Article details	
Title	Prevalence and determinants of cannabinoid prescription for the management of chronic non-cancer pain: A postal survey of physicians
Authors	Huguette St. Amant, Mark Ware, Nancy Julien, Anais Lacasse
Abstract	Objectives: Cannabinoid prescription patterns for the management of chronic non-cancer pain (CNCP) are inadequately studied in Quebec as well as in the rest of Canada and internationally. The objectives of this study were to measure the prevalence and identify the determinants of cannabinoid prescription in the management of CNCP. Methods: In February 2013, a postal survey was sent out to all physicians of the Abitibi-Témiscamingue region (Quebec) using a modified Dillman method. Multivariate logistic regression models were used to identify determinants of cannabinoids prescription. Results: The response proportion was 52.2%, for a total of 166 physicians. A majority of physicians (79.2%) had not attended continuing medical education (CME) activities concerning cannabinoids in the past year. The prevalence of cannabinoid prescription for the management of CNCP was 23.0%, with 91.1% of these physicians prescribing cannabinoids to ≤5 patients. Among prescribers, 92.1% reported having prescribed nabilone, 18.4% medical marijuana, and 5.3% nabiximols. Multivariate modelling **showed that physicians' comfort level with cannabinoid** prescribing was the principal determinant of increased likelihood of cannabinoid prescription. Prescribers and non-prescribers reported that CME activities could increase their comfort level with cannabinoid prescribing. According to physicians, more studies are needed about the efficacy and safety of cannabinoids for the treatment of CNCP. Conclusions: Although cannabinoids are not products of first line in the therapeutic arsenal for the treatment of CNCP, they appear to have their For Peer Review Only Confidential place in the toolbox of physicians. Researchers and educators must work with physicians for optimal and informed cannabinoid prescription and use.
Version 1	
Reviewer 1	
Name	Hazekamp, A
Position	
Institution	
Competing interests	
Date review returned	14-Nov-2014
General comments	See Appendix 2, available at www.cmajopen.ca/content/1/1/E251/suppl/DC1
Author response	This information was already present in the Abstract methods: Page 2. The reviewer is right, new evidence has to be provided

regarding cannabinoids efficacy and safety for the treatment of chronic non cancer pain to guide medical practice.

The conclusion of the abstract was reformulated: Page 2.

The study population was made clear in the objectives presented in the abstract and the introduction sections of the manuscript: Pages 2 and 4.

This aspect was verified throughout the manuscript.

More details regarding this aspect were added to the introduction: Page 3.

According to more than one recommendation provided regarding our manuscript, a more complete description of the questionnaire development and response formats is now **presented in the "Questionnair**e development and **measures" section of the manuscript: Pages 7**-8.

The manuscript reports on the prevalence and the determinants of cannabinoid prescription in the management of CNCP. This topic is a portion of the results of a research thesis in preparation. To our opinion, all results could unfortunately not be presented in a single manuscript without any loss of information. The questionnaire thus contained more questions than those who are presented in our manuscript such as knowledge level and barriers to cannabinoids use. All questions were designed by an expert committee to answer our specific research questions and no **questions were reduced. For readers' information, the** complete questionnaire is presented in the Appendix.

Thank you for the very interesting reference.

Some precautions support the content validity of our questionnaire (i.e., the extent to which a measure covers all aspects of the topic it is supposed to measure (McDowell et Newell, 1996);

-        Development of the questionnaire by an expert committee

-        Use of previous work as a base for the formulation of some questions

-        Use of recognised and straightforward type of questions (closed-ended, semi-closed-ended, numeric rating scale)

-        Pretest of the questionnaire

These aspects are now underlined in our method section: Page 7.

Thank you again for the reference.

More detailed information about questionnaires received and response rates obtained at each rounds of postal mail-outs is now presented in Table 1 and should better inform the reader: Page 22.

Response rate (%) was calculated by dividing the number of completed questionnaires (n=166) by the number of eligible physicians (n=318) to whom questionnaires were sent.

It is suggested that if the amount of missing data is low (less than 5-15%), imputation techniques are not required (Fox-Wasylyshyn et El-Masri, 2005).

Since the amount of missing data was low in our study (as

| | reported in Table 2, Figure 1 and Figure 2 footnotes), imputation techniques were not used and missing data were automatically excluded from the analysis conducted with the SPSS software.

These aspects are now underlined in our method section: Page 7.

This precision was added to our method section: Page 9.

Although years of practice, was not associated with prescription patterns in univariate models, we felt that it was important to consider in multivariate analysis.

Here are some clarifications regarding our numbers :

Among the 166 survey respondents, prevalence of cannabinoid prescription was 27.3% (45/165, 1 missing data). This prevalence is not shown in Figure 1.

As presented in the Figure 1 legend, the numbers presented represent percentages (prevalence of prescription among the 166 respondents). For chronic non cancer pain (CNCP) for example, prevalence = 23.0%.

We agree with the reviewer that results presented in Figure 2 could be explained in words. However, considering clarifications added in the manuscript according to editors and both reviewers comments, we decided to keep Figure 2 to respect the word count limitation: Page 30.

In fact, the statistics presented in Table 3 (previously identified as Table 2) were a little bit cumbersome. Finally, we chose to keep only means, SD and medians to describe continuous variables in our table: Pages 24-35.

Because emergency rooms are physical parts of hospital buildings but were categorized and analyzed as separate work environments in our study, we thought that this information would demonstrate that our categories are mutually exclusive.

Thank you very much for finding this error. Rows and columns were inverted in our SPSS results ouput. The correction was made in Table 4 (previously identified as Table 3): Page 26.

We would like to specify that all numbers presented in Table 4 were verified twice. Since the amount of missing data was low in our study (as explained in our response to Comment 10), missing data were automatically excluded from the analysis conducted with the SPSS software. For this reason, proportions presented in the parenthesis add up to 100% but numbers could add up to a total is lower than 127 (prescribers) or 38 (non-prescribers).

The reviewer is right. One important finding of our study is that survey respondents want more clinical data and new studies. This is now better underlined in the discussion of our results (page 13) and in our conclusions (pages 15 and 16).

More information was added in the manuscript: Pages 14-15.

All references were verified.

The conclusions presented in the abstract and at the end of the manuscript were reformulated: Pages 2 and 15-16. |
| Reviewer 2 | |

Name	Karen Burns
Position	
Institution	St Michael's Hospital, Critical Care Medicine
Competing interests	
Date review returned	Nov 3, 2014
General comments	Major comments appear in bold font. Abstract Comment 1: Abstract Methods Please explicitly state that this was a postal survey Comment 2: Abstract Conclusion I do not agree that the conclusion as formulated highlights the key findings of this survey or addresses the research objective. I believe that the authors need to state something about prescription prevalence and determinants in the conclusion. I would recommend removing the first sentence. The authors also need to acknowledge that the evidentiary basis for use of cannabinoids for CNCP may also be a factor, in addition to broader education, in limiting physician prescribing behavior for cannabinoids. To have informative guidelines and education on this topic, there needs to be an evolving **evidenciary basis…..I am not certain that this exists….for** CNCP at present. The BMJ systematic review and the editorial cited by the authors do not support this. Are there many large, well designed RCTs that have been conducted since the BMJ Systematic Review that support use of cannabinoids for CNCP? Introduction Comment 3: Study Population Please include the study population in the research objective (second last sentence of the introduction). Comment 4: Terminology throughout the manuscript **In general, the term 'survey' is used to refer to the methodology and the term 'questionnaire' is used to refer to** your postal instrument. Comment 5: Evidence **Please cite the evidence for treating clinical conditions….ie** MS, neuropathic pain (fibro, RA) with cannabinoids and CNCP. Please also highlight the evidence/lack of evidence supporting use of cannabinoids for other conditions. I think the article would benefit from specific information pertaining to the current knowledge base in the introduction, especially pertaining to CNCP. Methods Comment 6: How were items generated for inclusion in the questionnaire? How were items reduced to identify only those for inclusion in the questionnaire? Were all domains of relevance covered (e.g., clinician knowledge of evidence for use of cannabinoids) Comment 7: Was the questionnaire pretested or pilot tested? With how many individuals? Please see reference below for distinction between these two phases of questionnaire

development/testing.

Burns KE, Duffet M, Kho M, Meade MO, Adhikari NK, Sinuff T, Cook DJ: ACCADEMY Group. A guide for the design and conduct of self-administered surveys of clinicians. CMAJ 2008;179:245-52.

Comment 8: Were any of the clinimetric properties (face validity or clinical sensibility testing, content validity, inter or intra-rater reliability) of the questionnaire assessed?

Comment 9: Please define how response rates were tabulated? I refer the author to the following:

The American Association for Public Opinion Research. Standard Definitions: Final Dispositions of Case Codes and Outcome Rates for Surveys. 7th edition. http://www.aapor.org/Standard_Definitions2.htm. Accessed June 25, 2014.

Comment 10: Please describe briefly how missing data/incomplete questionnaires were handled?

Comment 11: Please describe in one sentence the type of response formats used in the questionnaire?

Comment 12: A priori did you decide to include variables with p-value < 0.15 plus yrs in practice in the multivariate model?

Results

Comment 13: Figure 1

23/x (where x=84) = 27.3% (referred to in the text of the **results)...however, I am not sure where the denominator of** 84 comes from? Please clarify this discrepancy between the text of the results and figure 1.

Comment 14: Figure 2

Please include mean +/- sd in the text. I am not convinced that this figure represents this data well or is necessary. Consider deleting figure.

Comment 15: Table 2

Please provide the (median, IQR) instead of (median, min, max) for several rows in this table. I believe that it is more meaningful.

Comment 16: Table 2

Why does the subtitle for row 4 state excluding ER...but ER is including among the options presented below?

Comment 17:Table 3

The first row 92 and 55 under "No" do not add to 127? The percentages however, add to 100%. Similarly under "Yes", the proportions do not add to 38? Please clarify in the legend or verify the statistics provided.

Discussion:

Comment 18: Discussion/Interpretation

I found it interesting that most respondents (67.8%, and 50%)) identified guidelines/algorithms and clinical data, in addition to, educational interventions are required to enhance their comfort with prescribing cannabinoids. In my mind, guidelines and educational initiatives require primary studies or evidence/data to base recommendations upon. I wonder if your results simply suggest that more

	research/evidence is required in this area.......to enhance practitioner comfort with prescribing cannabinoids. That is, more evidence for use of cannabinoids and information on adverse events for CNCP may enhance clinician comfort in using them. Your discussion does not directly state this. The **fact that most prescribers...infrequently prescribed....suggests to me that this is an important point.** Please comment. Comment 19 Strengths/Limitations **Please justify "high response rate"........usual**ly survey of **physicians....have response rates of at least 60%. Please** include a reference. The response rate to your questionnaire was 52%.While survey response rates of less than 60%, between 60 and 70%, or of at least 70% have traditionally been considered acceptable, lower mean response rates are reported for physicians compared to non-physicians. Notwithstanding, some authors opine that there is no scientifically established minimum acceptable response rate and assert that response rates may not be associated with survey representativeness or quality. For these authors, the more important consideration in determining representativeness is the degree to which sampled respondents differ from the population (or nonresponse bias) which can be assessed using a variety of techniques. Comment 20: References I could not locate reference 38? Comment 21: Conclusion See points made above regarding conclusion in the abstract and discussion sections. I strongly suggest that the author address the research objectives directly in the conclusion. The conclusion should be limited to 2 or 3 succinct sentences.
Author response	We would like to thank the reviewer for his careful revision **of our manuscript's form. Corrections were made throughout** the manuscript. Requested details (including additional references) were added in the introduction of the manuscript: Page 3. More details regarding this aspect were added to the introduction: Pages 3-4. **Mark Ware's previous work about experiences and** educational needs of physicians described self-reported factors that could increase their comfort level with prescribing cannabinoids for all potential indications (Ziemianski, Tekanoff, Luconi et al., 2012). A measure of the degree of comfort (numeric rating scale) such as the one used in the present study was not used in Ziemianski et al. study. Then we are able to put forward that the degree of comfort regarding cannabinoid prescription in the specific context of CNCP management has not been studied. For this reason, no changes were made to the manuscript. In our study, we used logistic regression models for the identification of the predictors of cannabinoid prescription (dependent variable). In the case of categorical independent variables, one category has to be designated as the **'reference' to which the others will be compared for the**

	interpretation of odds ratios. In our models, the odd ratio for an independent variable such as sex is the ratio of the odds that female physicians prescribed cannabinoids, compared to the odds that male physicians prescribed cannabinoids (reference category). A short table footnote was added to Table 4 (previously identified as Table 3) to ensure clarity: Page 27.
	The modification was made: Page 29.
	We agree with the reviewer that results presented in Figure 2 could be explained in words. However, considering clarifications added in the manuscript according to editors and both reviewers comments, we decided to keep Figure 2 to respect the word count limitation: Page 30.
	We don't understand? Yet, Figure 3 appears in the manuscript that was submitted and in the attached PDF copy of the manuscript containing the reviewer comments. In the new version of the manuscript, it appears on page 31.