On what basis did Health Canada approve OxyContin in 1996? A retrospective analysis of regulatory data

Jessie Pappin\textsuperscript{1}, Itai Bavli\textsuperscript{2,3} and Matthew Herder\textsuperscript{4,5}

Abstract
The marketing and sale of oxycodone (OxyContin) by Purdue Pharma has commanded a great deal of legal and policy attention due to the drug's central role in the ongoing overdose crisis. However, little is known about the basis for OxyContin's approval by regulators, such as Health Canada in 1996. Taking advantage of a recently created online database containing information pertaining to the safety and effectiveness of drugs, we conducted a retrospective analysis of Purdue Pharma's submission to Health Canada, including both published and unpublished clinical trials. None of the trials sponsored by Purdue Pharma sought to meaningfully assess the risks of misuse or addiction associated with OxyContin. The trials were short in duration (maximum length was 24 days) and only assessed safety and efficacy of a 12-h dosing interval. Also, the two trial reports that explicitly mentioned (but did not formally evaluate) the risk of misuse were not published, making it unclear how Health Canada concluded that there was no risk of misuse. In our view, these findings underscore the need for transparency of not only of clinical trial data, but also the regulator's interpretation of such data, which is currently lacking in Canada. Furthermore, they call into question why Health Canada's role in precipitating the overdose crisis has not received greater scrutiny, including in the context of recent litigation surrounding OxyContin.

Keywords
Health Canada, OxyContin, transparency, regulation, overdose crisis

Purdue Pharma, Health Canada and the overdose crisis

Physician overprescribing of controlled-release oxycodone (OxyContin) following the drug's approval in the 1990s is one of the early drivers of the overdose crisis in North America. OxyContin’s manufacturer, Purdue Pharma, and other companies engaged in its distribution, have been the subject of thousands of lawsuits in the United States\textsuperscript{1} and, to a lesser degree, Canada\textsuperscript{2} owing to the marketing tactics they allegedly employed.\textsuperscript{3,4} Despite this scrutiny, there is limited public knowledge about how OxyContin garnered regulatory approval in the first place. While opioid-based pharmaceuticals were understood to carry significant risks for decades,\textsuperscript{5,6} clinical resistance to prescribing opioids began to soften in the mid-1980s.\textsuperscript{7,8} It is unclear whether this shift dovetailed with, or fed into, the evidence supplied by Purdue to regulators.

Questions have been raised about whether regulators, including Health Canada, contributed to the current overdose crisis\textsuperscript{9} by understating the risk of misuse in the original product monograph at the time of approval in 1996\textsuperscript{10} and failing to take stronger enforcement actions in view of aggressive marketing tactics that were deployed by Purdue Pharma post-approval.\textsuperscript{3,11,12} Health Canada also neglected to follow the United States' Food and Drug Administration in changing the OxyContin label to add a statement about...
the potential for misuse in 2001\textsuperscript{9,13} despite the evidence that emerged post-approval revealing the increased demand for OxyContin among people who use drugs.\textsuperscript{14} Until now, however, no systematic investigation of the clinical data originally submitted by Purdue Pharma to Health Canada has been conducted because the data were not publicly available.

Taking advantage of recent changes in Canadian law, we aim to shed light on the evidence underlying Health Canada’s approval of OxyContin. Specifically, following the passage of ‘Vanessa’s Law’ in 2014 Health Canada has put into place a new online portal named the ‘Public Release of Clinical Information’.\textsuperscript{15} The portal includes a wealth of data pertaining to safety and effectiveness related to drugs approved by Health Canada after March 2019, when the portal was launched, and also pertaining to older drugs, including OxyContin. Downloading a range of data available from the portal, we report findings from our retrospective analysis of the clinical evidence underpinning Health Canada’s 1996 approval of OxyContin.

The evidence behind OxyContin’s approval

OxyContin clinical data that were submitted by Purdue Pharma to Health Canada for regulatory evaluation were retrieved from the portal’s website\textsuperscript{16} for document-based retrospective analysis. Due to the voluminous amount of data in the submission, we first sought to identify all of the research studies that were included or referenced in the submission. We then categorized all studies by study type, including bioavailability reports, comparative bioavailability and bioequivalence reports, healthy subject pharmacodynamic and pharmacokinetic study reports, and clinical study reports. Focusing on the clinical trials sponsored by Purdue (see complete list of trials in Appendix 1), we determined whether or not each safety/efficacy trial had been published in a peer-reviewed journal and deduced the key elements of each trial’s design (trial phase, sample size, randomization and blinding, intervention and study timeframe, and number of subjects that reported adverse effects). In addition, we looked at side effect profiles, dosing regimens, misuse potential, and other literature referenced in the body of the submission. The findings in the studies that Purdue relied upon to establish OxyContin’s safety and efficacy were further compared against historical literature regarding the safety, efficacy, and misuse potential of opioid analgesics. Finally, the original OxyContin product monograph was used to ascertain what Health Canada concluded based on the evidence contained in the submission.

Safe and effective absent an evaluation of the risks of misuse and addiction?

OxyContin’s product monograph concluded that the drug was safe and effective for the treatment of ‘moderate’ – as opposed to acute end-of-life, cancer-related – pain. Furthermore, the monograph recommended that dosage should be increased if pain relief did not persist for the full 12 h, stating: ‘If a breakthrough pain repeatedly occurs at the end of the dosing interval it is generally an indication for a dosage increase rather than more frequent administration’. Consistent with how the drug was subsequently marketed by Purdue,\textsuperscript{17} no maximum dose was specified in the monograph. As well, the monograph stated that the risk of misuse ‘is not a problem in patients with pain in whom [OxyContin] is indicated’. The monograph was silent with respect to the risk of addiction.

A variety of clinical evidence underlies the conclusions contained in the product monograph. Specifically, a total of six clinical trials designed to assess the safety and efficacy of OxyContin (including an open-label study continuing two randomized trials) were identified in Purdue’s submission (see Table 1 for key details). The trials ranged from 57 to 182 participants, and durations between 24 h and 24 days (excluding the open-label study that spanned 12 weeks beyond the two randomized trials it continued). Two of the six trials were not published in peer-reviewed journal articles. Beyond the six Purdue-sponsored trials included in the submission, an additional 24 clinical studies, reports and reviews were also referenced in the submission package (see Appendix 2 for a complete list).

The conclusions reached in the product monograph were not supported by this body of clinical evidence. The trials performed by Purdue were all short in duration and did not assess OxyContin’s effectiveness for treating moderate, chronic pain.

Risk of misuse (described pejoratively as ‘abuse’) of OxyContin was mentioned in only two (OC88-1105 and OC91-402B) of the six safety and efficacy trials submitted to Health Canada. In the body of the report for trial OC88-1105, a statement is made that the controlled-release formulation of oxycodone may have less abuse potential than drugs such as Percodan [which also contains oxycodone] for several reasons. Most illicit drug abusers prefer a drug that is rapidly acting. The [...] formulation will have longer acting effect without producing an immediate euphoria

Study OC88-1105 did not attempt to assess or show whether the abuse/misuse potential of OxyContin was in fact less than Percodan or other similar, but
| Clinical trial identifier (Health Canada identifier) | Trial phase | Design | Participants enrolled (completed) | Intervention timeframe | Study timeframe | Publication status | I+ adverse effects (%) | Reference abuse potential (yes/no) |
|---------------------------------------------------|-------------|--------|-----------------------------------|------------------------|----------------|-------------------|---------------------|--------------------------|
| OC88-1105 (HC6-24-0367683)                        | 2           | Randomized, double-blind           | n = 182, >18 years (n = 181) | 24 h                   | 26 May 1989–9 May 1991 | Not published      | 57%                  | Yes                      |
| OC91-0402A (HC6-24-0367683)                        | 3           | Randomized, double-blind, parallel groups | n = 111, >18 years (n = 65) | 6 days                  | 31 January 1992–29 December 1991 | Not published      | 70%                  | Yes                      |
| OC91-0402B (HC6-24-037683)                         | 3           | Randomized, double-blind, parallel groups | n = 164, >18 years (n = 119) | 6 days                  | 30 January 1992–3 January 1994 | Published (1998) | 65%                  | No                       |
| OC92-1102 (HC6-24-037638)                          | 3           | Randomized, double-blind, parallel group | n = 133, >18 years (n = 63) | 14 days                 | 15 June 1993–15 April 1994 | Published (2000) | 65%                  | No                       |
| OC92-1201 (HC6-24-037683)                          | Not stated  | Randomized, double-blind, 2 period cross-over | n = 57, >18 years (n = 39) | 24 days (inclusive of titration periods) | 31 August 1993–1 July 1994 | Published (1999) | 90%                  | No                       |
| OC91-0907A/OC91-0907B (HC6-24-037683)              | 3           | Continuation of OC91-0402A/B Open-label | n = 87, >18 years (n = 40) | 12 weeks                | OC910907A: 12/15/92–01/24/94 OC91-0907B: 8 December 1992–29 March 1994 | Not clear          | 87.2%                 | No                       |
differently formulated, drugs. Similarly, OC91-402B listed withdrawal as an ‘unusual and rare adverse experience’. Yet, this statement was not formally measured nor supported by evidence generated in the trial.

Despite the absence of a statement about the risk of addiction in OxyContin’s product monograph, five (of the 24) studies that were referenced in Purdue’s submission (studies numbered 4, 6, 7, 8, and 22 in Appendix 2) discuss the addictive potential of opioid-based drugs. One retrospective analysis of patient records reported 7% of patients narcotic analgesics were considered physiologically addicted. The authors nevertheless concluded that the addiction rate is likely higher than 7%, referencing a study conducted in 1976 that observed upwards of 25% of patients addicted. References 7, 8, and 22 similarly emphasize the risk of addiction with opioid-based analgesics, including products like OxyContin where oxycodone is the active ingredient. As well, a 1938 report (Appendix 2; 22) concluded that Eukodol (a previous brand name for oxycodone) is comparable in both addictiveness and withdrawal symptoms to morphine.

Contrary to the findings of this referenced literature, a number of statements contained in Purdue’s submission were to the effect that the risk of addiction was ‘minimal’ due to the controlled-release formulation and the recommended time between doses. Purdue also did not account for – either in the trials it sponsored or in response to the literature it referenced in the body of its submission – the possibility of the tablets being consumed at intervals other than 12 h.

Finally, we found no reference to two publications – a letter to the editor by Porter and Jick that was published in the New England Journal of Medicine in 1980 and a 38-patient case series by Portenoy and Foley published in Pain in 1986 – that have been shown to have played an important role in liberalizing prescriber attitudes towards opioids during the 1980s, 1990s, and early 2000s.

Gaps in transparency and a lack of accountability: continuing fallout from health Canada’s decision to approve OxyContin

Our retrospective analysis of the data tendered by Purdue in support of its submission to Health Canada reveals that the evidence base behind OxyContin’s approved indication for the treatment of non-cancer related chronic pain was weak. Although chronic pain has been long understood as persistent pain for over 3–6 months, the longest Purdue-sponsored trial spanned a mere 24 days and dosing was only evaluated at 12-h intervals. Therefore, Purdue’s submission did not provide persuasive evidence in support of the indication for chronic pain, nor did it supply meaningful evidence pertaining to the risks of addiction and misuse associated with use of OxyContin.

Importantly, regulators, such as Health Canada had not – at the time of OxyContin’s original approval – fully developed their guidance to standardize how the risk of ‘abuse potential’ was to be assessed during the different phases of drug development. How best to assess that risk in the context of pre-clinical studies involving animal models was, for instance, the subject of significant scientific debate. Regulators only formalized their guidance through the mid-2000s as concerns about addiction and misuse of OxyContin grew. The fact that the preferred methods to evaluate these risks was not yet clear, however, does not mean that these risks can be ignored altogether. Indeed, at the time of OxyContin’s approval it was generally understood that substantial physiologic addiction occurs over periods of several days to weeks. Yet, with the exception of one 24-day trial, none of the evidence generated by Purdue was long in duration. Thus, Purdue’s claim that the risk of misuse was low was not well supported.

Consistent with previous research, our analysis also shows that the evidence pertaining to OxyContin was only partially reported in the published medical literature. The two studies which included statements about – but did not actually evaluate – the risk of misuse related to OxyContin were not published.

It is also important to note the stigma towards people who use drugs that is, at times, explicit within, but also underlies the entirety of, Purdue’s submission. Purdue claimed that ‘the tablet formulation of the controlled release oxycodone will be more difficult to dissolve in a solution, hence not desired by the “street” addict who prefers an injectable solution’ (emphasis added). Given that stigma continues to plague the practice of addiction medicine, this language is not surprising. Yet, the stated assumptions about what the ‘street addict’ or ‘abuser’ prefers and the inattention to the risks of misuse and addiction that is shot through Purdue’s entire submission, reveals a deeper disregard for people who use drugs.

Our study has two limitations. First, subsequent decisions involving the same sponsor and different formulations of OxyContin, in particular, the subsequent regulatory decision to replace controlled-release OxyContin with a tamper-resistant formulation in view of the overdose crisis which had by then developed, are not included in our analysis. Second, the study does not include information regarding Health Canada’s interpretation of the evidence provided by Purdue; Health Canada has long possessed the authority to make such interpretive information publicly available but it chose not to include it within its portal.

The latter limitation, coupled with our findings, underscore both the potential of, and pitfalls associated with, the transparency that has been added to Canada’s regulatory system since the passage of
Vanessa’s Law. In theory, the data now available from Health Canada have the potential to enhance evidence-based medicine by improving access to clinical trial data and other studies that were conducted but not incorporated into the published literature. On the other hand, the evidence we examined raises more questions than it answers. How did Purdue persuade Health Canada to approve OxyContin given the lack of evidence about the potential risk of addiction and/or misuse? Studies that were subsequently used to promote OxyContin were not cited within the submission. What other evidence, if any, did Purdue provide in support of the claims that appeared in the product monograph? This is important because pharmaceutical companies are permitted by law to use regulator-approved information in their promotional practices. What impact, if any, did shifting clinical interpretations about opioid prescribing have upon the regulator’s evaluation? How much weight did Health Canada place upon the absence of treatment options for non-cancer chronic pain at the time? How did reviewers reconcile Purdue’s claims that the risk of misuse was non-existent for the proposed indication with the lack of evaluation of that very same risk in the course of clinical trials? None of these considerations is illustrated by the case of OxyContin.

Our study has policy and legal implications. First, it suggests that despite the creation of the portal significant gaps remain in Health Canada’s approach regulatory transparency. Building upon existing initiatives, there are steps that Health Canada can take to make its decision-making processes more transparent to enhance trust and public health. Second, the weak evidence underlying Health Canada’s decision to approve OxyContin for chronic pain raises questions about the regulator’s close relationship with industry, which may have played a role in precipitating the overdose crisis. There has been a great deal of litigation against Purdue Pharma and other entities involved in the manufacture, sale, and distribution of OxyContin. Including Health Canada as a defendant in those proceedings could provide important insight into why it approved OxyContin with minimal evidence about its potential risks of addiction and misuse.

Declaration of conflicting interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M. Herder is a member of the Patented Medicine Prices Review Board (PMPRB), Canada’s national drug pricing regulator, and reports receiving honoraria for his public service. The PMPRB had no role whatsoever in the design, conduct, or reporting of this research. No other conflicts of interest were reported.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by the Canadian Institutes of Health Research (grant no. CIHR PJT 156256); and the Gladys Osman Estate Studentship Award provided by the Faculty of Medicine at Dalhousie University.

ORCID iD
Matthew Herder https://orcid.org/0000-0001-5319-6199

References
1. Ausness RC. Is litigation the way to combat the opioid crisis. J Law Med Ethics 2020; 48(2): 293–306.
2. Howlett K. Provinces plan legal push against Purdue Pharma in wake of U.S. opioid deal. The Globe and Mail, https://www.theglobeandmail.com/canada/article-provinces-plan-legal-push-against-purdue-pharma-in-wake-of-us-opioid/(2021, accessed 3 October 2021).
3. Van Zee A. The promotion and marketing of OxyContin: commercial triumph, public health tragedy. Are J Public Health 2009; 99(2): 221–227.
4. United States General Accounting Office. GAO-04-110 prescription drugs: OxyContin abuse and diversion and efforts to address the problem – d04110.pdf, http://www.gao.gov/new.items/d04110.pdf (2003, accessed 24 November 2016).
5. Miller NS. The pharmacology of narcotics: natural, semi-synthetic, and synthetic. In: Miller NS (ed.) The Pharmacology of Alcohol and Drugs of Abuse and Addiction. New York: Springer, 1991, pp. 227–239.
6. Bloomquist ER. The addiction potential of oxycodone (Percodan®). Calif Med 1963; 99(2): 127–130.
7. Sud A, Cheng DK, Moineddin R, et al. Time series-based bibliometric analysis of a systematic review of multidisciplinary care for opioid dose reduction: exploring the origins of the North American opioid crisis. Scientometrics 2021; 126(11): 8935–8955.
8. Tafreshi S, Steiner A and Sud A. Shifting interpretations in evidence and guidance in pain and opioids research: a bibliometric analysis of a highly cited case series from 1986. J Eval Clin Pract. Epub ahead of print 21 April 2022. DOI: 10.1111/jep.13680.
9. Bavli I. Industry influence and health Canada’s responsibility: lessons from the opioid epidemic in Canada. Addiction 2020; 115(9): 1605–1606.
10. Purdue Pharma. OxyContin [product monograph]. Purdue Pharma, Pickering, ON, 1996.
11. Kolodny A. How FDA failures contributed to the opioid crisis. AMA J Ethics 2020; 22(1): E743–E750.
12. Persaud N. Questionable content of an industry-supported medical school lecture series: a case study. J Med Ethics 2014; 40(6): 414–418.
13. Bavli I and Steel D. Inductive risk and OxyContin: the ethics of evidence and post-market surveillance of
15. Egilman AC, Ross JS and Herder M. Optimizing the data available via Health Canada’s clinical information portal. CMAJ 2021; 193(33): E1305–E1306.

16. Gomes T, Mamdani MM, Paterson JM, et al. Trends in high-dose opioid prescribing in Canada. Can Fam Physician 2014; 60(9): 826–832.

17. Hanks GW and Hoskin PJ. Pain control in advanced cancer: pharmacological methods. J R Coll Physicians Lond 1986; 20(4): 276–281.

18. Maruta T, Swanson DW and Finlayson RE. Drug abuse and dependency in patients with chronic pain. Mayo Clin Proc 1979; 54(4): 241–244.

19. Small LF, Eddy NB, Mossettig E, et al. Studies on drug addiction: with special reference to chemical structure of opioid derivatives and allied synthetic substances and their physiological action. JAMA 1939; 113(5): 447.

20. Porter J and Jick H. Addiction rare in patients treated with narcotics. N Engl J Med 1980; 302(2): 123.

21. Portenoy RK and Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain 1986; 25(2): 171–186.

22. Leung PTM, Macdonald EM, Stanbrook MB, et al. A 1980 Letter on the Risk of Opioid Addiction. N Engl J Med 2017; 376(22): 2194–2195.

23. Treede R-D, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. Pain 2015; 156(6): 1003–1007.

24. Pugsley MK, Authier S and Curtis MJ. Principles of safety pharmacology. Br J Pharmacol 2008; 154(7): 1382–1399.

25. Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 1. Pain Physician 2017; 20(2S): S93–S109.

26. Botticelli MP and Koh HK. Changing the language of addiction. JAMA 2016; 316(13): 3161–3162.

27. Herder M. Unlocking Health Canada’s cache of trade secrets: mandatory disclosure of clinical trial results. CMAJ 2012; 184(2): 194–199.

28. Herder M. Toward a jurisprudence of drug regulation. J Law Med Ethics 2014; 42(2): 244–262.

29. Edmonds S, MacGregor A, Doll A, et al. Transparency too little, too late? Why and how Health Canada should make clinical data and regulatory decision-making open to scrutiny in the face of COVID-19. J Law Biosci 2020; 7(1): jsa083.

30. Makary MA, Overton HN and Wang P. Overprescribing is major contributor to opioid crisis. BMJ 2017; 359: j4792.

**Appendix 1**

**OC88-1105.** Double-blind randomized, single-dose, parallel group study to assess the relative analgesic effectiveness and safety of graded doses of controlled-release oxycodone compared to immediate-release oxycodone, Percocet and placebo in patients with postoperative pain due to abdominal gynaecological surgery.

**OC91-0402A.** Controlled-release oxycodone tablets (30 mg Q12 h) versus immediate-release oxycodone tablets (15 mg, Q.I.D.): comparative efficacy, safety and acceptability in patients previously stabilized on fixed combination opioid analgesics for chronic cancer-related pain.

**OC91-0402B.** Controlled-release oxycodone tablets (Q12 h) versus immediate-release oxycodone tablets (Q.I.D.): comparative efficacy, safety and acceptability in patients previously stabilized on strong opioid analgesics for chronic cancer-related pain.

**OC92-1102.** A randomized, double-blind, parallel group, analgesic efficacy, safety, acceptability and quality of life study of fixed doses of controlled-release oxycodone tablets versus placebo in chronic non-malignant pain due to osteoarthrits.

**OC92-1201.** A randomized, double-blind, two-period crossover comparison of the pharmacokinetic and pharmacodynamic profiles of immediate-release oxycodone and controlled-release oxycodone in patients with chronic low back pain.

**Appendix 2**

1. Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. I. Comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. J Pharmacol Exp Ther 1978a;207:92–100.

2. Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. II. Comparisons of intramuscular oxycodone with intramuscular morphine and codeine. J Pharmacol Exp Ther 1978b;207:101–108.

3. Chen ZR, Irvine RJ, Somogyi AA, Bochner. F. Mu receptor binding affinity of some commonly used opioids and their metabolites. Life Sci 1991; 48: 2165–2171.

4. Evans PJD. Narcotic addiction in patients with chronic pain. Anaesthesia 1981; 36: 597–602.
5. Glare PA, Walsh TC. Dose-ranging study of oxycodone for chronic pain in advanced cancer. *J Clin Oncology* 1993; 11(5): 973–978.
6. Hansks GW, Hoskin PJ. Pain control in advanced cancer. *Pharmacological methods. JR Coll Physicians Lond* 1986; 20: 276–81
7. Houde RW. The use and misuse of narcotics in the treatment of chronic pain. *Advances in Neurology* 1974; Raven Press, New York; 4: 527–536
8. Jasinski, DR. Assessment of the abuse potential of morphine-like drugs. Drug Addiction I, Martin WR, ed, pp. 197–258, Springer-Verlag, New York, 1977.
9. Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. *Clin Pharmacol Ther* 1990; 47: 639–46.
10. Kalso E, Poyhia R, Onnela P, Linko K, Tigerstedt I, Tammisto T. Intravenous morphine and oxycodone for pain after abdominal surgery. *Acta Anaesthesiol Scand* 1991; 35: 642–646.
11. Korttilla K, Pentti OM, Auvinen J. Comparison of I.M. lysine acetylsalicylate and oxycodone in the treatment of pain after operation. *Br J Anaesth* 1980; 52: 613
12. Leow KP, Smith MT, Williams B, Cramond T. Single-dose and steadystate pharmacokinetics and pharmacodynamics of oxycodone in patients with cancer. *Clin Pharmacol Ther* 1992; 52: 487–95.
13. Mandema JW, Kaiko RF, Oshlack B, Reder RF, Stanski DR. Pharmacokinetic model for a new oral controlled release formulation of oxycodone. *Am Pain Soc, 13th Ann. Meeting; Abstract #94738:A-124*
14. The Medical Letter 1972; 14: 44
15. Nuutinen LS, Wuoliwoki E, Pentikainen IT. Diclofenac and oxycodone in treatment of post-operative pain: a double blind trial. *Acta Anaesthesiol Scand* 1986; 30: 620–624.
16. Otton SV, WU, D, Joffe RT, Cheung SW, Sellers EM. Inhibition by fluoxetine of cytochrome P450 2D6 activity. *Clin Pharmacol Ther* 1993; 53: 401–409.
17. Poyhia R, Olkkola K, Seppala T, Kalso E. The pharmacokinetics of oxycodone after intravenous injection in adults. *Br J Clin Pharmacol* 1991; 32(4): 516–518
18. Poyhia R, Seppala T, Olkkola KT, Kalso E. The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. *Br J Clin Pharmac* 1992a; 33: 617–621
19. Poyhia R, Kalso E, Seppala T. Pharmacodynamic interactions of oxycodone and amitriptyline in healthy volunteers. *Current Ther Res* 1992b; 51: 739–749.
20. Saarialho-Kere U, Mattila MJ, Seppala T. Psychomotor, respiratory and neuroendocrinological effects of a J,1.-opioid receptor agonist (oxycodone) in healthy volunteers. *Pharmacology & Toxicology* 1989; 65: 252–257.
21. Sawe J, Dahlstrom B, Paalzow L, Rane A. Morphine kinetics in cancer patients. *Clin Pharmacol Ther* 30(5): 629–635
22. Studies on Drug Addiction, with Special Reference to Chemical Structure of Opium Derivatives and Allied Synthetic Substances and Their Physiological Action. (1939). *Journal of the American Medical Association, 113*(5), 447
23. Takki S, Tammisto T. A comparison of pethidine, piritramide and oxycodone in patients with pain following cholecystectomy. *Anaesthesist* 1973; 22:1 62–166
24. Tatro DS. (ed) *Drug Interaction Facts*. St. Louis: J. B. Lippincott, 1993: 521.