PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Nonmedical use of prescription pain relievers among high school students in China: A multilevel analysis</th>
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<tr>
<td>AUTHORS</td>
<td>Lan, Guo; Xu, Yan; Jianxiong, Deng; Yuan, He; Xue, Gao; Li, Pengsheng; Wu, Hong; Zhou, Jinghua; Lu, CiYong</td>
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</table>

VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Wei-Hong Zhang</th>
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<tbody>
<tr>
<td></td>
<td>Université Libre de Bruxelles</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>22-Mar-2015</td>
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GENERAL COMMENTS

This is good written paper even the English language editing could be improved by a native English speaker.

There has been a several study addressing the Nonmedical use of prescription drugs among young people. This study presents an advance on previous works as it conducted in a large sample size in China

In the method section
1. A multistage stratified random cluster sampling procedure was used by author. But, the unit of stratification is not clear?
2. What were the eligibilities of cluster, if there are any? Among how many the eligible cluster, 29 GHS and 11 VHS were selected? And what is the method used for selecting those clusters?
3. There was any sample size estimation?
4. There was any eligibility for the individual participants?
5. Page 6, line 13, the age of majority is 18 years in China for either gender. For getting the consent from participants, do you take into account the age of majority?
6. There was no any information on the ethics approval.

In the result section
1. Table 1. “Total (n,%)” need to be changed to “Total, n (%)” which corresponds the content of the table. Same comment for GHS (n, %) to GHS, n (%) ; VHS (n,%) to VHS , n (%). Same comments for the table 2.
2. Table 1. Please use the footnote for indicating the statistic test used for p-value? Do you exclude the missing value for p-value estimation? Please indicate the unit for the age (year) in the table.
3. Authors showed that there was a positive association between NMUPD and pocket money; and a negative association between NMUPD and socio-economic. The explanation given by authors is that students from lower-income families had less pocket money and, thus, less access to prescription drugs. Did this explication has been supported by the current data by testing the association
between variables of pocket money and socio-economic?

In the reference section:
Below references which were not included in paper would be useful for authors.


REVIEWER
Barbara Prudhomme White
University of New Hampshire, USA

REVIEW RETURNED
03-Apr-2015

GENERAL COMMENTS
This paper poses a very interesting and timely topic, namely what might be some of the characteristics associated with nonmedical use of prescription medications. Some of the descriptive data presented in the paper are fascinating....i had no idea of the extent to which
Chinese students also have access to medications, similar to US, and how they are inclined to misuse them, also similar to US. However, there is a major flaw in the design that needs to be addressed, if to be published. The authors have combined different classes of prescription medications and analyzed as if they constitute one group. There are vastly different reasons for which students would take prescription opioids for pain versus stimulant medications versus sedatives/tranquilizers. Thus, they should not be combined and discussed as if they are of the same class of medications. This primary design issue makes the remaining analyses and conclusions moot, in my opinion. If the authors were able to disentangle reporting to exclusive classes of medications, then the paper could realistically look at the relations of medication use to the variables of interest they discuss. A simple example of this: The authors report interest in associations among academic stress, personal relationships, and emotional health. We know from work in various disciplines that students who feel under high academic pressure tend to use stim meds, and that students who are depressed would tend toward opioids and/or sedatives. The authors found low stress associated with prescription drug misuse overall in their sample....but I would not be able to understand how their reported relationships make sense given the collapsing of three medication types into the one variable "medication misuse." They have groups of reported high stress students in both school types, which differs significantly.....it would be great to know if their medication misuse patterns differed. Another example would be the variable relationship problems....one would expect based on the literature that this would load more heavily on opioid or sedative use more than stimulants for attentional problems. As a result of this mix of student motivations and their tendencies to select out the medication that best serves them, it is hard to interpret the findings presented. We also have no idea of how students procure the medications, and the paper reports several studies but they have not made clear that some of the research is situated in the US while some is in Asia. Of note, I have never seen a response rate this high (96%) and wonder if students really have the freedom to opt out as they would elsewhere?

I think some of this paper is publishable....if medication types can be disentangled, or even if the authors stick to the descriptives of characteristic differences among the two types of high school students, removing medication misuse as a variable.

VERSION 1 – AUTHOR RESPONSE

Review 1
Comment 1: This is a good written paper even the English language editing could be improved by a native English speaker.

Response 1: According to the reviewer's suggestion, we have invited a native English speaker to carefully revise the entire manuscript. We hope that the language is now acceptable for the next step of the review process.

Comment 2: A multistage stratified random cluster sampling procedure was used by author. But, the unit of stratification is not clear?

Response 2: We apologize for the incomplete information about the sampling procedure in the
original manuscript. We have adjusted the contents of the multistage stratified cluster sampling procedure in the revised Methods section (Pages 7-8) to clarify the unit of stratification. In stage 1, based on the surveillance data on the population of “nonmedical prescription drug users of cough syrup with codeine” during 2010-2011 from the Center for ADR Monitoring of Chongqing, we divided the districts in Chongqing into three categories: (1) high (districts accounting for more than 5% of this population); (2) middle (districts accounting for 1-5% of this population); and (3) low (districts accounting for less than 1% of this population). Then, we selected two representative districts (or primary sampling units) from each category by simple randomization using SAS software. In stage 2, high schools (or secondary sampling units) in each selected district were divided into three categories based on teaching quality: key high school, regular high school, and vocational high school. All high schools in the selected districts were surveyed (including four key high schools, five regular high schools, and four vocational high schools in each of the high and low districts as well as five key high schools, six regular high schools, and three vocational high schools in the middle districts). In total, 29 GHSs and 11 VHSs within these primary units were selected. In stage 3, two classes (or minimum sampling units) were randomly selected from each grade within the selected schools. In addition, we also added a flowchart to illustrate the sampling procedure in our revised manuscript (see Figure 1).

Comment 3: What were the eligibilities of cluster, if there are any? Among how many the eligible cluster, 29 GHS and 11 VHS were selected? And what is the method used for selecting those clusters?

Response 3: Thank you for your questions. We have adjusted the sampling procedure in the revised Methods section (Pages 7-8). There were no special eligibility criteria for the clusters. In addition, the total number of selected districts included 29 GHSs and 11 VHSs (including four key high schools, five regular high schools, and four vocational high schools in each of the high and low districts as well as five key high schools, six regular high schools, and three vocational high schools in the middle district). Actually, we surveyed all the high schools in each of the selected districts, and there were no special methods employed for selecting those clusters.

Comment 4: There was any sample size estimation?

Response 4: Thank you for your kind suggestion. Actually, we estimated the sample size before our investigation, and we did this assuming a prevalence of nonmedical prescription drug use among Chinese adolescents of 6.0%, a α of 0.05, and a sampling error of 0.005. The number of high school students in Chongqing is estimated at 3.8114 million, and we calculated a required sample size of 6,009. With adjustment for the clustering design effect and the non-response rate, the sample size was expanded to 9,014 (1.5*6,009). These data has been added in the revised manuscript (Page 7, lines 12-17). Additionally, the total sample in our study was larger than the estimation, as we investigated 12,406 high school students, and of those, 11,906 students’ questionnaires were completed and qualified for the survey.

Comment 5: There was any eligibility for the individual participants?

Response 5: There were no special eligibility criteria for the individual participants. Our survey was carried out in classrooms without the presence of the teachers during thirty minutes of the students’ regular class time, and all the high school students in the selected classroom were invited to participate in our survey voluntarily. This sample only did not include individuals who had dropped out of school or were not present in school on the day of survey administration.
Comment 6: Page 6, line 13, the age of majority is 18 years in China for either gender. For getting the consent from participants, do you take into account the age of majority?

Response 6: We thank the reviewer for these comments. We took the age of participants into account when obtaining consent letters. We have added the age of students to the following sentence “written consent letters were obtained from each participating student who was at least 18 years of age. If the student was under 18 years of age, a written consent letter was obtained from one of the student’s parents” (Page 8, lines 18-21).

Comment 7: There was no any information on the ethics approval.

Response 7: Thank you for your kind suggestion. As requested, we have added an ethics statement in the Methods section (Page 8, lines 15-21).

Comment 8: Table 1. “Total (n,%)” need to be changed to “Total, n (%)” which corresponds the content of the table. Same comment for GHS (n, %) to GHS, n (%); VHS (n,%)) to VHS , n (%). Same comments for the table 2.

Response 8: We thank the reviewer for this suggestion. We have replaced “Total (n,%)” with “Total, n (%)” in the revised Table 1 and Table 2, and we made similar revisions to “GHS (n, %)” and “VHS (n,%)”.

Comment 9: Table 1. Please use the footnote for indicating the statistic test used for p-value? Do you exclude the missing value for p-value estimation? Please indicate the unit for the age (year) in the table.

Response 9: Thank you for your kind suggestion. We have added a footnote that indicates the statistical tests used for determining the p-values in the revised Table 1. Missing data were excluded for p-values estimation, and we have added this information in the revised manuscript (Page 11, lines 4-5). Additionally, we have added the unit for age (years) in Table 1, Table 2, and Table 4.

Comment 10: Authors showed that there was a positive association between NMUPD and pocket money; and a negative association between NMUPD and socio-economic. The explanation given by authors is that students from lower-income families had less pocket money and, thus, less access to prescription drugs. Did this explication has been supported by the current data by testing the association between variables of pocket money and socio-economic?

Response 10: Thank you for carefully and patiently reviewing our manuscript. According to the suggestion of another reviewer, we have re-examined the manuscript and re-analyzed the data. The final results of the two-level multivariate logistic regression model still demonstrated that a below-average family economic status was negatively correlated with nonmedical use of prescription pain relievers (AOR=0.77, 95% CI=0.60-0.98), and students with more pocket money were more likely to be engaged in nonmedical use of prescription pain relievers (Page 13, lines 28-30). Additionally, the discussion about these relationships has been revised for clarity (Page 16, lines 13-23). We used a two-level multivariate logistic regression to explore the independent predictors of nonmedical prescription pain reliever use, and the mutual influence between pocket money and family economic status was controlled in this model. The final results showed that receiving 100-299 RMB
as pocket money per month (AOR=1.21, 95% CI=1.02-1.43) and receiving more than 300 RMB as pocket money per month (AOR=1.24, 95% CI=1.04-1.47) were independent risk predictors of nonmedical prescription pain reliever use, and below average family economic status (AOR=0.77, 95% CI=0.60-0.98) was independent protective predictor of nonmedical prescription pain reliever use. Unfortunately, considering the goals of the current study, we did not reveal the association between pocket money and family economic status.

However, according to your suggestion, we used the Chi-square test to examine the association between pocket money and family economic status, and the result demonstrated that there was a significant association between pocket money and family economic status ($\chi^2=903.2$, p<0.001). This result is not suitable for use in the current study, but we will adopt other study designs in our future research to further examine this relationship.

Comment 11: In the reference section: Below references which were not included in paper would be useful for authors.

Response 11: We thank the reviewer for this suggestion. We have adjusted the structure and content of the Introduction and Discussion to make these sections more logical, and we have read the studies that you recommended and cited some of them in the Introduction and Discussion sections (see References: No. 24, No. 27, No. 29 and No. 35).

Review 2

Comment 1: The authors have combined different classes of prescription medications and analyzed as if they constitute one group. There are vastly different reasons for which students would take prescription opioids for pain versus stimulant medications versus sedatives/tranquilizers. Thus, they should not be combined and discussed as if they are of the same class of medications. This primary design issue makes the remaining analyses and conclusions moot, in my opinion. If the authors were able to disentangle reporting to exclusive classes of medications, then the paper could realistically look at the relations of medication use to the variables of interest they discuss. A simple example of this: The authors report interest in associations among academic stress, personal relationships, and emotional health. We know from work in various disciplines that students who feel under high academic pressure tend to use slim meds, and that students who are depressed would tend toward opioids and/or sedatives. The authors found low stress associated with prescription drug misuse...
overall in their sample....but I would not be able to understand how their reported relationships make sense given the collapsing of three medication types into the one variable “medication misuse.”

Response 1: Thank you for carefully and patiently reviewing our manuscript and for noticing this problem in the original manuscript. As requested, we only included four pain relievers: cough syrup with codeine, Percocet, tramadol, and scattered analgesics (traditional Chinese medicine) in the revised manuscript. The list of medications was developed based on medicines reported to be widely used by adolescent drug abusers in rehabilitation centers and a list provided by the Center for ADR Monitoring of Chongqing (Pages 8-9). Additionally, we have re-examined the manuscript and re-analyzed the data. The dependent variable has been changed to “the lifetime nonmedical use of prescription pain relievers”, and the title of this study has been changed to “Nonmedical use of prescription pain relievers among high school students in China: A multilevel analysis”.

Comment 2: They have groups of reported high stress students in both school types, which differs significantly....it would be great to know if their medication misuse patterns differed. Another example would be the variable relationship problems....one would expect based on the literature that this would load more heavily on opioid or sedative use more than stimulants for attentional problems. As a result of this mix of student motivations and their tendencies to select out the medication that best serves them, it is hard to interpret the findings presented. We also have no idea of how students procure the medications.

Response 2: We thank the reviewer for these comments. Unfortunately, considering that opioids are difficult to obtain for nonmedical use by high school students in China, we did not investigate the nonmedical use of opioids in our research. However, according to your suggestion, we have adjusted the classes of prescription drugs, and we only included four pain relievers: cough syrup with codeine, Percocet, tramadol, and scattered analgesics (traditional Chinese medicine), according to a list provided by the Center for ADR Monitoring of Chongqing that reveals the pain relievers reported to be widely used by adolescent drug abusers in rehabilitation centers. This information has been added to our revised manuscript (Pages 8-9). Additionally, we have added the percentages of different classes of prescription pain relievers used nonmedically by high school students in our revised manuscript, and the results suggested that the most common nonmedically used prescription pain reliever among high school students was scattered analgesics, at approximately 5.8% (4.9% in GHS and 8.4% in VHS students, p<0.001), followed by cough syrup with codeine (5.5% in total, 5.0% in GHS and 7.3% in VHS, p<0.001), Percocet (5.4% in total; 4.7% in GHS and 7.7% in VHS students, p<0.001), and tramadol (0.6% in total; 0.6% in GHS and 0.6% in VHS students, p=0.871). In addition, as requested, we have added information about the sources of prescription pain relievers for nonmedical use, and the results showed that high school students most frequently obtained these pain relievers from peers (6.3% in total, 5.9% in GHS and 7.5% in VHS students, p<0.001), followed by others (4.6% in total, 3.9% in GHS and 6.8% in VHS students, p<0.001) and family members (2.0% in total, 1.5% in GHS and 3.7% in VHS students, p<0.001). In the revised manuscript, we also found that the most prevalent motivation for the nonmedical use of prescription pain relievers by high school students was ‘to relax or relieve tension’ (4.9% in total; 4.4% in GHS and 6.3% in VHS students, p<0.001), followed by ‘to experiment’ (2.6% in total, 2.3% in GHS and 3.5% in VHS students, p=0.001) and ‘to get high’ (2.5% in total, 2.2% in GHS and 3.4% in VHS students, p<0.001) (Page 13, lines 4-19 and Table 3). Furthermore, the discussion about these results has also been added in the revised manuscript (Page 15, lines 3-7; page 17, lines 20-23; page 18, lines 9-12).

Comment 3: The paper reports several studies but they have not made clear that some of the research is situated in the US while some is in Asia.
Response 3: We thank the reviewer for these comments. In the revised manuscript, we have added the locations of the studies cited in the Introduction and Discussion sections.

Comment 4: Of note, I have never seen a response rate this high (96%) and wonder if students really have the freedom to opt out as they would elsewhere?

Response 4: First, we must gratefully acknowledge the contribution of the Chongqing Education Bureau and its participating schools, which helped us receive 96% completed and qualified questionnaires without pay. We have expressed our great thanks in the Acknowledgments section (Page 19, lines 22-23). We are certain that all the participants were fully informed of the purpose of the survey and were invited to participate voluntarily. To protect the privacy of the students, a rigorously anonymous method for collection of the self-report questionnaires was guaranteed, and the questionnaires were administered by research assistants in the classrooms without the presence of the teachers (to avoid any potential information bias) during thirty minutes of the students’ regular class time. To some extent, the method of data collection is helpful to get the higher response rate. Additionally, in our previous study in Guangdong, the students who were not surveyed or refused to participate accounted for less than 1% of the sampled students.2

References:

VERSION 2 – REVIEW

| REVIEWER       | Barbara Prudhomme White  
|                | University of New Hampshire  
|                | USA  
| REVIEW RETURNED| 21-May-2015  

<table>
<thead>
<tr>
<th>GENERAL COMMENTS</th>
<th>The authors did well addressing the concerns I raised in its prior submission. Constraining to the one class of pain medications made it a much clearer study. The results are compelling, and confirms some anticipated relationships (e.g. students with lower supportive adult relationships and/or emotional health problems ---suicide attempts/ideations--- are most at risk). It is also now easier to read and understand the comparisons of studies done in China and elsewhere, including the US. The only lingering suggestions are to give more explanation about what &quot;scattered analgesics&quot; are in traditional Chinese medicine. I assume these are different that NSAIDS for inflammation, and have some sort of potential to obtain a &quot;high&quot; from them? This would be helpful for those of us outside of China who are not familiar with them. Another point is that there does not need to be a restating of statistics and percentages in the results section since they are so nicely presented in the Tables. It makes for a more difficult read of the narrative.</th>
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Comment 1: The only lingering suggestions are to give more explanation about what "scattered analgesics" are in traditional Chinese medicine. I assume these are different that NSAIDS for inflammation, and have some sort of potential to obtain a "high" from them? This would be helpful for those of us outside of China who are not familiar with them.

Response 1: Thank you for your questions. We have explained what "scattered analgesics" are in traditional Chinese medicine in our revised manuscript. (Page 7) As you think, scattered analgesics surveyed in this study is the commonly used traditional Chinese medicine, such as Ephedra Herb and Aconitum carmichaeli Debx, not only having the function of relieving pain, but also having complex compositions which can make people addicted when reaching a high dose.1

Comment 2: Another point is that there does not need to be a restating of statistics and percentages in the results section since they are so nicely presented in the Tables. It makes for a more difficult read of the narrative.

Response 2: Thank you for your kind suggestion. We have deleted the restating of statistics and percentages in the results section to make it more clearly for reading.

References: