

Article details	
Title	Characteristics of Patients Receiving Long-Term Opioid Therapy for Chronic Non-Cancer Pain: A Cross-Sectional Survey of Pain Clinic Attendees
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Abstract	<p>Abstract: Background: Characteristics of patients receiving long-term opioid therapy (&gt;6 months) for chronic non-cancer pain are poorly understood.</p> <p>Methods: We approached 260 patients presenting to a Canadian, hospital-based chronic pain clinic to complete a 20-item survey that inquired about demographic variables, pain relief, functional improvement, side-effects, and impressions regarding an educational pamphlet.</p> <p>Results: 170 patients completed our survey, a response rate of 65%. Most respondents (88%; 149 of 170) were receiving long-term opioid therapy (&gt;6 months), and of these 58% had been prescribed opioids for &gt;5 years. The median morphine equivalent dose was 180mg/day (IQR=441). Chronic low back pain (65% of patients) was the most common complaint for which long-term opioid therapy was prescribed. The majority reported at least modest (&gt;40%) pain relief (74%) and functional improvement (68%), and 47% reported troublesome side-effects. Most patients were receiving disability benefits (68%) and, among the 82% of respondents who were of working age (&lt;65 years), 8% were working full-time and 11% part-time. Neither pain relief nor functional improvement were associated with employment. In an analysis adjusted for age, higher morphine equivalent dose was associated with greater self-reported pain relief (OR=1.37; 95%CI=1.00 to 1.88) and functional improvement (OR=1.14; 95%CI=1.02 to 1.27), but not opioid-related side-effects or employment.</p> <p>Interpretation: Outpatients receiving care for chronic non-cancer pain at a tertiary care chronic pain clinic commonly receive high-dose, long-term opioid therapy. Most patients report at least moderate pain relief and functional improvement; side effects are common and few patients are engaged in competitive employment.</p>
Version 1	
Reviewer 1	
Name	Lacasse, Anaïs
Position	
Institution	Université du Québec en Abitibi-Témiscamingue, Département des sciences de la santé
Competing interests	
Date review returned	19-Jan-2015

General comments	<p>Characteristics of Patients Receiving Long-Term Opioid Therapy for Chronic NonCancer Pain: A Cross-Sectional Survey of Pain Clinic Attendees - Comments to the authors - The authors proposed an interesting study about characteristics of long-term users of opioids for the treatment of chronic non-cancer pain (CNCP) and impressions regarding an educational pamphlet about painkillers. In a cross-sectional way, they also sought to identify if morphine equivalent dose and other variables are associated with pain relief, functional improvement, opioids-related side effects and employment. In my opinion, the manuscript needs revision. The following suggestions could help the authors to improve their work. Major comments 1. Abstract, page 3: I noted that the study aims/research questions are not presented in the Background section of the abstract (see CMAJ Open guidelines). 2. Abstract, page 3: The following sentence is presented: "The majority reported at least modest (&gt;40%) pain relief (74%) and functional improvement (68%), and 47% reported troublesome side-effects." The authors should specified if these variables were opioid-specific of not. 3. Abstract, page 3: The authors have to be cautious about the interpretation of the statistical significance of the OR measuring the association between morphine equivalent dose and self-reported pain relief (OR=1.37; 95%CI=1.00 to 1.88). If the 95% confidence interval includes the null value of 1, then there is insufficient evidence to conclude that the association is statistically significant. The same comment is applicable to results presented at page 11 and in Appendix Table 1. 4. Introduction, pages 4-5: I would recommend that the authors be more specific about their study objectives. - In the introduction, the authors explain the lack of real-world effectiveness data about the long-term use of opioids for CNCP. The objective presented right after (characterize patients receiving long-term opioids) is not consistent with this rationale. In addition to a description of patients' profile, the study intended to provide preliminary insights about clinical outcomes in opioid long-term users. This should be explained as one of the objectives of the study. The term "preliminary" is important to use because of the cross-sectional nature of the study, i.e. an observational longitudinal design would have been more appropriate for effectiveness research/causal relationships. - Moreover, the investigation of the impressions regarding the educational pamphlet is not presented as an objective in the introduction. 5. Methods, page 6-7: I would suggest a more fluid structure for the presentation of the study methodology. First the study design, then the study setting and recruitment (before the explanation of the questionnaire development). Moreover, the manuscript would benefit from a clear and complete section about main study variables, questions and questions' format that were used in the questionnaire. 6. Analysis, page 8, second paragraph: An important methodological flaw of the study is the analysis of determinants. In order to obtain valid results when identifying variables associated with a given outcome, the use of multivariate models is primordial and will minimise the possibility of confusion bias in observational designs. In order to verify if the morphine equivalent dose (MED) is a determinant of pain relief, functional improvement, employment and self-reported adverse events, the authors used multivariate analysis that adjusted only for age. Many other variables could be potential confounders such as other treatments used and duration of opioid use, i.e. could be associated with the exposure and independently with the outcomes of interest. Using the recognized rule of thumb presented by the authors, more than two</p>
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	<p>independent variables could have been used in the models. The authors should explain their analysis (choice of age only as a co-variable) or improve it. They should also provide a clear explanation of the impact of the type of statistical analysis used on the interval validity of the study in their discussion. 7. Results, page 10: I understand that 154 patients had a confirmed prescription for an opioid. However, the first row of Table 1 sums at 178. Table 1's title specify a sample size of 149. Could these numbers be explained with more clarity? I would suppose that some patients are using more than one type of opioid? Is there missing data? 8. Results, page 10: In the same vein, authors reported that 149 CNCP patients where long-term users of opioids. A sample size of 145 patients is reported in Table 2? 9. Results, page 11: The authors present that the most common complaint for which long-term opioid therapy was prescribed is chronic low back pain. Were prescription indications reviewed in medical charts or pain conditions are simply "presenting clinical conditions" as presented in Table 2? 10. Table 3: Following comments 2 and 5, the reader does not have enough information to understand how survey questions where formulated. Were patients asked specifically about opioid-related pain relief and self-perceived impact of opioids on functioning and employment status? Can the three first variables presented in Table 3 be categorized as "impacts" of long-term opioid therapy or simple clinical variables among long-term opioid users? 11. Discussion, Page 12: A high response rate contributes to a better representativeness of the sample but does not guarantee it. In fact, characteristics of survey respondents and non-respondents can still be different and bring a selection bias. Minor comments 12. Analysis, page 7: Categorical data can be binary or have more than two categories. The following words "Binary and the" that are presented in the second sentence of page 8 last paragraph could be deleted. In this same sentence, "mean and standard deviation" should be in plural form. 13. Analysis, page 8: Fisher's exact tests were used to compare categorical variables. Which tests were used to compare continuous variables? In the beginning of page 8, the authors state that normality of continuous variables was tested. Testing normality normally serves the choice of t-tests vs non parametric Wilcoxon tests. 14. Discussion: Strengths and limits of the study could be presented at the end of the discussion, after the interpretation of study results. Reviewer: Anaïs Lacasse, Ph.D. Professor in clinical sciences Département des sciences de la santé Université du Québec en Abitibi-Témiscamingue I certify that I have no conflicts of interest with any financial organization regarding the material discussed in the manuscript.</p>
<p>Author response</p>	<p>1. Abstract, page 3: I noted that the study aims/research questions are not presented in the Background section of the abstract (see CMAJ Open guidelines).</p> <p>Reply: We have amended our Abstract Background section as follows to address this issue:</p> <p>"Background: Characteristics of patients receiving long-term opioid therapy (&gt;6 months) for chronic non-cancer pain are poorly understood. We conducted a cross-sectional survey of this patient population to explore demographic variables, pain relief, functional improvement, side-effects, and impressions of an educational pamphlet regarding long-term</p>

opioid therapy."

2. Abstract, page 3: The following sentence is presented: "The majority reported at least modest (>40%) pain relief (74%) and functional improvement (68%), and 47% reported troublesome side-effects." The authors should specify if these variables were opioid-specific or not.

Reply: We thank the reviewer for pointing this out and have amended this sentence as follows:

"Most respondents (88%; 149 of 170) were receiving long-term opioid therapy (>6 months), and the median morphine equivalent dose was 180mg/day (IQR=441). The majority reported at least modest (>40%) opioid-specific pain relief (74%) and functional improvement (68%), and 47% reported troublesome side-effects which they attributed to their opioid use."

3. Abstract, page 3: The authors have to be cautious about the interpretation of the statistical significance of the OR measuring the association between morphine equivalent dose and self-reported pain relief (OR=1.37; 95%CI=1.00 to 1.88). If the 95% confidence interval includes the null value of 1, then there is insufficient evidence to conclude that the association is statistically significant. The same comment is applicable to results presented at page 11 and in Appendix Table 1.

Reply: We agree and have clarified in the Abstract and main text that, at a level of  $p < 0.05$ , the association with MED does and pain relief is not statistically significant.

4. Introduction, pages 4-5: I would recommend that the authors be more specific about their study objectives. - In the introduction, the authors explain the lack of real-world effectiveness data about the long-term use of opioids for CNCP. The objective presented right after (characterize patients receiving long-term opioids) is not consistent with **this rationale. In addition to a description of patients' profile,** the study intended to provide preliminary insights about clinical outcomes in opioid long-term users. This should be explained as one of the objectives of the study. The term "preliminary" is important to use because of the cross-sectional nature of the study, i.e. an observational longitudinal design would have been more appropriate for effectiveness research/causal relationships.  
- Moreover, the investigation of the impressions regarding the educational pamphlet is not presented as an objective in the introduction.

Reply: We have added the following statement at the end of our Introduction section to address these concerns:

"Our objective was to explore demographic variables and provide preliminary insights about clinical outcomes in opioid long-term user; specifically, pain relief, functional improvement, and side-effects. We also solicited patients' impressions of an educational pamphlet regarding long-term opioid therapy."

5. Methods, page 6-7: I would suggest a more fluid structure for the presentation of the study methodology. First the study design, then the study setting and recruitment (before the explanation of the questionnaire development). Moreover, the manuscript would benefit from a clear and complete section about main study variables, questions and **questions' format that were used in the questionnaire.**

Reply: We thank the reviewer for these suggestions and we have amended the beginning of our Methods section as follows, and provided both our survey and the educational pamphlet in Appendices:

#### "Methods

We administered a cross-sectional survey to establishing the demographic characteristics (e.g. age, primary presenting complaint) of patients receiving long-term opioid therapy for CNCP, the types of narcotics prescribed and duration of opioid therapy, employment and disability benefit status, and patient's self-reported pain relief, functional improvement, and impact of adverse events attributed to opioid therapy. We also explored the concordance between patient-reported opioid use and their clinical records. We also provided a 1-page educational pamphlet, titled "Are You Thinking About Taking Opioids (Painkillers) for Your **Pain?**" (**Appendix A**) [15] to elicit patient's impressions of this material; specifically, was the information provided helpful, comprehensive, and succinct. This pamphlet was developed by investigators associated with the Canadian Opioid Guideline National Faculty Working Group on Knowledge Translation to Patients and the Public in an effort to provide pertinent information and encourage informed decision-making for patients considering opioid therapy for their chronic pain, and was previously tested among a group of 20 Canadian patients with CNCP who were not receiving opioid therapy [16]. We administered this pamphlet to patients engaged in long-term opioid therapy to acquire insights from individuals with practical experience using opioids to manage their CNCP.

#### Setting

The Pain Management Center at the Hamilton General

Hospital, Ontario, Canada.

#### Participants

Adult patients ( $\geq 18$  years of age) presenting to the Pain Management Center. Individuals who were attending for procedures (e.g. nerve blocks) were not approached in order to avoid disrupting the operating room schedule. We surveyed all patients who provided verbal informed consent, but we only included patients with chart-confirmed long-term opioid use in our analyses of this population."

6. Analysis, page 8, second paragraph: An important methodological flaw of the study is the analysis of determinants. In order to obtain valid results when identifying variables associated with a given outcome, the use of multivariate models is primordial and will minimise the possibility of confusion bias in observational designs. In order to verify if the morphine equivalent dose (MED) is a determinant of pain relief, functional improvement, employment and self-reported adverse events, the authors used multivariate analysis that adjusted only for age. Many other variables could be potential confounders such as other treatments used and duration of opioid use, i.e. could be associated with the exposure and independently with the outcomes of interest. Using the recognized rule of thumb presented by the authors, more than two independent variables could have been used in the models. The authors should explain their analysis (choice of age only as a co-variable) or improve it. They should also provide a clear explanation of the impact of the type of statistical analysis used on the interval validity of the study in their discussion.

Reply: We originally limited our regression analyses to adjustment for 2 independent variables as there were only 24 patients that were working in any capacity, and we made the decision to run the same model for all 4 dependant variables. However, we agree with the reviewer that better adjustment for potential confounders would strengthen our regression models in cases where we do have sufficient observations. We are aware of literature supporting an association between higher level of education and improved outcomes. Accordingly, we have re-run 3 of our regression analyses with adjustment for 3 potential confounders: (1) age, (2) level of education, and (3) Morphine Equivalent Dose. We have revised our manuscript to reflect this modification.

7. Results, page 10: I understand that 154 patients had a confirmed prescription for an opioid. However, the first row of **Table 1 sums at 178. Table 1's title specify a sample size of 149.** Could these numbers be explained with more clarity? I would suppose that some patients are using more than one

type of opioid? Is there missing data?

Reply: There were 154 patients with a confirmed prescription for an opioid, but only 149 were long-term opioid users ( $\geq 6$  months) and formed the basis for our analyses. The reviewer is correct that in Table 1 the raw numbers across rows total more than 149 as some patients were prescribed more than 1 opioid. We have now made this explicit in the table legend.

8. Results, page 10: In the same vein, authors reported that 149 CNCP patients where long-term users of opioids. A sample size of 145 patients is reported in Table 2?

Reply: The reviewer is correct. We have now clarified in the table legend that 4 patients provided incomplete information for 1 or more of the items in Table 2, and we restricted our presentation to the 145 of 149 that provided complete information.

9. Results, page 11: The authors present that the most common complaint for which long-term opioid therapy was prescribed is chronic low back pain. Were prescription indications reviewed in medical charts or pain conditions are **simply "presenting clinical conditions" as presented in Table 2?**

Reply: We derived all presenting complaints from review of patient's medical charts, and we have now made this explicit.

10. Table 3: Following comments 2 and 5, the reader does not have enough information to understand how survey questions were formulated. Were patients asked specifically about opioid-related pain relief and self-perceived impact of opioids on functioning and employment status? Can the three first variables presented in Table 3 be categorized as **"impacts" of long-term opioid therapy** or simple clinical variables among long-term opioid users?

Reply: Yes, all of the questions regarding pain relief, functional improvement, and adverse events were all asked in the context of relation to patient's long-term opioid use. We have now included the full survey in Appendix A, and we have made this clearer in the manuscript.

11. Discussion, Page 12: A high response rate contributes to a better representativeness of the sample but does not guarantee it. In fact, characteristics of survey respondents and non-respondents can still be different and bring a selection bias.

Reply: We agree and have tempered our statement as follows:

"Our response rate of 65% provides some assurances that our findings are likely representative of CNCP patients attending the Pain Management Center at the Hamilton General Hospital."

12. Analysis, page 7: Categorical data can be binary or have more than two categories. The following words "Binary and the" that are presented in the second sentence of page 8 last paragraph could be deleted. In this same sentence, "mean and standard deviation" should be in plural form.

Reply: We have made these changes as recommended.

**13. Analysis, page 8: Fisher's exact tests were used to** compare categorical variables. Which tests were used to compare continuous variables? In the beginning of page 8, the authors state that normality of continuous variables was tested. Testing normality normally serves the choice of t-tests vs. non parametric Wilcoxon tests.

Reply: We did not compare continuous variables. We tested the normality of our continuous variables in order to inform the appropriate presentation in our table of patient characteristics (for example, age was normally distributed and was presented as mean and SD, whereas morphine equivalent dose [MED] was not normally distributed and was presented as a median and interquartile range). Further, to inform the appropriate manner in which to enter independent variables into our regression analyses - because of the skewed non-normal distribution of MED, we log transformed these data for our regression analyses.

14. Discussion: Strengths and limits of the study could be presented at the end of the discussion, after the interpretation of study results.

Reply: We have revised the structure of our Discussion section as per recommendations by the Editors as follows: main findings; explanation and comparison with other studies; limitations; and conclusions and implications for practice and future research.

	<p>Attention by the editor and reviewer has resulted in a number of improvements to our manuscript and we thank them for their efforts. We appreciate your attention to our study, and remain hopeful that our manuscript will be suitable for publication in CMAJ Open. All authors of the original manuscript have read and approved the revised version of the paper.</p>
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