical use of OxyContin increased from 1.9 million to 3.1 million people between 2002 and 2004 . . . By 2004, OxyContin had become the most prevalent prescription opioid abused in the United States” [16].

The GAO could not assess the relationship between the growth in OxyContin prescriptions or increased availability with the drug’s abuse and diversion because of data inadequacies but it did state that the large amount of OxyContin on the market may have increased opportunities for abuse and diversion [14]. At the same time, the Administrator for the Drug Enforcement Agency believed that “a disproportionate abuse of OxyContin may be partially due to a very aggressive marketing and promotion campaign, particularly as it was presented as a less abusable substitute for a variety of less addictive medications . . . [T]he aggressive marketing to the pharmaceutical industry, as well as the medical community, I believe has contributed to the extraordinary and disproportionate abuse of this drug” [15].

Significantly, although Purdue used very detailed information on physician prescribing practices to promote OxyContin since it first appeared on the market in 1996, it was not until 6 years later that the company began to use this information “to identify patterns of prescribing that could point to possible improper sales representative promotion or physician abuse and diversion of OxyContin” [14].

5. Purdue and OxyContin promotion in Canada

There has been much less publicity about OxyContin promotion in Canada than in the US but what material there is seems to indicate that aggressive promotion has influenced OxyContin prescribing here also. A Newfoundland and Labrador Government Task Force on OxyContin concluded that Canadians are very much subjected to US promotional material through US media, and are influenced by it [18]. The Task Force stated further that, “OxyContin has become a preferred drug for the treatment of chronic, non-malignant pain in Canada”. The Task Force made no comment as to whether the marketing of OxyContin in Canada was overly aggressive or fraudulent. However, it did tellingly make a recommendation that the Department of Health and Community Services request that Health Canada ensure that pharmaceutical manufacturers use appropriate marketing strategies that includes information on the dangers of drug abuse and diversion.

A 2007 class action submitted to the Supreme Court of Nova Scotia claimed that the marketing of OxyContin in Canada was highly abusive and led to detrimental health outcomes for patients. In other words, the marketing strategies and tactics that were employed in the United States were also alleged to have been used in parts of Canada. There were allegations that Purdue (and Abbott Laboratories Inc. the company that was involved in the distribution of OxyContin in Canada) engaged in coercive marketing techniques, which included paying costs and fees for doctors to attend pain management meetings and that pharmacists were advised that if they did not renew prescriptions of OxyContin for their patients their patients would suffer. The class action also claimed that doctors who prescribed the medication were not initially informed about the serious risk of abuse and addiction with OxyContin ingestion [19]. (The suit and an appeal were subsequently dismissed).

Since 2000, the University of Toronto has given a one-week course on pain management to all of its health science students. Between 2002 and 2006, the course was funded by unrestricted educational grants from four pharmaceutical companies, including Purdue. Up until 2010, students were given a book on pain management that was Purdue produced, one of the co-authors of the book, and an unpaid guest lecturer for the course, was on the speakers' bureau for Purdue [20, 21]. The controversy over Purdue's involvement eventually led to the University of Toronto holding an informal inquiry into the management of the course [22].

Finally, a study looking at the relationship between the prescriptions for opioid analgesics and related mortality before and after the introduction of OxyContin felt that the promotion associated with the introduction of the drug "may have contributed to it being prescribed more liberally than other highly potent opioids" [23].

There is no information about any reaction to OxyContin's promotion from Health Canada, Canada's Research-Based Pharmaceutical Companies, the organization that oversees the brand-name industry's marketing code, or the PAAB, the body that develops and administers the rules about journal marketing.

6. OxyContin misuse and abuse in Canada

Since its approval for introduction in the Canadian market by Health Canada in 1996, OxyContin has been commonly prescribed for pain. In 2010, there were over 1.6 million prescriptions written for the product, putting it in the top 60 most prescribed drugs in the country [24]; five years previous OxyContin was not among the top 100 drugs by prescription numbers in Canada [25], indicating the rapid growth in prescriptions for the drug. The original product monograph stated that the long-acting formulation had a lower risk of abuse compared to other opioid analgesics [23]. The GAO report states that this type of labeling may have been a factor in the abuse and diversion of OxyContin. The product monograph was revised in 2006 and 2009 given the evidence that emerged since the original monograph was issued. OxyContin is still advertised as "... for the relief of moderate to severe pain requiring the continuous use of an opioid analgesic preparation for several days or more" but does contain a warning about abuse potential and when to use the 80 mg tablets [26].

The widespread abuse of OxyContin is a serious health and crime issue in parts of Canada. As an example, the Government of Newfoundland and Labrador, recognizing the dire consequences associated with the use of the drug, commissioned an OxyContin Task Force that issued a comprehensive report on the issue in 2004 [18]. It includes reports about how the diversion of OxyContin for non-medical purposes was widespread in the province and abuse among adolescents was growing. Opioids are in the top 3 most popular substances for youth. They seem accessible and there is a perception that they are safer because they are prescription drugs [27]. OxyContin is becoming a drug of choice and the addict profile is a young male, in school or work, from a suburban family [28]. The addition of OxyContin to the Ontario drug formulary was associated with a 5-fold increase in oxycodone-related mortality and a 41% increase in overall opioid-related mortality [23].

OxyContin has had some adverse societal effects. In Manitoba, for example, there was a surge of armed robberies targeting pharmacies in Winnipeg [29]. The thefts took place after the provincial government tightened restrictions on the prescription of the medicine in March 2010 [30]. In Saskatchewan, the police department confirmed that "OxyContin is one key reason why an average of thirty pharmacies in Saskatchewan are broken into each year" [31]. In Edmonton, drug store thefts almost doubled between 2009 and 2010 and for the first three months of 2011, 13 drug stores have already been burglarized [32].

7. Are drug regulatory agencies modern enough?

There are undoubtedly multiple reasons for the widespread misuse and abuse of OxyContin in the US and Canada. We believe that one of the main reasons is the inadequate control over the promotion of the drug by the regulatory authorities in both countries. We are now faced with fall-out from imperfect institutions. Patients have become addicted to OxyContin and have had to deal with the deleterious consequences of drug dependence. To avoid a repetition of this scenario with another drug we offer the following recommendations for strengthening the regulatory system:

1. Prior to the approval of any product that has a high potential for abuse the company marketing the product needs to develop a plan to deal with misprescribing;
2. For the first two years, or until the potential for abuse can be evaluated, promotion of the product needs to be strictly overseen by regulatory authorities. This should include a review of the marketing plan for the drug in question;
3. There should not be any distribution of samples;
4. A panel of doctors who see sales representatives should be recruited to provide feedback about the messages that the sales representatives are delivering;
5. Regulatory authorities should set up a prescription event monitoring program for these drugs where identifying details for all patients receiving a prescription are recorded for the 6 months after the drug is marketed. Doctors who wrote the prescriptions would then be contacted to ask about any adverse events that happened to these patients in order to identify early trends [33, 34];
6. Drugs felt to have a high abuse potential should have a special mark on all prescriptions to alert doctors and patients of this danger.

Competing interest

Joel Lexchin was a consultant to a legal firm representing Apotex Inc in 2007. In 2007-08 he was a consultant to the Canadian federal government in its defence of a challenge to the ban of direct-to-consumer advertising. In 2010 he was a consultant to a legal firm representing the family of a patient who allegedly died from an adverse drug reaction from a drug made by Allergan. He is on the Management Group of Healthy Skepticism Inc.

Jillian Clare Kohler is an expert witness on OxyContin marketing practices for Wagners Law Firm in Nova Scotia.

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References

- [1] J.C. Kohler and L.C. Esmail, Scientific misconduct, the pharmaceutical industry and the tragedy of institutions, *Medicine and Law* **26** (2007), 431–446.
- [2] J. Lexchin, Those who have the gold make the evidence: How the pharmaceutical industry biases the outcomes of clinical trials of medications, *Science and Engineering Ethics* **17** (2011), in press.

- [3] M.A. Gagnon and J. Lexchin, The cost of pushing pills: A new estimate of pharmaceutical promotion expenditures in the United States, *PLoS Medicine* **5** (2008), e1.
- [4] N. Othman, A. Vitry and E.E. Roughead, Quality of pharmaceutical advertisements in medical journals: A systematic review, *PLoS One* **4**(7) (2009), e6350.
- [5] C. Elliott, The drug pushers, *The Atlantic Monthly* (2006), 82–93.
- [6] G.K. Spurling, P.R. Mansfield, B.D. Montgomery, J. Lexchin, J. Doust, N. Othman, et al., Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: A systematic review, *PLoS Medicine* **7** (2010), e1000352.
- [7] L. Ziganshina and J. Lexchin, Regulation of pharmaceutical promotion: Why does regulation matter. In: B. Mintzes, D. Mangin and L. Hayes, (eds), *Understanding and responding to pharmaceutical promotion: A practical guide*, World Health Organization/Health Action International (2009), p. 123–144.
- [8] Government Accounting Office, Prescription drugs: FDA's oversight of the promotion of drugs for off-label uses, Washington, 2008.
- [9] Rx for the pharmaceutical industry: Focus on innovation, not marketing, Knowledge@Wharton; 2009 [updated October 14; cited 2011 May 22]; Available from: <http://knowledge.wharton.upenn.edu/article.cfm?articleid=2353>.
- [10] J. Lexchin and I. Kawachi, Voluntary codes of pharmaceutical marketing: Controlling promotion or licensing deception. In: P. Davis, (ed.), *Contested ground: Public purpose and private interest in the regulation of prescription drugs*, Oxford University Press, New York, (1996), p. 221–235.
- [11] Angus Reid Group. Credibility and the marketing mix, Toronto April 1991.
- [12] J. Lexchin, The pharmaceutical industry and the pursuit of profits, In: J.C. Cohen, P. Illingworth and U. Schüklenk, *The power of pills: Social, ethical & legal issues in drug development, marketing & pricing*, Pluto Press, London, (2006), p. 11–24.
- [13] D.C. Cameron, Sedatives and stimulants: Use and misuse, *JAMA* **196** (1966), 143.
- [14] General Accounting Office, Prescription drugs: OxyContin abuse and diversion and efforts to address the problem. Washington, 2003.
- [15] OxyContin: Subcommittee on the Departments of Commerce, Justice, and State, the Judiciary, and Related Agencies, House Committee on Appropriations, 107th Congress, Part 10 Sess. (December 11, 2001).
- [16] A. Van Zee, The promotion and marketing of Oxycontin: Commercial triumph, public health tragedy, *American Journal of Public Health* **99** (2009), 221–227.
- [17] S.H. Roth, R.M. Fleischmann, F.X. Burch, F. Dietz, B. Bockow, R.J. Rapoport, et al., Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: Placebo-controlled trial and long-term evaluation, *Archives of Internal Medicine* **160** (2000), 853–860.
- [18] OxyContin task force final report: Government of Newfoundland and Labrador, 2004.
- [19] Amended statement of claim, 2007 [updated December 5; cited 2011 May 22]; Available from: <http://www.oxycontinclassaction.ca/oxycontin/court.php>.
- [20] N. Persaud, High cost, dubious benefit, *CMAJ* **182** (2010), 175–176.
- [21] S. Ubelacker, Med school pain course revised over concerns about possible pharma influence. *Macleans.ca*; 2010 [updated December 23; cited 2011 May 22]; Available from: <http://www.macleans.ca/article.jsp?content=n5482287>.
- [22] L.E. Ferris, Report on the informal inquiry into concerns raised about the University of Toronto's interfaculty pain curriculum (IPC), 2010.
- [23] I.A. Dhalla, M.M. Mamdani, M.L.A. Sivilotti, A. Kopp, O. Qureshi, N. David, et al., Prescribing of opioid analgesics and related mortality before and after the introduction of long acting oxycodone, *CMAJ* **181** (2009), 891–896.
- [24] L. Campeau, Top Rx drugs of 2010, *Pharmacy Practice* (2011), 40–46.
- [25] Top products by the number of prescriptions dispensed from Canadian retail pharmacies - 2004, *IMS Health*, 2005.
- [26] C. Repchinsky, editor. Compendium of pharmaceuticals and specialties, Toronto: *Canadian Pharmacists Association*, 2010.
- [27] J. Follert, M. Mancini and J. O'Meara, Special report: Wasted youth. *Torstar digital*; 2011 [updated March 31; cited 2011 May 22]; Available from: <http://newsdurhamregion.com/life/article/174403>.
- [28] C. Kitching, Oxycodone becoming a drug of choice, *Winnipeg Sun* (Mar 2010).
- [29] OxyContin thefts put Man. pharmacists on alert. *CBCNews*; 2010 [updated May 28; cited 2011 May 22]; Available from: <http://www.cbc.ca/news/canada/manitoba/story/2010/05/28/mb-pharmacist-alert-robbery-manitoba.html>.
- [30] Manitoba takes aggressive action on OxyContin misuse: Rondeau. Government of Manitoba; 2010 [updated March 24; cited 2011 May 22]; Available from: <http://news.gov.mb.ca/news/index.html?archive=2010-3-01&item=8040>.

- [31] Safeway targets OxyContin thefts. CBCNews; 2010 [updated July 6; cited 2011 May 22]; Available from: <http://www.cbc.ca/news/canada/saskatchewan/story/2010/07/06/sk-oxycontin-theft-prevention.html>.
- [32] Drugstore heists alarm Edmonton police. CBCNews; 2011 [updated March 29; cited 2011 May 22]; Available from: <http://www.cbc.ca/news/canada/edmonton/story/2011/03/29/edmonton-drugstore-robberies.html>.
- [33] Medsafe: New Zealand Medicines and Medical Devices Safety Authority. New Zealand Regulatory Guidelines for Medicines. Volume 1: Guidance notes for applicants for consent to distribute new and changed medicines and related products, *Ministry of Health* 2001, [cited 2008 February 19]; Fifth edition: [Available from: <http://www.medsafe.govt.nz/regulatory/Guideline/medicines.asp>].
- [34] E. Heeley, L.V. Wilton and S.A.W. Shakir, Automated signal generation in prescription-event monitoring, *Drug Safety* **25** (2002), 423–432.