Author's response to reviews

Title: Predictors of Opioid Misuse in Patients with Chronic Pain: A Prospective Cohort Study

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Author's response to reviews: see over
Reviewer's report

Title: Predictors of Substance Misuse in Patients with Chronic Pain, A Prospective Cohort Study

Version: 5 Date: 7 January 2006

Reviewer: James Zacny

Reviewer's report:

General

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

This revised version is confusing to read, and I fear that readers could also be confused or draw inappropriate conclusions. My main concern in the previous version of the manuscript was that the paper did not identify predictors of prescription opioid misuse, and I asked if an analysis could be done on those patients who only abused prescription opioids, and if not, that this should be labeled as a caveat in the Discussion section of the paper. The authors did perform an analysis on those patients who showed evidence of opioid misuse and the results are portrayed in Table 6 (bivariate analysis), mentioned in one sentence on p. 11, and briefly discussed in the Discussion section (p. 12). I will try to express my major concern succinctly but different things said in the paper as well as in the authors' letter addressing reviewers' concerns could make this confusing. I will start off with the opening of a sentence in the Discussion section: "In an analysis of only those patients with evidence of opioid misuse....." The analysis was done on 37 patients and their evidence of opioid misuse is listed as 5 criteria (negative urines, inconsistent urines, doctor collecting, prescription fraud, diversion) in Table 2, entitled "Serious Substance Abuse." However in the Abstract, opioid misuse includes those 5 criteria as well as "Stimulants detected on urine toxicology screen." When one goes to the Methods section to find the criteria, there is no mention of stimulant-positive urines as being a criterion for opioid misuse.

1. We inadvertently dropped the criterion related to stimulant-positive urine from the Methods section in the last revision. It is an essential part of our a priori definition of opioid misuse and has been added back on the bottom of page 6, along with an explanation of our rationale for including it as part of the definition: "Evidence of cocaine or amphetamines in the urine while being prescribed opioid was considered opioid misuse because it was in violation of the patient’s medication agreement and because concurrent use of cocaine and amphetamines is felt to increase the risk of diversion in order to procure additional stimulants.”

So in the Abstract the authors are arguing that having a positive urine for stimulants is a criterion for opioid misuse, but do not say that in the Methods, and in the Discussion state that evidence of opioid misuse is apparently (unless I am misreading them) negative urines, inconsistent urines, doctor collecting, prescription fraud, and diversion. It appears to me that the major part of the paper is still elucidating predictors of substance abuse amongst pain patients who are prescribed opioids. But the title of the paper now is "Predictors of Opioid Misuse" and no longer "Predictors of Substance Abuse." The authors state in their letter that the manuscript has been clarified to focus upon opioid misuse. I do not agree — how can the authors say this when the data analyses tables 2-5 focus on substance abuse and have identical data to that in the previous version of the paper which did focus on substance abuse (substance abuse is in the title of the tables)? The only way tables 2-5 could focus on opioid abuse is if all the criteria that are listed in the Abstract are used, including a debatable one, stimulants detected on urine toxicology screens. In the beginning of this review I stated that some readers might draw inappropriate conclusions from the paper. Showing cocaine positive urines is evidence of polydrug abuse in this study, but I would argue is not a marker for opioid abuse. The authors appear to agree by saying in the Discussion, "In an analysis of only those patients with evidence of opioid misuse...." The authors I believe are overestimating prescription opioid misuse. Rather than 31.6% of the patients in the pain clinic showing evidence
of opioid misuse (62 out of 196 patients), I would argue it is 18% (37 out of 196 patients).

The authors absolutely need to clarify the nature of this study: is it primarily on opioid misuse (a substantial part of the paper suggests it is) or is it on substance abuse in general with a sub-analysis of opioid misuse? If the authors argue that it is on opioid misuse because cocaine-positive urines are to them a marker of opioid misuse, I disagree with them and in some parts of the paper they themselves make statements contradictory to this notion.

2. We agree that there was inconsistent use of terms such as opioid abuse and misuse, and substance abuse. Our paper is focused on measuring opioid misuse. In the Methods and Discussion, we have attempted to make the definitional issues clear with regard to what constitutes misuse under our definition and to make more explicit that we were not evaluating for medico-psychiatric substance abuse/dependence. We have relabeled the tables to reflect our working definition of opioid misuse.

As previously stated, we were not in a position to assess patients for the psychiatric conditions of substance abuse/dependence. We did not apply standardized diagnostic interviews (which would not be practical in primary care settings) and, more importantly, DSM-IV substance abuse diagnoses do not apply well to prescription opioids - the definitions of abuse and dependence focus on tolerance and withdrawal, which cannot be used to identify aberrant behavior in patients who are prescribed and regularly taking the medication that they may or may not be abusing as well. We and others have struggled with this conundrum, and have chosen to focus on opioid misuse, as defined in the Methods. Our definition is consistent with previous definitions proposed in the literature: Portenoy, R. K. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage. 1996 Apr; 11(4):203-17 and Turk, Dennis C. Clinicians’ Attitudes About Prolonged Use of Opioids and the Issue of Patient Heterogeneity. Journal of Pain and Symptom Management. 1996 Apr; 11(4):218-230 are examples.

We have amended the section of the Discussion (Page 13, Line 17) explaining our choice of terminology to reflect this. We hope that a more explicit differentiation of abuse and misuse in the text clarifies these issues.

There is another confusing thing and that is in the authors' letter addressing my previous concerns, point #2: They say "Overall, the manuscript has been clarified to focus upon opioid misuse; that is those categories of patients who were found to be stimulant abusers (N=37). In general we found that the relationships between predictors and outcomes persisted and were consistent. For reasons of clarity and statistics (i.e., loss of power) we have not provided this data in the manuscript as it was not our predefined endpoint of interest. We do provide these tables below."

I have several points to make over this confusing (at least to me) response: 1) the first sentence does not make sense. 2) the N of 37 the authors are referring to are 37 patients who did NOT have stimulant-positive urines (and were not stimulant abusers). 3) The authors say the data with 37 patients is not in the manuscript; it is (at least results of the bivariate analysis, Table 6. 4) If the paper has been revised to focus on prescription opioid misuse, then what does "For reasons of clarity and statistics (i.e., loss of power) we have not provided this data in the manuscript as it was not our predefined endpoint of interest." It appears to me that the data they are referring to is the data with the 37 patients who met criteria for opioid misuse, and is in Table 6. So if this was not the predefined endpoint of interest (I assume the predefined endpoint of interest are predictors of opioid misuse in patients who showed evidence of opioid misuse (p. 11, line 23; page 12, line 12), then what was the predefined endpoint of interest?

3. We agree that the stimulant abusers (N=25) may differ qualitatively from our other categories of misusers but we chose a priori to include them in our composite definition of misuse and in our analyses. Our composite definition and analyses include both the stimulant and non-stimulant misusers. We offered a sub-analysis of the non-stimulant misusers (Last paragraph of results and Table 6) at the request of this reviewer but now realize that our presentation of this data was confusing.
Below find a table comparing characteristics of Stimulant and Non-Stimulant Misusers. Interestingly, stimulant misusers are somewhat older, have higher achievement on two measures of educational attainment, have higher depression scores, are more likely to have had a criminal conviction and less likely to have cannabinoids detected on UTS.

<table>
<thead>
<tr>
<th>Misusers</th>
<th>Stimulant (N=25)</th>
<th>Non-Stimulant (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>Race, % White</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>Gender, % Male</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>High School Graduate, %</td>
<td>75</td>
<td>57</td>
</tr>
<tr>
<td>REALM Score</td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td>H/O ETOH Abuse, %</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>H/O Cocaine Abuse, %</td>
<td>75</td>
<td>46</td>
</tr>
<tr>
<td>Drug or DUC Conviction, %</td>
<td>56</td>
<td>30</td>
</tr>
<tr>
<td>CESD</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Cannabis on UTS, %</td>
<td>24</td>
<td>38</td>
</tr>
</tbody>
</table>

4. The reviewer is correct that the data with the 37 non-stimulant misusers is in the manuscript (Table 6). (There was a miscommunication among the authors over whether or not to include it in the revised manuscript.)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

P. 8: patients were asked specifically about ongoing or previous history of drug or alcohol misuse. One example is given and that is of cocaine. Were other drugs mentioned to patients (did you abuse PCP, LSD, methamphetamine, heroin) or was it an open-ended question? This reviewer had asked in the last review to please provide data on past history of heroin use and prescription opioid abuse. The authors say in their cover letter, “These questions were asked to study participants. This point has been clarified.” I do not see in the paper where this was clarified. Further, there is a sentence in the Discussion section that might allude to past opioid misuse but there is no data from the Results section to back it up: “This observation that past opioid misuse is predictive of current prescription opioid misuse is in contrast to a previous investigation.” (p.12)

This was meant to refer to a reference provided by the reviewer and linked to the appropriate reference. The sentence has been modified in the first paragraph of the Discussion (p. 12) to reflect its intended meaning: “Our findings stand in contradistinction to other research that has found no predictive relationship between past alcohol and substance abuse and future opioid abuse in patients with chronic pain.” The pattern of drug misuse in the study population suggested the potential for multiple co-morbid diagnoses of substance abuse or dependence, placing these individuals at especially high risk of morbidity and mortality.

With regard to histories of past alcohol and drug abuse, we initially did ask about a long list of illicit drugs in addition to alcohol and cocaine but found that our survey instrument was too cumbersome and these items were eliminated as part of a process to streamline the instrument as a whole. We chose to limit survey of past substance abuse to alcohol and cocaine. On page eight and in the Discussion and Conclusions, the manuscript has been edited to reflect not only the limited number of substances surveyed but the fact that these were self-reported histories of abuse. It now reads: “Previous history of cocaine or alcohol abuse was assessed by self report.” We have also added this as a limitation of the study on page 15.

11, last sentence: I believe “opioid abuse or dependence” should be changed to opioid misuse.

The reviewer is correct- we have made this change.

12, first sentence: grammatical error...We identified that predicted opioid misuse should be "We identified predictors of opioid misuse..."

Fixed. Thank you.
p. 12, lines 12-13: the last table in the cover letter detailing responses to reviewers’ requests shows that the multivariate analysis on predictors of opioid misuse produced two predictors of opioid misuse (and notably one was not cocaine use history); the multivariate analysis in Table 5 of the manuscript shows four predictors. Therefore part of this sentence (lines 12,13) is not accurate, and further the reader may be left wondering what the multivariate analyses refers to since it was not presented in the manuscript (only the bivariate analysis was). The reviewer is correct. There was no multivariate analysis for the subset of non-stimulant misusers; this has been eliminated from the text. Table 6 is provided to show that the magnitudes of the odds ratios are similar in this subset. This is reflected in the text of the last paragraph of the results (p. 11) and in the following text from the first sentence of the discussion: In a separate bivariate sub-analysis of non-stimulant abusers, the relationships between predictors and outcomes were similar as the magnitudes of the odds ratios attest (Table 6). We do not present measures of statistical significance, as they would not be appropriate for this analysis of a small sub-set of the total patients.

P. 14, last sentence: I would argue that in the last several years, there has been very little prosecution of pain-treating physicians (as evidence, please see J Pain Symptom Manage 29:206-212, 2005). There is prosecution of physicians who engage in illicit activities (e.g., pill mills). This sentence will only serve to make physicians worry about their opioid prescribing habits, and could result in patients being under-medicated for pain. I am for physicians being vigilant but I do not think an argument for that is “continued prosecution of pain-treating physicians.”
Agree. Amended to read: “The recent clarification in the Drug Enforcement Administration regulations with regard to the provision of controlled substances, along with rare but high-profile prosecutions of pain-treating physicians, have highlighted the need for continued care in prescribing these agents. Systematic approaches to pain management and detecting opioid misuse can reassure physicians that they can alleviate suffering with opioids without inviting criminal sanction or negatively impacting public health.”

p. 16, last sentence of first paragraph: perhaps change to “Based upon these data, patients with a history of alcohol or cocaine misuse should be…..” Thanks. Amended.
Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.