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Title	A cross-sectional examination of medicinal substance abuse and use of non-medicinal substances among canadian youth: findings from the 2012/2013 Youth Smoking Survey
Authors	Cesar Leos-Toro BSc, David Hammond PhD, Stephen Manske EdD
Reviewer 1	Dr. Siavash Jafari
Institution	University of British Columbia, School of Population and Public Health
General comments (in bold) and author response in bold	<p>It was a great pleasure reading your article. You have done great work on analyzing the YSS data and have used a very simple language with no jargon. Abstract section has summarized the study very well. Appropriate background review has been provided. Methods section is well explained.</p> <p>1. Page 3 line 47: (DXM), a synthetic opioid.... DXM is not a synthetic opioid.</p> <p>According to (Miller, 2005), DXM is a synthetic opioid, a dextroisomer of the codeine levorphanol. The World Health Organization's Expert Committee on Drug Dependence on Dextromethorphan agrees with this characterization as well. If there are other sources that indicate otherwise, we would be pleased to revise.</p> <p>2. Page 4: Design section: is the participation in the YSS survey voluntary or obligatory? if voluntary, what was the response rate and what would be the impact of potential non-response on study finding?</p> <p>Participation in all research surveys is voluntary according to basic ethical standards. For the YSS, a mixture of active and passive permission protocols were used for the YSS project and depended on the permission method most typically used to obtain parental permission from each school. Only those students with "Yes" marked on permission form were able to participate in the survey in the active permission schools, students also had the opportunity to decline participation in these environments. In the passive permission settings, information was sent out in a variety of modes (e-mails, calls, or letters) and if no call or letter was returned, it was assumed that parents passively provided permission for their child to participate in the survey. Students in these settings also had the opportunity to decline participation on the day of data collection. Participation was ultimately voluntary.</p> <p>The response rate across Canada was 72% and ranged from 59% in Ontario to 92% in Quebec. At the student level this would have been due to refusal of parents to allow child(ren) to participate, student refusal even with parental permission or absence from school or class on the day of data collection. Of the 65,812 students eligible to participate – 47,203 completed the questionnaires. As we make note of in our limitations, it is quite possible that children that were not or could not be present on the day of data collection may represent a high-risk subgroup that was not captured – the implication being that the results presented in this study may be an underrepresentation or a very conservative estimate of prevalence of different kinds of substance use.</p> <p>Overall, the YSS is the largest youth survey conducted in Canada and serves as the benchmark for assessing prevalence of drug use behaviour. The response rates associated with the YSS are unusually high compared to current industry standards. Therefore, while it is always important to evaluate the potential risk of bias due to non-response, the YSS is among the most reliable data sources in Canada available.</p> <p>3. Page 11, table 2: under the medicinal substances, it says Dextromethorphan. Is this the exact term used in the study or does it as about any cough medications? With the former, most clients who would use cough medicines might get the desired effects from medicines other than DXM, which is common. If the later is what was asked then there is a risk of participants not knowing the specific name and some risk of information bias.</p> <p>For that particular item in the survey it asks about use of a variety of substances in the last 12 months. With respect to DXM it asks "Dextromethorphan such as cold and cough medicine like Robitussin DM, Benlyn DM (robos, dex, DXM)".</p>
Reviewer 2	Dr. Chizumuzo T. Okoli
Institution	University of Kentucky, College of Nursing
General comments (in bold) and author response in bold	<p>Summary: This paper aims to examine medicinal substance abuse among students in grades 7 to 12 from a sample of schools in Canada. The goal is to provide proportions of youth in Canada who abuse medicinal substances in comparison to those with non-medicinal substance abuse and both medicinal/non-medicinal substance abuse. In addition several factors are examined to examine correlates of medicinal substance abuse. The authors approach this aim by using data from the 2012/2013 youth smoking survey (n = 38,667) which represents students from 9 of 13 Canadian jurisdictions. The authors use multinomial regression analysis to examine factors associated with medicinal substance abuse. The authors found that at least 5% of youth reported abusing medicinal substances in the past year. In addition, girls were more likely to abuse medicinal substances than boys, and there were regional differences in medicinal substance abuse. General Evaluation: This is a well written paper overall. Medicinal substance abuse is a growing problem among youth and its identification is an important issue in order to determine measures for prevention and treatment. The approach to this study is reasonable. Appropriate statistical tests and methodology was used although issues regarding multiple comparisons need to be clarified. Major comments:</p>

	<p>1. Page 5, line 23. The survey was of 450 schools in Canada. What percentage of representative schools with grade 7 to 12 during 2012/2013 does this sample represent? The available documentation makes distinctions between primary and secondary schools but further breaks it down by grade levels given the provincial variability in defining these; of the 47,203 students that participated, 41,057 or 87% of those surveyed were initially included in our analyses.</p> <p>2. Page 5, line 39. Why were the schools divided into two strata based on smoking rates? Do you mean low vs. high smoking rates? Please clarify.</p> <p>The Youth Smoking Survey was originally designed as a comprehensive survey on youth smoking behaviour to provide national and provincial benchmark tobacco use prevalence rates. Schools were stratified based on health regions' smoking rates defined as high or low based on the median smoking rate for that particular province, current Canadian Community Health Survey data, postal code and health region.</p> <p>3. Page 7, line 10. The main concern is that the authors did not explain why they set a p=.01 for significance. With multiple comparisons they run an increased risk for Type 1 errors. For example in Table 3, with 'region' the authors examine at least 6 different comparisons.</p> <p>The sample size of the study is very large, with provides a high level of power to detect small effect sizes. To address the issue of multiple comparisons, we have applied a Bonferroni correction to account for multiple comparisons.</p> <p>4. Page 9, line 21-33. As the author's note, there are several limitations that may affect the 'representativeness' of the estimates of medicinal substance use, particularly the fact that several provinces and types of schools were excluded—which could potentially have higher rates of Medicinal substance abuse. Every population-based survey has limitations and we have tried to identify these limitations in the paper. As noted in our response above, the YSS is the largest youth survey in Canada and provides the best available estimates of substance use in Canada.</p> <p>Minor comments:</p> <p>5. Page 3, line 36. In the selection of key words, it seems odd that "girls' health" is a key word and not "youth" or "adolescents", especially with the title of the article being "Medicinal substance abuse among Canadian Youth..." I recommend changing the key word to "youth" ii. On page 4, line 15, the authors use the terms 'Controlled substance abuse' but then later on use the term 'medicinal substance abuse'. It is unclear if they are attempting to make a distinction between these two terms or if they are synonyms. For consistency with the title, I would suggest that for the first sentence revise to something like... "Medicinal substance abuse (also known as controlled substance abuse) has been associated with...."</p> <p>The umbrella term of 'medicinal substances' was used to capture those substances in the Youth Smoking Survey not included in Canada's 1996 Controlled Drugs and Substances Act but which are commonly used as medicinal therapies, for example cough syrups (dextromethorphan) or certain brands of sleeping pills.</p> <p>6. On page 4, line 42, since the cited commentary/study was comparing high-school students to adult populations, the authors should include the word 'adult' and revise to '...young Canadians compared to the general adult population'</p> <p>This change has been made.</p>
Reviewer 3	Monica Bawor
Institution	McMaster University, Neuroscience
General comments (in bold) and author response in bold	<p>The reviewed manuscript presents data on the prevalence of medicinal and non-medicinal substance abuse among Canadian youths in grades 7-12. This survey highlights an important area of research as prescription medication use is rapidly on the rise in the general population and adolescents alike. The use of the Youth Smoking Survey, a large nationally representative sample of students across Canada, is a key strength of this study. Despite a large representative sample and topic relevance, there are still a few concerns that require attention. Major Comments</p> <p>1. Why are some provinces/territories excluded from the survey? Please provide a justification for this exclusion as this would limit the representativeness of the sample.</p> <p>The province of Manitoba declined participation in the 2012/2013 YSS. YSS is funded by Statistics Canada, but nevertheless requires approval from provincial ministries of education and school boards in order to allow for school-based data collection. Manitoba's decision not to participate in the 2012/2013 survey was based on factors related to separate provincial initiatives and other underlying factors that were not specific to YSS content or methodology.</p> <p>Based on the comparative analysis using 2010/2011 survey data, there were no significant differences in national estimates with and without Manitoba. The territories, Northwest Territories, Nunavut and Yukon, have never been included in the survey based on reasons not present in YSS documentation.</p> <p>2. What is the reasoning for including Blacks, Asians, and Latin Americans in one category when assessing ethnicity? It is likely that medicinal substance use rates differ among the three ethnicities so this categorization should be explained. The different ethnicities have been separated in the most current version of the manuscript, as noted above.</p>

	<p>3. Was multiple testing error corrected and if so, using which method? This should be discussed. Alternatively, a rationale for choosing a p-value <0.01 for statistical significance should be provided.</p> <p>As noted above, a more stringent p value was used given the large sample size and ample power to detect very small differences. We have also revised the analysis using a Bonferroni correction to adjust for multiple comparisons, as described above. This addition has been made on line 98-99 in page 6: “Accepted statistical significance of results was set at p<0.01 and a Bonferroni Correction applied to reduce risk of Type 1 error.”</p> <p>Since the focus of the paper is on describing substance use and risk factors associated with it, potential implications (i.e. policy) and future research for this area should be discussed. Also the importance of prevalence and correlate data should be briefly mentioned as well. Within the length constraints, the importance of addressing the lack of data is addressed in the discussion which was also touched upon in the background. This is addressed in lines 149-154 in the Discussion : “Direct comparisons with national estimates from other studies are not possible due to a lack of data. According to the Canadian Alcohol and Drug Use Monitoring Survey (CADUMS), which surveys Canadians aged 15 and older, abuse of DXM was not reportable among youth because less than 1% of Canadians reported its abuse, in contrast to the current estimate of 3%. CADUMS was not able to report prevalence of abuse of many MSs due to high sampling variability and much lower samples sizes among youth than the current study, sustaining a continued dearth of comparable prevalence estimates.” And in the Background lines 35-37: “Patterns of substance abuse and misuse among youth, also predict use in adulthood.i,ii,iii To date, however, there are no national estimates of medicinal substance abuse among Canadian youth.”</p> <p>4.</p> <p>5. Self-reporting of data should be included as one of the limitations of the study.</p> <p>This has been included in the most current version of the manuscript on line 163 page 8.</p> <p>Minor Comments</p> <p>6. Page 3, line 26: When mentioning “best-available evidence”, it would be appropriate to provide references for this statement. What evidence is being referred to and what classifies it as the “best”? This reference cites Benedikt Fischer’s most recent review on prescription opioid related misuse. The manuscript describes that this is based on provincial and locally available indicators which is the best available evidence a by virtue of being the only available evidence at the moment.</p> <p>7. Page 3, line 42: It seems like reference 14 doesn’t fit here; the study by Brands mentions that the rate of non-medicinal opioid use is 6% in Ontario students not in the general population as was stated. This sentence is based on the Fischer study and should be more specific (i.e. add the years for the reported rates, and specify that the 15-20% rates in secondary students are compared to 6% in the general adult population in Ontario).</p> <p>Thank you for noting this oversight – the changes have been included in the most current version of the manuscript.</p> <p>8. Page 3, line 53: This statement is not supported by the reference provided. The statement mentions stimulant use but the reference provided is for a document on prescription opioids. Additionally, it would be best to specify again what the general population is that you are referring to in this statement.</p> <p>Thank you for noting this oversight – the change has been included in the most current version of the manuscript.</p> <p>9. Page 4, line 8: I would suggest specifying how medicinal substance abuse is defined in this statement. There are some national estimates of prescription drug use (Hammond et al. 2011), so it should be specified that this survey will be providing these estimates for medicinal substance abuse including the specific medications surveyed (pain meds, sedatives, etc.)</p> <p>The terms of use, abuse and misuse are operationalized in the third sentence of the background. The 2011 Hammond paper includes an aggregate measure of prescription drugs where the interest in this particular paper regards medicinal substances, substances that may be prescription drugs but may also be ones available over the counter such as dextromethorphan or certain kinds of sleeping medications in a disaggregated way.</p>
Reviewer 4	Dr. Jennifer Nicol
Institution	University of Calgary, Emergency Medicine
General comments (in bold) and author response in bold	<p>Overall impression: - Very nice epidemiologic study examining the current drug use trends in Canadian youth. The results are important, and as pointed out have potential policy implications.</p> <p>Introduction: - The content of the introduction is good, but the language can be tightened up a bit to make it easier to read.</p> <p>Thank you for your observation, we have revised the background to account for increased clarity and flow while maintaining the level of information we wish to disseminate.</p>

- Try to remove some of the colloquialisms i.e. "getting high" (Page 4 para 1) can be changed to desired psychotropic effects, and I don't think you need the example of misuse of sleeping pills as you've clearly described it and it doesn't add much to the point you are making.

Modified in most current version.

- Throughout the text, you do not clearly define what are medicinal substances, non-medicinal substances, and illicit and licit substances. Many readers may have some confusion differentiating between them. You also use some of this terminology interchangeably throughout the text which is confusing, and the use of abbreviations (i.e. MS and NMS) are sometimes inconsistent (ie using NS instead of NMs).

This has been modified in most current version. **Methods:** - It would be good to include a sentence or 2 explaining some of the exclusions, as this makes the sample less representative of the general population i.e. Manitoba, territories excluded. This is important because the patterns of substance use among youth may differ substantially in these regions compared to the rest of Canada. This may be important to include in the manuscript, so readers don't have to go to the YYS website to understand these important population group exclusions.

As noted above, province of Manitoba declined participation in the 2012/2013 YSS, based on the comparative analysis using 2010/2011 survey data, there were no significant differences in national estimates with and without Manitoba. The territories, Northwest Territories, Nunavut and Yukon, have never been included in the survey based on reasons not present in YSS documentation. This has been included in lines 46-49: ". Manitoba's decision to decline participation was based on factors related to separate provincial initiatives not specific to YSS content or methodology. Comparative analyses from 2010/2011 YSS indicate no significant differences in national estimates with and without Manitoba."

- In the multinomial regression model, why was age not included? The trends of substance, tobacco and alcohol use observed in table 2 are interesting and not touched on much in the paper.

Grade was used as a proxy for age. There is a very high correlation between age and grade among this age group, to the extent that it causes issues of multicollinearity in the models.

We agree that the trends of alcohol and tobacco are interesting; however, these trends have been explored in greater detail in other papers. Although we believe it is important to report concurrent use with alcohol and tobacco, the paper focuses on other substance use given the constraints on word limits/length.

Results: - Please clarify this sentence (Pg 6 para 3): "Compared to substance abstaining youth, as students progressed from grade 7 through 12..." – do you mean students that do not abstain? That use NMs? Not clear which group of students you are referring to here in comparison to abstaining youths.

Hopefully the wording has been clarified and perhaps Table 3 can be used as a reference to map this wording. That particular sentence refers to students that reported abuse of medicinal substances with the reference group (indicated at the bottom of the table) being their abstinent counterparts.

- Please clarify (Page 6 para 5): I think here you are referring to information from both table 2 and table 3 – table 2 describes the drug use trends through the grades, while table 3 describes the regression model and girls having more concurrent use than boys.

Here we only really refer to Table 3. We included a variable for Grade in our multinomial regression models present in Table 3.

- In the text portion of the results section, you point out the significant trends in the use of concurrent substances, but you don't mention the differences in associations with MSs and NMSs – are you less interested in these? It is unclear what you have chosen what to state in the text section of the results. Ideally, you shouldn't need to restate a large part of the table, as they should be stand alone.

We agree that the associations between MS and NMS use is of interest and additional results were included in earlier versions of the manuscript. However, we were unable to include this in the final paper due to the 2,500 word limit. We would be pleased to add additional information on these association if the editor wished to allow greater length.

i Trenz RC, Scherer M, Harrell P, Zur J, Sinha A, Latimer W. Early onset of drug and polysubstance use as predictors of injection drug use among adult drug users. *Addict Behav* 2012;37(4):367-372.

ii De Graaf R, Radovanovic M, Van Laar M, Fairman B, Degenhardt L, Aguilar-Gaxiola S, et al. Early cannabis use and estimated risk of later onset of depression spells: Epidemiologic evidence from the population-based world health organization world mental health survey initiative. *Am J Epidemiol* 2010;172(2):149-159.

- I'm not sure if you are able to describe this given your survey tool, but does MS use lead later to NMS use?

The survey is cross-sectional in nature; therefore, the study is unable to establish temporality and longitudinal patterns of use. We agree that this is an important question and one for which virtually no data exists among youth. We are actively working on a large cohort study of youth in which we hope to elucidate these patterns.

Interpretation: - Page 7 paragraph 3: risk behavior → you did not assess risky behavior in this study. While it is clearly often associated with illicit drug use I don't think you can state that risk behavior is synonymous with illicit drug use, and therefore less prevalent in girls.

This statement was based on use of illicit substance and abuse of medicinal substances, which constitutes one type of "risk behaviour". We have revised the wording so that it refers to "one type" of risk behaviour to avoid the impression that we are generalizing to other risk behaviours though we have added some support to our findings that indeed there is other evidence for gendered pathways

	<p>in substance abuse : see page 7.</p> <p>- You state that MS use is elevated in this study, but NMS use is more common in all age groups in both sexes. Are you referring to MS use in girls being higher than boys? Please clarify this.</p> <p>Yes, girls were found to be 1.7 times likelier than boys to abuse medicinal substances. We have inserted the OR explicitly in the first line of the second paragraph under the Interpretation subheading.</p> <p>- How do the results from this study compare to those from other similar nations i.e. USA, European countries?</p> <p>To our knowledge, the YSS is the only instrument that explicitly asks about <i>abuse</i> of substances – our interest is to point out the insufficiency of Canadian and global data about substance abuse in these populations.</p> <p>iii Schmid B, Hohm E, Blomeyer D, Zimmermann US, Schmidt MH, Esser G, et al. Concurrent alcohol and tobacco use during early adolescence characterizes a group at risk. Alcohol Alcohol 2007;42(3):219-225.</p>
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